

# Supplementary Data

## **Legends of supplementary figures**

### **Fig S1**

Supplementary Figure S1. Effect of low adiponectin dose and high adiponectin dose potency on ROS production. **A:** Detection of total ROS production by Carboxy-H<sub>2</sub>-DCFAD in HRMECs revealed that HG treatment significantly enhanced ROS production and green fluorescent.

**B:** Bars show the significant changes of ROS production between the different treatment groups presented as mean and SEM. \*p <0.05 HG is significantly different from the NG (control) group. Φ p<0.05 HG is significantly different than with HG+Adiponectin group.

Abbreviations, Normoglycemia cells (NG= C); High Glucose (HG); and High Glucose +adiponectin (30μg/ml) (HG+APN).

These data highlight that a high dose of ApN is superior to a low dose in ameliorating ROS production, which is well known to be a significant contributing factor in the pathogenesis of DR. Based on that, high dose of ApN (30 ug/ml) was used in the current study.

### **Fig S2.**

Panther enrichment pathways analysis demonstrated that the most critical pathways in percentage. Bars on X-axis represent the pathway, and Y-axis represents the percentage

### **Fig S3. Integrin signaling pathway and APN crosstalk using molecular prediction analysis.**

Network displays Integrin signaling pathway and crosstalk with APN in response of HRMECs cells to APN treatment. The upregulated (red) and downregulated (green) gens of the data set are shown. See legends and results for details.

### **Fig S4. p38 MAPK Signaling**

Network displays p38 MAPK Signaling in response of HRMECs cells to APN treatment. The upregulated (red) and downregulated (green) gens of the data set are shown. See legends and results for details.

### **Fig S5. IKBKB kinase and APN**

Network displays the upregulated (red) and downregulated (green) gens of data set under regulation by IKBKB kinase and crosstalk with APN over TFs in response of HRMECs cells to APN treatment are shown. See legends and results for details.

### **Fig S6. BRD4 and regulatory effect**

Network displays the upregulated (red) and downregulated (green) gens of data set, cellular function, agranulocyte adhesion, and diapedesis as CP Signaling in response of HRMECs cells to APN treatment are shown. See legends and results for details.

### **Fig S7. NW2 and NW3**

Fig A. NW2. The network shows interactions between dysregulated genes, functions, and upstream regulators in response of HRMECs cells to APN treatment. The figure illustrated the molecules and pathways involved in suppressing angiogenesis and adhesion of EC functions in response to APN treatment to HG cells. The network analysis displayed a score of 23 with three primary functions of cellular movements, hematological system and development, and immune cell trafficking. It involved 23 molecules, of which are 12 in focus which is ANG, CCL2, CD44, ITB2, TNC, SELP, VACN, CCL5, Cx3CL1, SPP1, CxCl5, ITGB1, and 11 non-focus, which are Adaptor protein 1, Cytokines, G protein alpha, Ped4, Rac, ADCY, chemokine, Dynammin, Gpcr, MAPK, Pdgr, Alp, ERK, IKK complex, metalloproteases, PLC, Via-4, CD3, G protein, PLC-gamma, and TCR. The upregulated (red) and downregulated (green) are illustrated. See legends for details, for the relationship label and prediction legend.

Fig B. NW3. The network shows interactions between dysregulated genes, functions, and upstream regulators in response of HRMECs cells to APN treatment. The figure illustrated the molecules and pathways involved in suppressing angiogenesis and adhesion of EC functions in response to APN treatment to HG cells. It involves 35 molecules, of which are 6 in focus which is ITGB5, ITGA1, ITGA5, THBS2, ITGA6, ANGPT1, and 29 non-focus, which are Actin, Cytokines, AKT, Alpha Actinin, C8, calpain, Collagen type I (complex), Collagen type ix, death receptor, Fascine, Fgf, Fgfr, Filamin Abp, Glycoprotein 1B, Hspg, ICAM, Integrin, Integrin $\alpha$ 3 $\beta$ 1, Integrin $\alpha$ 4 $\beta$ 1, Integrin $\alpha$ 5 $\beta$ , Integrin $\beta$ , ITG $\alpha$ 5-ITG $\beta$ 1/2, Lfa-1, Lymphotoxin, MAC, N-Cadherin, secreted MMP, Smad2/3-Smad4, TMSB4, and VLDL. The top functions of NW3 are Cell to cell signaling and interaction, Organismal Injury and Abnormalities, and Tissue development. See legends for details, for the relationship label and prediction legend.

### **Fig S8-APN- hypothesis action- abstract graphical summary**

Sites of APN actions, pathways, regulators, and downstream genes associated with molecular function related to DR pathogenesis. See legends for details and Tables S11, S12.

### **Fig S9 (A-F). Western Blot.**

#### **S9A, S9B. Protein expressions of ADR1 and ADR2 by immunoblot in HRMECs treated with APN.**

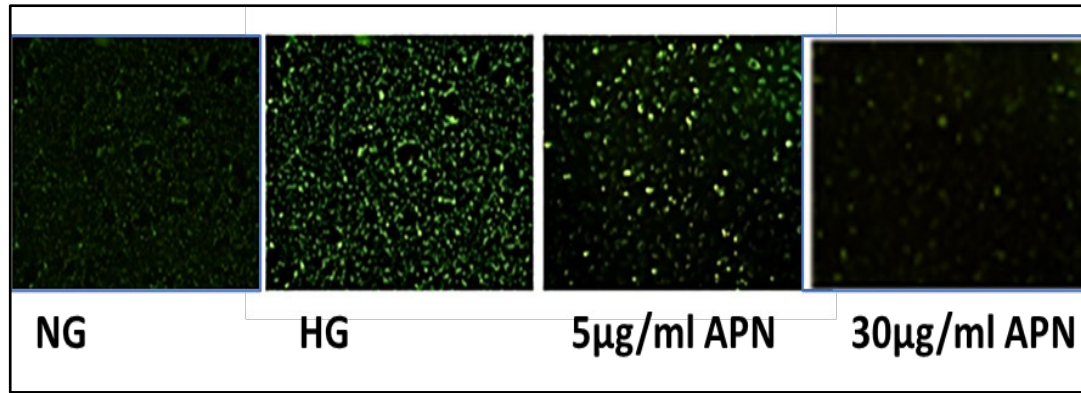
Figures A and B (upper panel) represented the AdipoR1 (A) and AdipoR2 (B) protein levels in the HRMECs at normoglycemia (NG), hyperglycemia (HG), and after treatment of hyperglycemic cells with adiponectin (HG+APN). The lower panels of Fig A and B demonstrate the densitometry analysis of the AdipoR1 and AdipoR2 protein expression in the NG, HG, and HG+APN. B- Actin is the housekeeping gene. Data represent 3-4 independent experiments. Statistical differences were established using ANOVA with multiple comparisons with the Tukey method,  $p < 0.05$ .

#### **S9C, S9D. Protein expressions of SOD2 and HMGB1 by immunoblot in HRMECs treated with APN.**

Figures C and D (upper panel) represented the anti-oxidant enzymes; Superoxide Dismutase 2 [SOD2] (A) and High mobility group box 1 [HMGB1] (B) protein levels in the HRMECs at normoglycemia (NG), hyperglycemia (HG), and after treatment of hyperglycemic cells with adiponectin (HG+APN). The lower panels of Fig C and D demonstrate the densitometry analysis of the SOD2 and HMGB1 protein expression in the NG, HG, and HG+APN. B- Actin is the housekeeping gene. Data represent 3-4 independent experiments. Statistical differences were established using ANOVA with multiple comparisons with the Tukey method,  $p < 0.05$ .

Fig S1

A



B

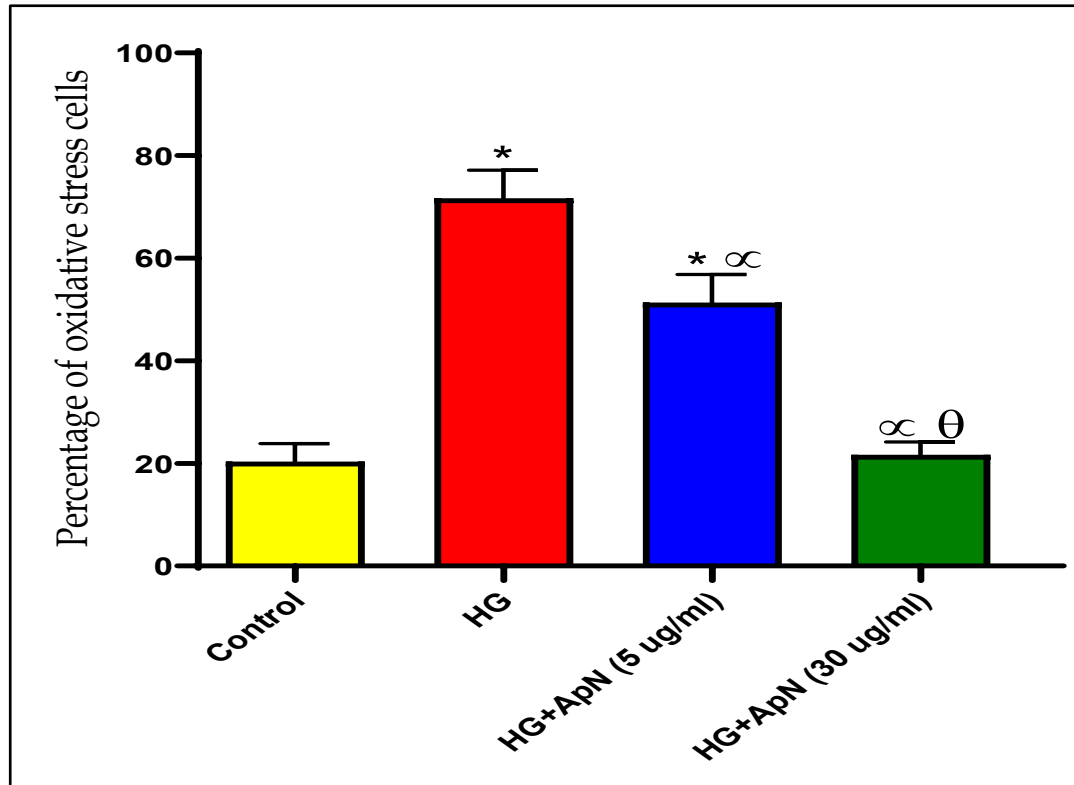
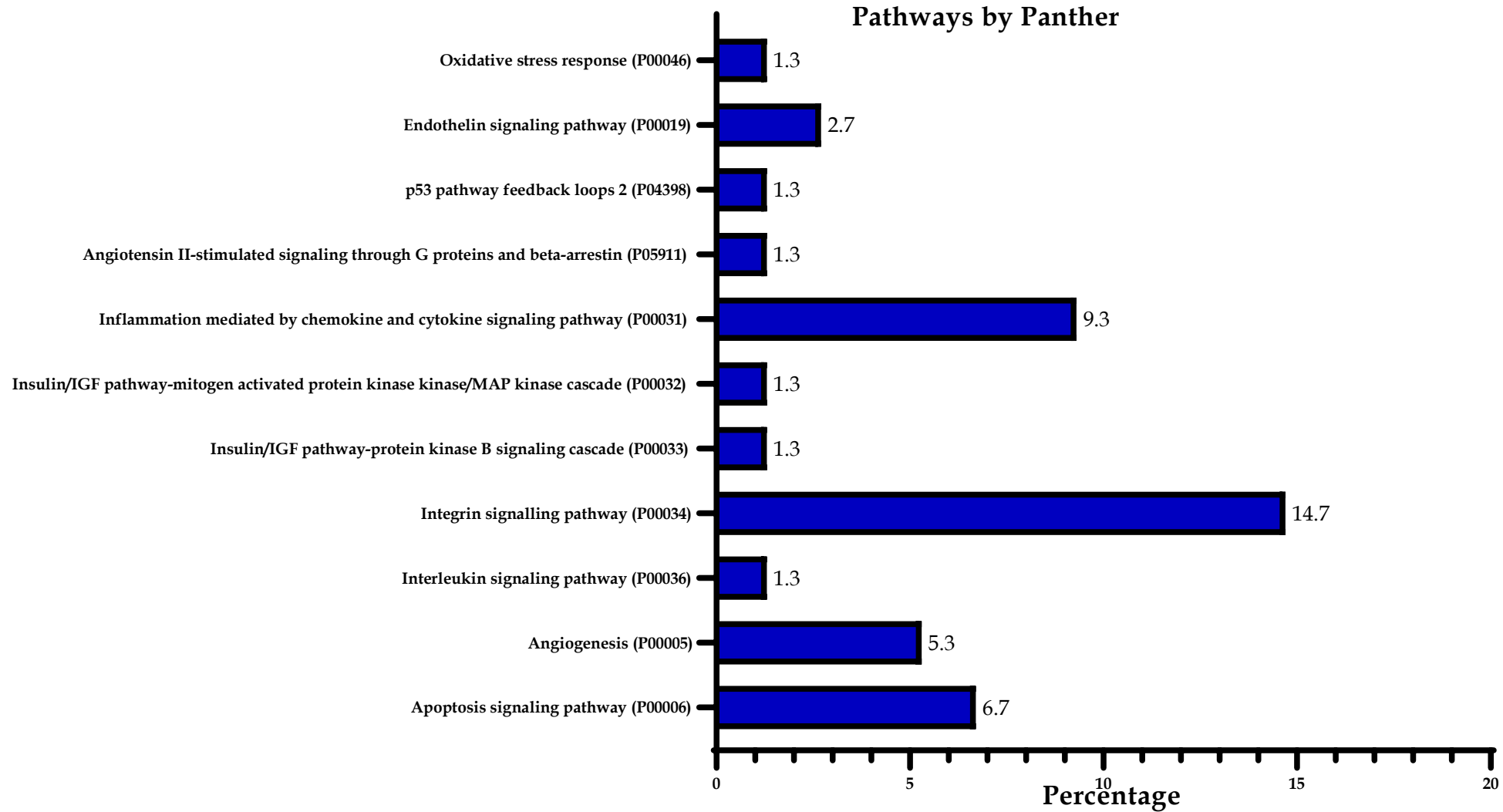
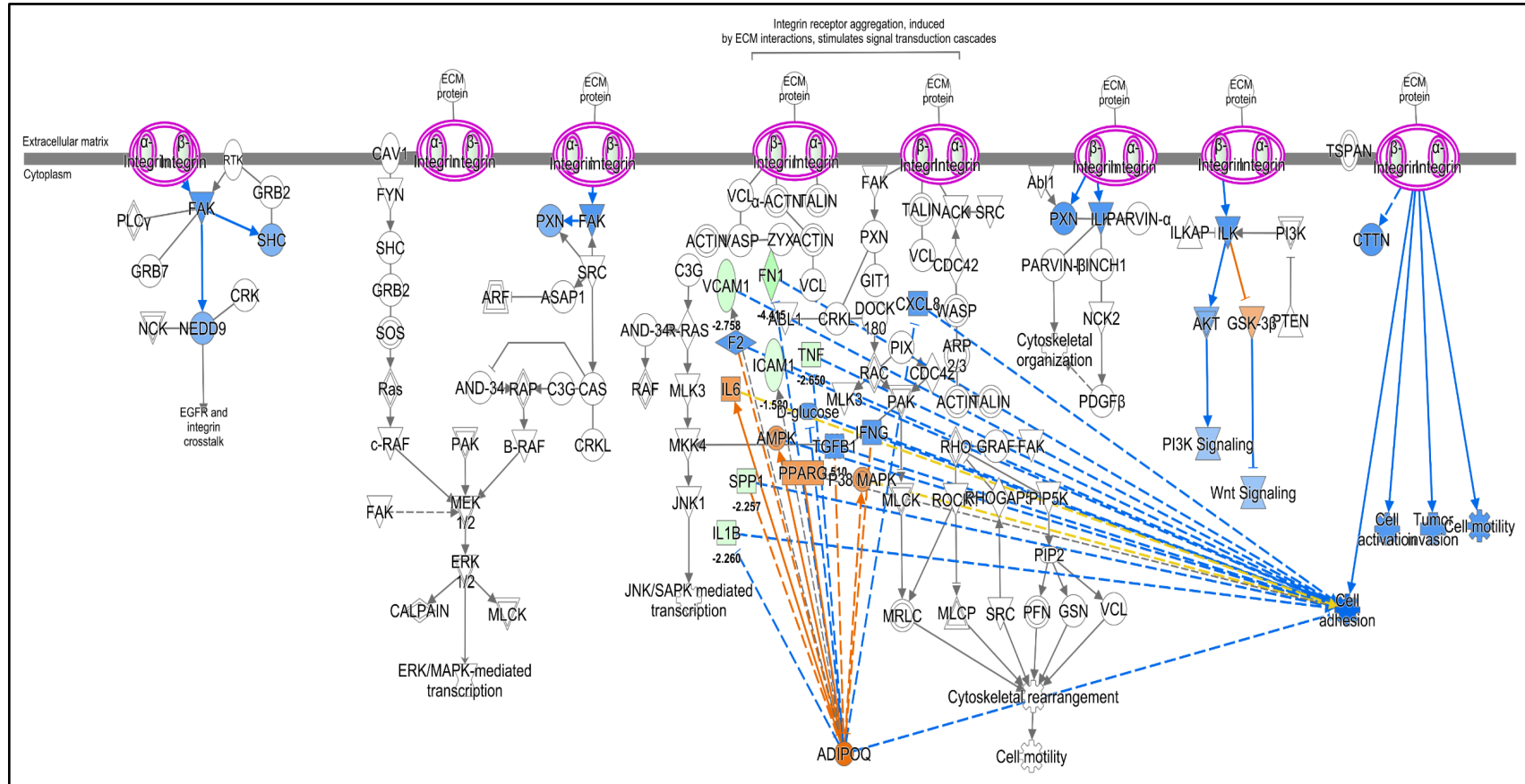


Fig S2.



**Fig S3. Integrin signaling pathway and APN and using MAP**



**Relationship Labels**

- A Activation
- B Binding
- C Causes/Leads to
- CC Chemical-Chemical interaction
- CP Chemical-Protein interaction
- E Expression (includes metabolism/ synthesis)
- EC Enzyme Catalysis
- I Inhibition
- L Proteolysis (includes degradation for Chemicals)
- LO Localization
- M Biochemical Modification
- miT microRNA Targeting
- MB Group/complex Membership
- nTRR Non-Targeting RNA-RNA interaction
- P Phosphorylation/Dephosphorylation
- PD Protein-DNA binding
- PP Protein-Protein binding
- PR Protein-RNA binding
- PY Processing Yields
- RB Regulation of Binding
- RE Reaction
- RR RNA-RNA Binding
- T Transcription
- TR Translocation
- UB Ubiquitination

**Prediction Legend**

more extreme in dataset  
● Increased measurement  
● Decreased measurement

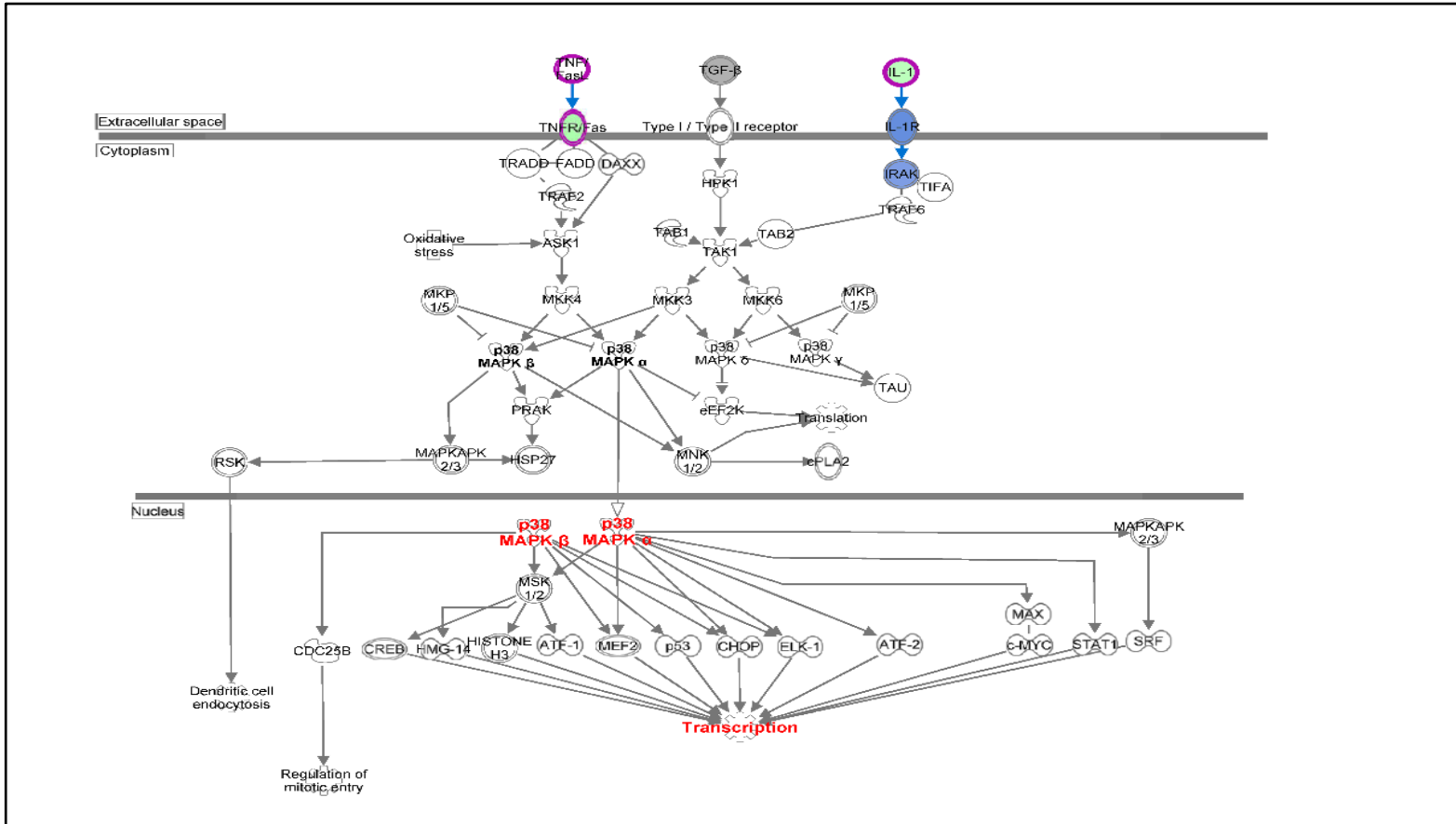
more confidence  
● Predicted activation  
● Predicted inhibition

Glow Indicates activity when opposite of measurement  
●  
●

**Predicted Relationships**

- Leads to activation
- Leads to inhibition
- Findings inconsistent with state of downstream molecule
- Effect not predicted

# Fig S4. p38 MAPK Signaling



| Relationship Labels |  |
|---------------------|--|
| A                   | Activation                                       |
| B                   | Binding  |
| C                   | Causes/Leads to                                  |
| CC                  | Chemical-Chemical interaction                    |
| CP                  | Chemical-Protein interaction                     |
| E                   | Expression (includes metabolism/ synthesis)      |
| EC                  | Enzyme Catalysis                                 |
| I                   | Inhibition                                       |
| L                   | Proteolysis (includes degradation for Chemicals) |
| LO                  | Localization                                     |
| M                   | Biochemical Modification                         |
| miT                 | microRNA Targeting                               |
| MB                  | Group/complex Membership                         |
| nTRR                | Non-Targeting RNA-RNA Interaction                |
| P                   | Phosphorylation/Dephosphorylation                |
| PD                  | Protein-DNA binding                              |
| PP                  | Protein-Protein binding                          |
| PR                  | Protein-RNA binding                              |
| PY                  | Processing Yields                                |
| RB                  | Regulation of Binding                            |
| RE                  | Reaction   |
| RR                  | RNA-RNA Binding                                  |
| T                   | Transcription                                    |
| TR                  | Translocation                                    |
| UB                  | Ubiquitination                                   |

| Prediction Legend                                       |                       |
|---|-----------------------|
| more extreme in dataset                                 | less                  |
| Increased measurement                                   | Decreased measurement |
| more confidence   | less                  |
| Predicted activation                                    | Predicted inhibition  |
| Glow Indicates activity when opposite of measurement    |                       |
| Predicted Relationships                                 |                       |
| Leads to activation                                     | Leads to inhibition   |
| Findings inconsistent with state of downstream molecule |                       |
| Effect not predicted                                    |                       |



**Fig S5. IKBKB kinase and APN**

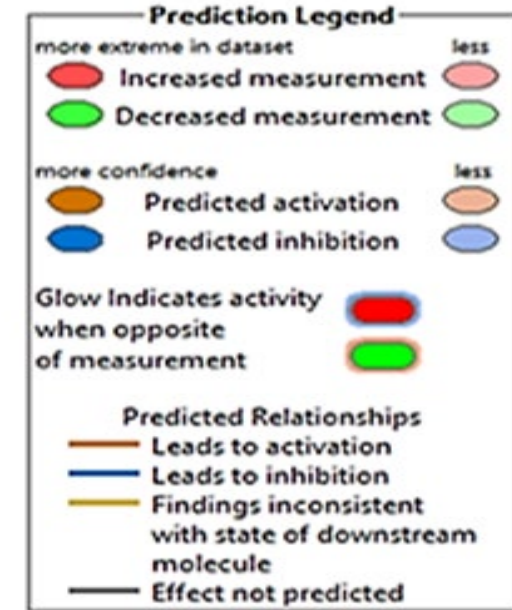
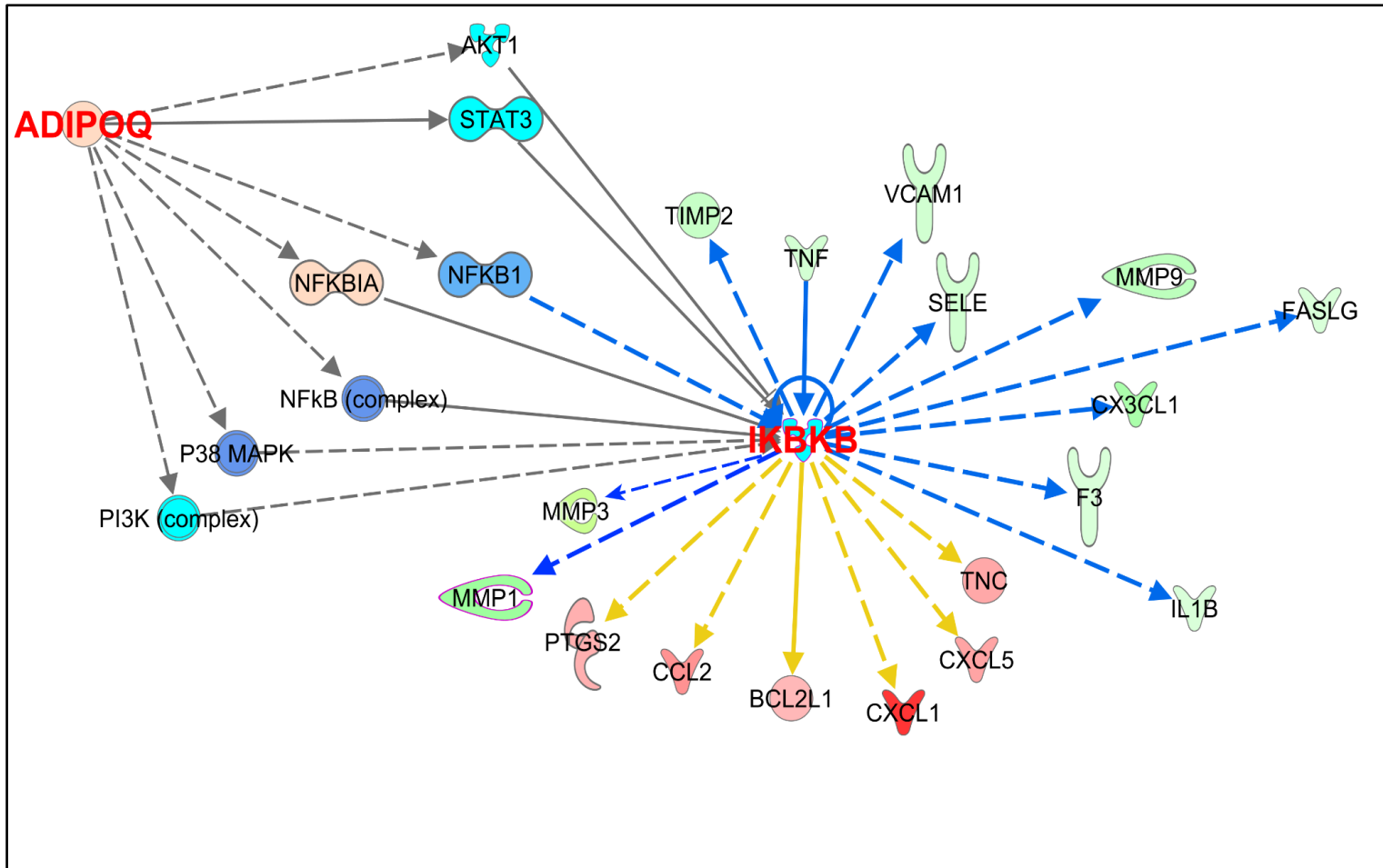
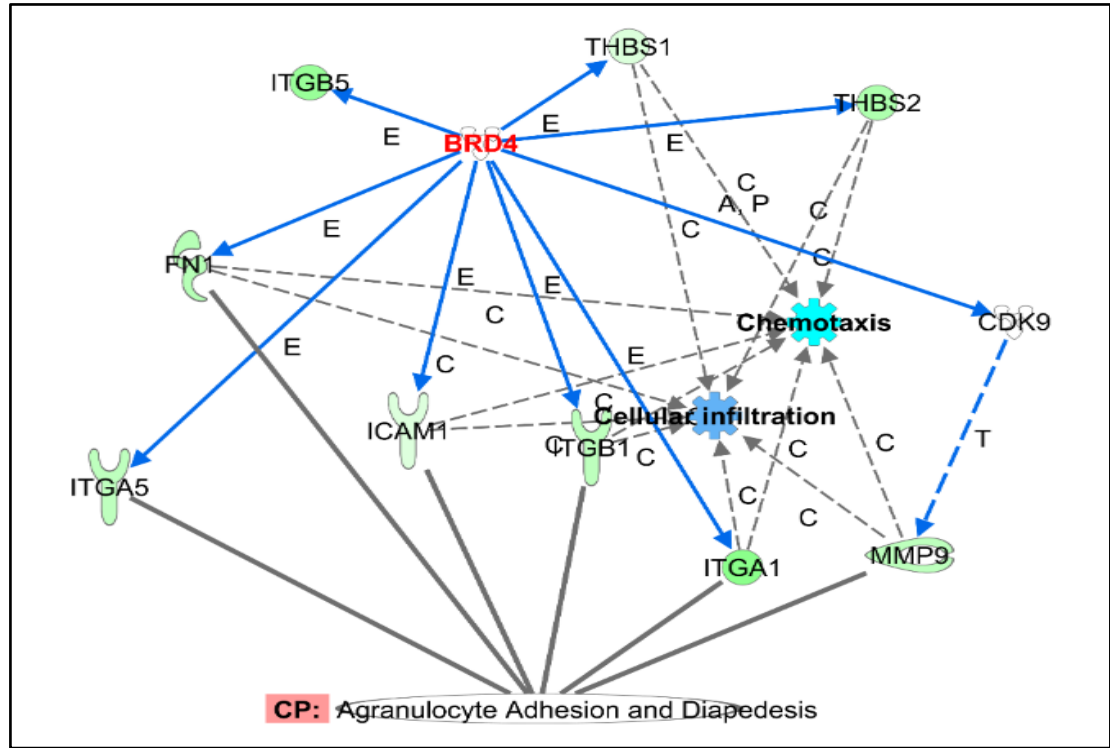


Fig S6. BRD4 and regulatory effect



| Relationship Labels |  |
|---------------------|--|
| A                   | Activation                                       |
| B                   | Binding  |
| C                   | Causes/Leads to                                  |
| CC                  | Chemical-Chemical interaction                    |
| CP                  | Chemical-Protein interaction                     |
| E                   | Expression (includes metabolism/ synthesis)      |
| EC                  | Enzyme Catalysis                                 |
| I                   | Inhibition                                       |
| L                   | Proteolysis (includes degradation for Chemicals) |
| LO                  | Localization                                     |
| M                   | Biochemical Modification                         |
| miT                 | microRNA Targeting                               |
| MB                  | Group/complex Membership                         |
| nTRR                | Non-Targeting RNA-RNA Interaction                |
| P                   | Phosphorylation/Dephosphorylation                |
| PD                  | Protein-DNA binding                              |
| PP                  | Protein-Protein binding                          |
| PR                  | Protein-RNA binding                              |
| PY                  | Processing Yields                                |
| RB                  | Regulation of Binding                            |
| RE                  | Reaction   |
| RR                  | RNA-RNA Binding                                  |
| T                   | Transcription                                    |
| TR                  | Translocation                                    |
| UB                  | Ubiquitination                                   |

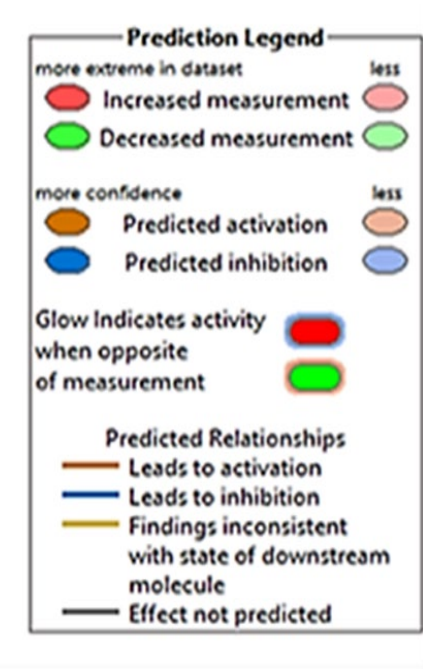
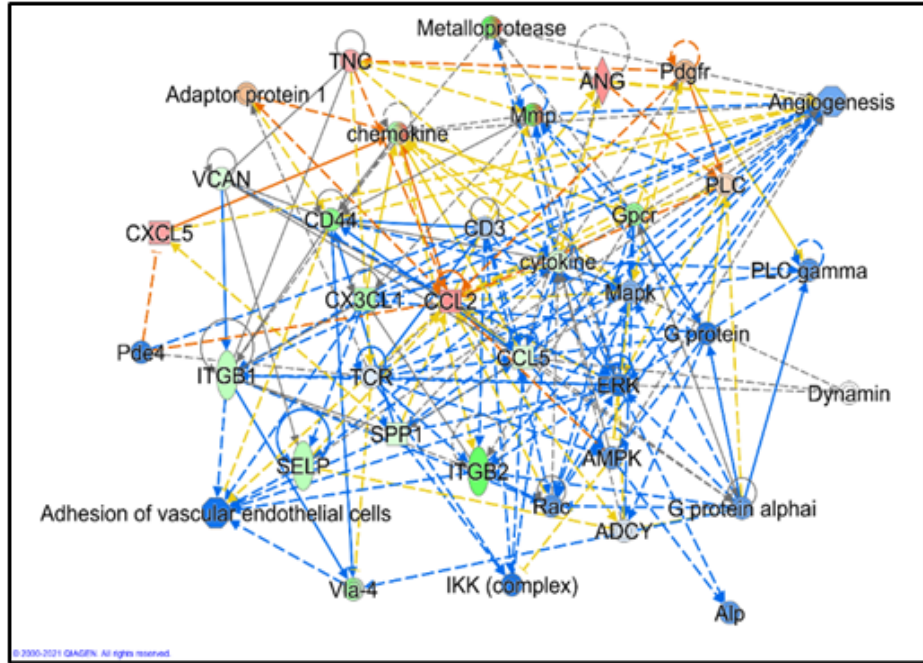
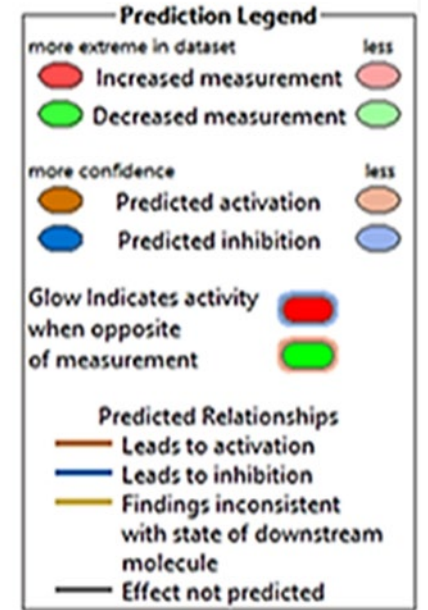
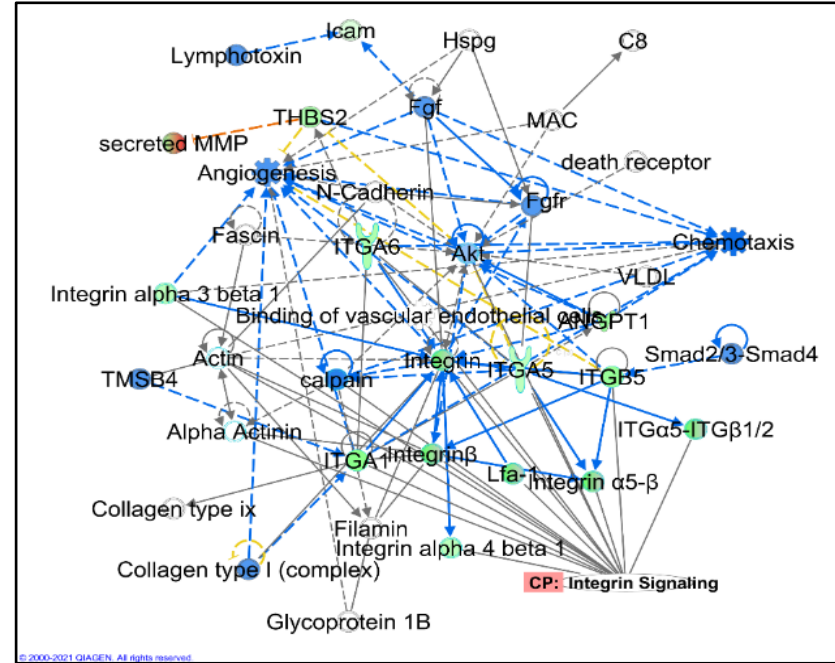


Fig S7. NW2 and NW3

A



B



# Fig S8-APN- hypothesis action- graphical abstract summary

Sites of APN actions associated with biological function related to DR pathogenesis

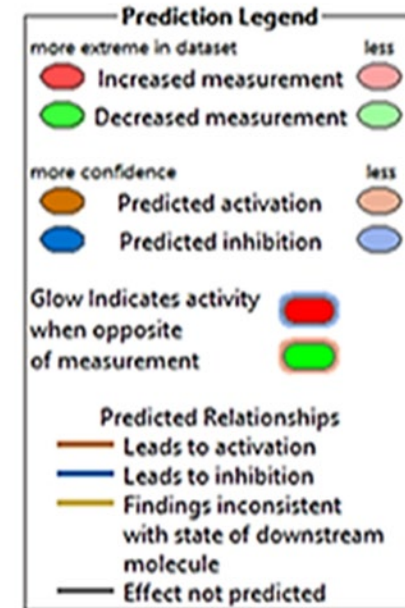
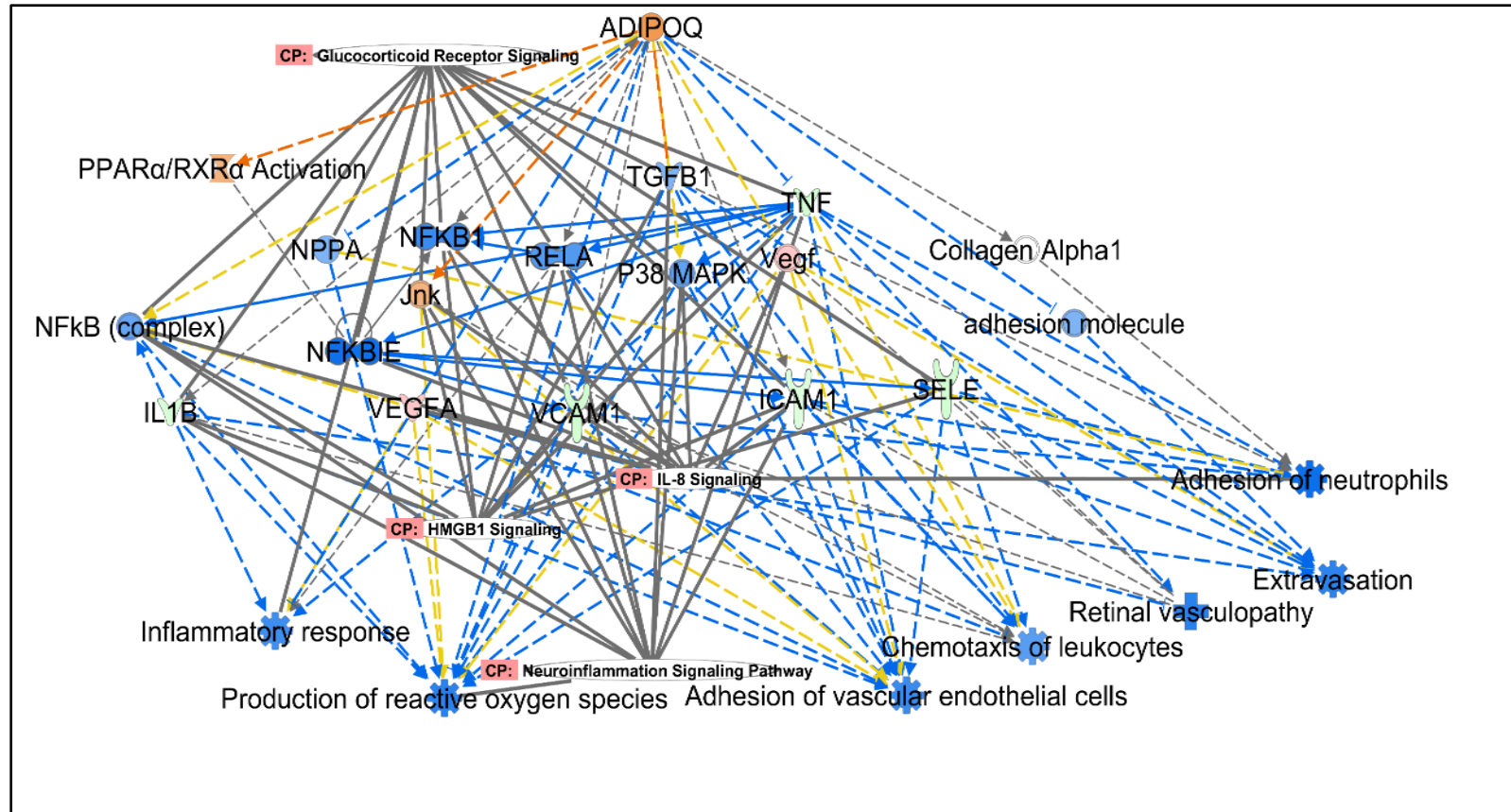


Fig S9A and S9B. Protein expressions of ADR1 and ADR2 by immunoblot in HRMECs

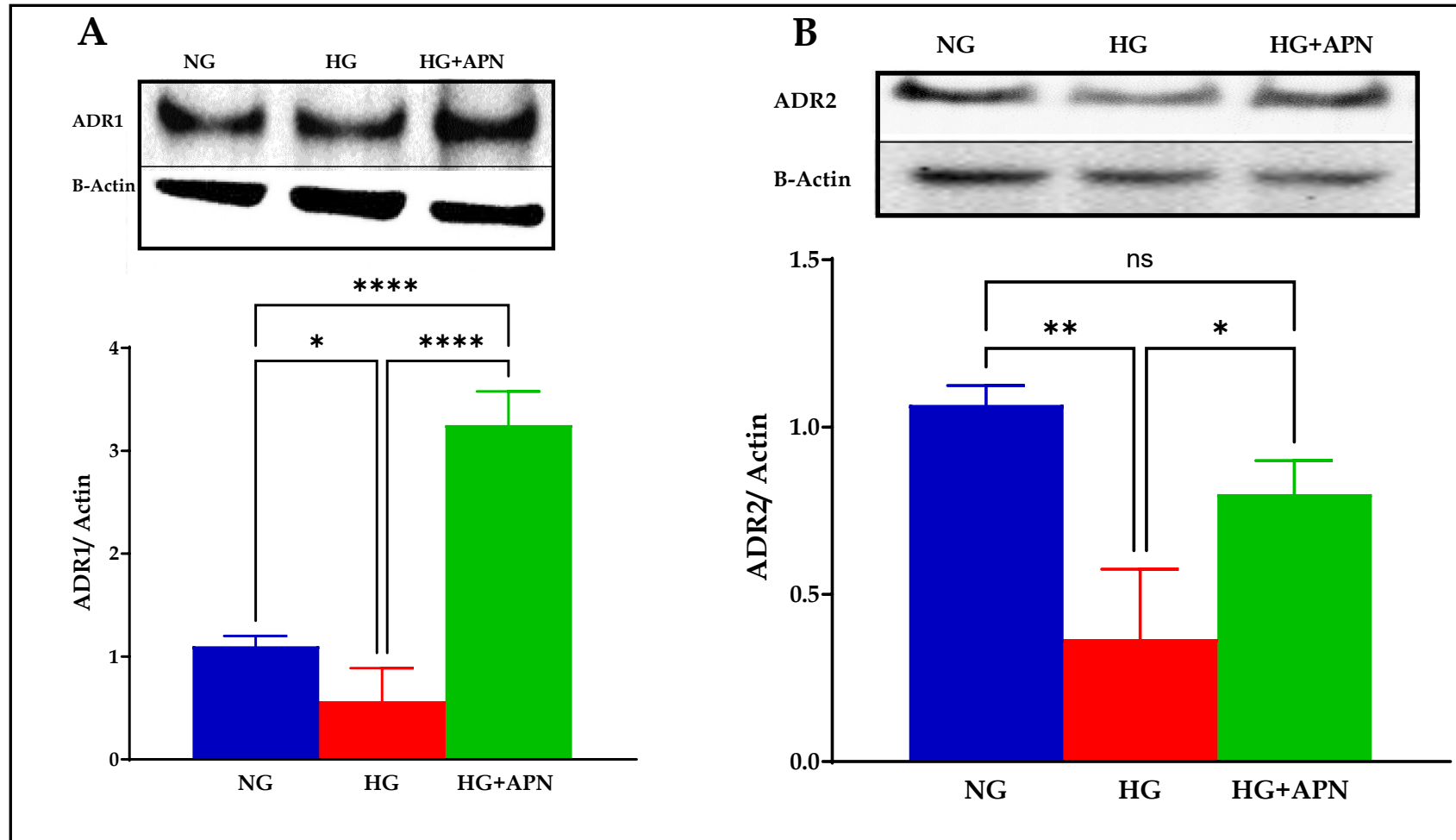
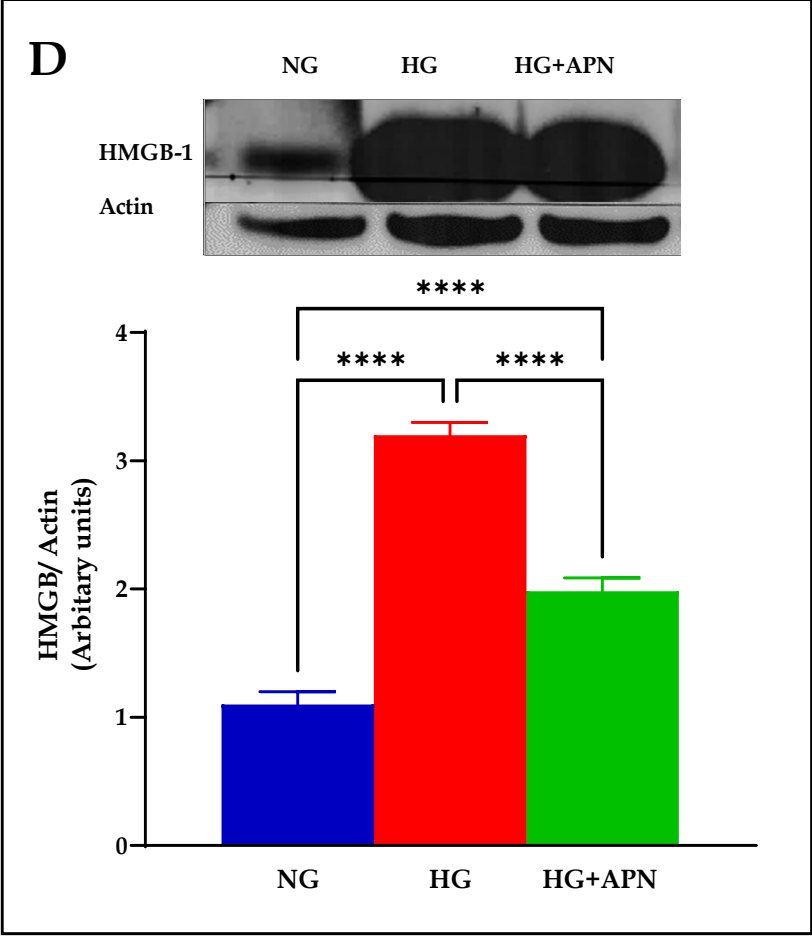
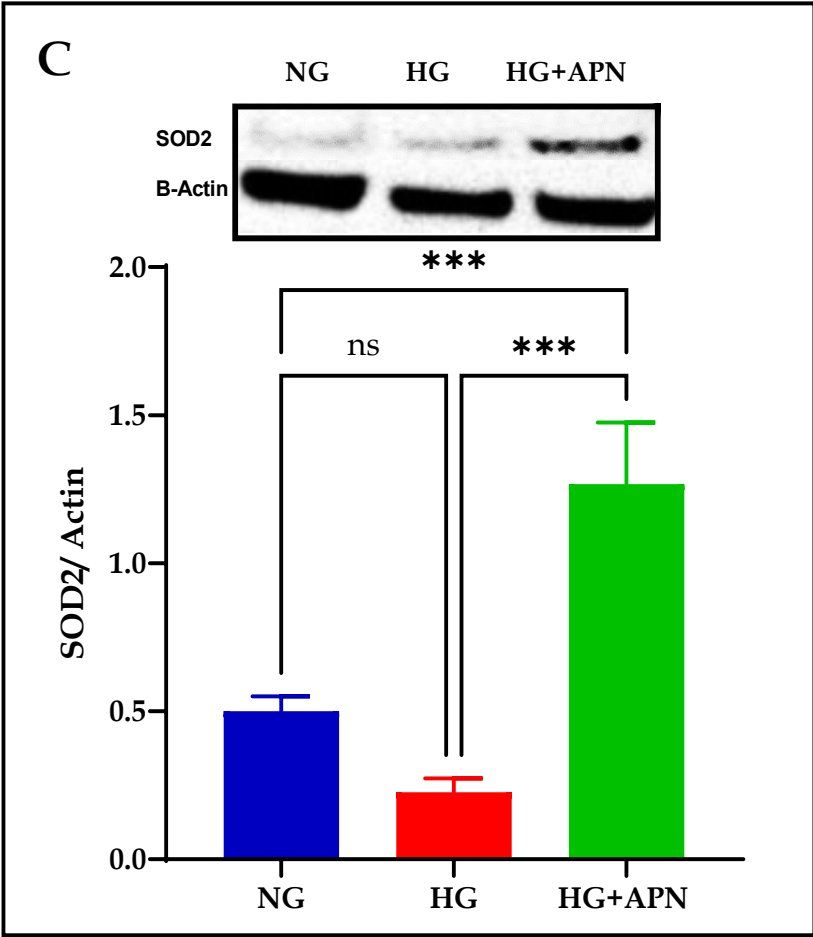




Fig S9C and S9D. Protein expressions of SOD2 and HMGB1 by immunoblot in HRMECs



**Supplementary tables****Suppl Table 1. Differential expressed genes (S1)**

| <b>Suppl Table 1. Differential expressed genes (S1)</b> |              |        |   |                     |                         |
|---|--------------|--------|---|---------------------|-------------------------|
| Expr Fold Change  | Expr p-value | Symbol | Entrez Gene Name                        | Location            | Type(s)                 |
| -2.66   | 0.025        | ADAM17 | ADAM metallopeptidase domain 17         | Plasma Membrane     | peptidase               |
| -2.26   | 0.025        | AGT    | angiotensinogen                         | Extracellular Space | growth factor           |
| 4.03  | 0.00203      | ANG    | Angiogenin                              | Extracellular Space | enzyme                  |
| -5.93   | 0.0002       | ANGPT1 | angiopoietin 1                          | Extracellular Space | growth factor           |
| -5.96   | 0.0001       | APOE   | apolipoprotein E                        | Extracellular Space | transporter             |
| -2.72   | 0.035        | BCL2   | BCL2 apoptosis regulator                | Cytoplasm           | transporter             |
| 2.65  | 0.035        | BCL2L1 | BCL2 like 1                             | Cytoplasm           | other                   |
| 4.06  | 0.000001     | CCL2   | C-C motif chemokine ligand 2            | Extracellular Space | cytokine                |
| -2.26   | 0.035        | CCL5   | C-C motif chemokine ligand 5            | Extracellular Space | cytokine                |
| -4.801  | 0.0002       | CCN2   | cellular communication network factor 2 | Extracellular Space | growth factor           |
| -7.23   | 0.035        | CD44   | CD44 molecule (Indian blood group)      | Plasma Membrane     | other                   |
| -3.443  | 0.00001      | COL4A2 | collagen type IV alpha 2 chain          | Extracellular Space | other                   |
| -13.555   | 0.0002       | COL8A1 | collagen type VIII alpha 1 chain        | Extracellular Space | other                   |
| -8.332  | 0.00004      | CTNNB1 | catenin beta 1                          | Nucleus             | transcription regulator |
| -5.08   | 0.0001       | CX3CL1 | C-X3-C motif chemokine ligand 1         | Extracellular Space | cytokine                |
| 7.57  | 0.000395     | CXCL1  | C-X-C motif chemokine ligand 1          | Extracellular Space | cytokine                |
| 3.41  | 0.00251      | CXCL5  | C-X-C motif chemokine ligand 5          | Extracellular Space | cytokine                |
| -10.162   | 0.035        | ECM1   | extracellular matrix protein 1          | Extracellular Space | transporter             |
| -6.05   | 0.000001     | EDNRA  | endothelin receptor type A              | Plasma Membrane     | transmembrane receptor  |
| -2.26   | 0.035        | F3     | coagulation factor III, tissue factor   | Plasma Membrane     | transmembrane receptor  |
| -3.31   | 0.001        | FAS    | Fas cell surface death receptor         | Plasma Membrane     | transmembrane receptor  |
| -2.26   | 0.035        | FASLG  | Fas ligand                              | Extracellular Space | cytokine                |
| -4.415  | 0.035        | FN1    | fibronectin 1                           | Extracellular Space | enzyme                  |

|        |          |          |   |                     |                        |
|--------|----------|----------|---|---------------------|------------------------|
| -1.58  | 0.04     | ICAM1    | intercellular adhesion molecule 1                 | Plasma Membrane     | transmembrane receptor |
| 2.42   | 0.000104 | IGF1     | insulin like growth factor 1                      | Extracellular Space | growth factor          |
| -2.26  | 0.035    | IL11     | interleukin 11                                    | Extracellular Space | cytokine               |
| -2.26  | 0.035    | IL1B     | interleukin 1 beta                                | Extracellular Space | Cytokine               |
| -8.96  | 1E-12    | IL3      | interleukin 3                                     | Extracellular Space | Cytokine               |
| -7.002 | 0.035    | ITGA1    | integrin subunit alpha 1                          | Plasma Membrane     | Other/ receptor        |
| -3.927 | 0.00001  | ITGA5    | integrin subunit alpha 5                          | Plasma Membrane     | transmembrane receptor |
| -4.916 | 0.035    | ITGA6    | integrin subunit alpha 6                          | Plasma Membrane     | transmembrane receptor |
| -2.694 | 0.035    | ITGAV    | integrin subunit alpha V                          | Plasma Membrane     | transmembrane receptor |
| -3.974 | 0.0002   | ITGB1    | integrin subunit beta 1                           | Plasma Membrane     | transmembrane receptor |
| -9.102 | 0.0004   | ITGB2    | integrin subunit beta 2                           | Plasma Membrane     | transmembrane receptor |
| -3.845 | 0.0005   | ITGB3    | integrin subunit beta 3                           | Plasma Membrane     | transmembrane receptor |
| -6.178 | 0.00001  | ITGB5    | integrin subunit beta 5                           | Plasma Membrane     | Other/ receptor        |
| -5.855 | 0.00001  | MMP1     | matrix metalloproteinase 1                        | Extracellular Space | Peptidase              |
| -9.666 | 1E-07    | MMP14    | matrix metalloproteinase 14                       | Extracellular Space | Peptidase              |
| 3.257  | 0.0002   | MMP3     | matrix metalloproteinase 3                        | Extracellular Space | Peptidase              |
| 7.657  | 0.00001  | MMP8     | matrix metalloproteinase 8                        | Extracellular Space | Peptidase              |
| -3.96  | 0.0428   | MMP9     | matrix metalloproteinase 9                        | Extracellular Space | Peptidase              |
| 3.257  | 0.0032   | NCAM1    | neural cell adhesion molecule 1                   | Plasma Membrane     | Other                  |
| -11.37 | 1E-12    | OCLN     | occludin  | Plasma Membrane     | Other                  |
| -4.938 | 0.00001  | PECAM1   | platelet and endothelial cell adhesion molecule 1 | Plasma Membrane     | Other                  |
| -2.26  | 0.035    | PTGIS    | prostaglandin I2 synthase                         | Cytoplasm           | Enzyme                 |
| 2.96   | 0.027    | PTGS2    | prostaglandin-endoperoxide synthase 2             | Cytoplasm           | Enzyme                 |
| -2.79  | 1E-14    | SELE     | selectin E  | Plasma Membrane     | transmembrane receptor |
| -4.139 | 0.000002 | SELP     | selectin P  | Plasma Membrane     | transmembrane receptor |
| 2.1    | 0.0328   | SERPINE1 | serpin family E member 1                          | Extracellular Space | Other                  |



|        |        |       |                                      |                     |                        |
|--------|--------|-------|--------------------------------------|---------------------|------------------------|
| -2.257 | 0.0021 | SPP1  | secreted phosphoprotein 1            | Extracellular Space | Cytokine               |
| 3.07   | 0.0142 | TEK   | TEK receptor tyrosine kinase         | Plasma Membrane     | Kinase                 |
| 2.51   | 0.305  | TGFB1 | transforming growth factor beta 1    | Extracellular Space | growth factor          |
| 2.36   | 0.03   | THBD  | thrombomodulin                       | Plasma Membrane     | transmembrane receptor |
| -2.156 | 0.031  | THBS1 | thrombospondin 1                     | Extracellular Space | Other                  |
| -4.91  | 0.0313 | THBS2 | thrombospondin 2                     | Extracellular Space | Other                  |
| -3.391 | 0.0002 | TIMP2 | TIMP metalloproteinase inhibitor 2   | Extracellular Space | Other                  |
| 3.257  | 0.0002 | TNC   | tenascin C                           | Extracellular Space | Other                  |
| -2.65  | 0.0378 | TNF   | tumor necrosis factor                | Extracellular Space | Cytokine               |
| -2.8   | 0.0132 | TYMP  | thymidine phosphorylase              | Extracellular Space | growth factor          |
| -2.758 | 1E-07  | VCAM1 | vascular cell adhesion molecule 1    | Plasma Membrane     | transmembrane receptor |
| -2.229 | 0.024  | VCAN  | versican                             | Extracellular Space | Other                  |
| 2.08   | 0.0217 | VEGFA | vascular endothelial growth factor A | Extracellular Space | growth factor          |

**Suppl table 2. (S2)**

**A. Top upregulated genes:**

| <b>Molecules</b> | <b>Expression Value</b> |
|------------------|-------------------------|
| MMP8             | 7.657                   |
| CXCL1            | 7.570                   |
| CCL2             | 4.060                   |
| ANG              | 4.030                   |
| CXCL5            | 3.410                   |
| MMP3             | 3.257                   |
| NCAM1            | 3.257                   |
| TNC              | 3.257                   |
| TEK              | 3.070                   |
| PTGS2            | 2.960                   |

**B. Top downregulated genes**

| <b>Molecules</b> | <b>Expression Value</b> |
|------------------|-------------------------|
| COL8A1           | -13.555                 |
| OCLN             | -11.370                 |
| ECM1             | -10.162                 |
| MMP14            | -9.666                  |
| ITGB2            | -9.102                  |
| IL3              | -8.960                  |
| CTNNB1           | -8.332                  |
| CD44             | -7.230                  |
| ITGA1            | -7.002                  |
| ITGB5            | -6.178                  |

**Supplementary Table 3 (S3) of Ingenuity Canonical Pathways (CP)**

| Ingenuity Canonical Pathways  | -log(B-H p-value) | Ratio    | z-score | Molecules   |
|---|-------------------|----------|---------|---|
| Agranulocyte Adhesion and Diapedesis                                  | 2.89E01           | 1.22E-01 | NaN     | CCL2,CCL5,CX3CL1,CXCL1,CXCL5,FN1,ICAM1,IL1B,ITGA1,ITGA5,ITGA6,ITGB1,ITGB2,MMP1,MMP4,MMP3,MMP8,MMP9,PECAM1,SELE,SELP,TNF,VCAM1 |
| Granulocyte Adhesion and Diapedesis                                   | 2.3E01            | 1.11E-01 | NaN     | CCL2,CCL5,CX3CL1,CXCL1,CXCL5,ICAM1,IL1B,ITGB1,ITGB2,MMP1,MMP4,MMP3,MMP8,MMP9,PECAM1,SELE,SELP,TNF,VCAM1                       |
| Glucocorticoid Receptor Signaling                                     | 1.29E01           | 3.42E-02 | NaN     | AGT,BCL2,BCL2L1,CCL2,CCL5,ICAM1,IGF1,IL1B,IL3,MMP1,MMP3,MMP8,MMP9,PTGS2,SELE,SERPINE1,TNF,VCAM1                               |
| Leukocyte Extravasation Signaling                                     | 1.27E01           | 6.81E-02 | -1.941  | CD44,CTNNB1,ICAM1,ITGB1,ITGB2,MMP1,MMP4,MMP3,MMP8,MMP9,PECAM1,TIMP2,VCAM1   |
| IL-8 Signaling  | 1.23E01           | 6.28E-02 | -0.832  | ANGPT1,BCL2,BCL2L1,CXCL1,ICAM1,ITGAV,ITGB2,ITGB3,MMP9,PTGS2,TEK,VCAM1,VEGFA   |
| Inhibition of Matrix Metalloproteases                                 | 1.15E01           | 2.05E-01 | 0.000   | ADAM17,MMP1,MMP14,MMP3,MMP8,MMP9,THBS2,TIMP2  |
| PI3K/AKT Signaling  | 1.13E01           | 6.15E-02 | -0.816  | BCL2,BCL2L1,CTNNB1,ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5,PTGS2  |
| TMGB1 Signaling   | 9.57E00           | 6.37E-02 | -2.121  | CCL2,FASLG,ICAM1,IL1B,IL3,SELE,SERPINE1,TNF,VCAM1   |
| PAK Signaling   | 9.41E00           | 7.89E-02 | NaN     | ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5,TNF   |
| Rac Signaling   | 8.87E00           | 6.67E-02 | NaN     | CD44,ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5  |
| Paxillin Signaling  | 8.37E00           | 7.69E-02 | NaN     | ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5   |
| Coronavirus Pathogenesis Pathway                                      | 7.58E00           | 4.64E-02 | -0.333  | ADAM17,AGT,BCL2,CCL2,CCL5,FASLG,IL1B,PTGS2,SERPINE1   |
| Actin Cytoskeleton Signaling  | 6.99E00           | 3.93E-02 | NaN     | FN1,ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5   |
| TXR/RXR Activation  | 6.5E00            | 5.69E-02 | -0.378  | AGT,APOE,CCL2,IL1B,MMP9,PTGS2,TNF   |
| Integrin Signaling  | 6.28E00           | 4E-02    | -2.828  | ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5   |
| IL1Ra Signaling   | 6.15E00           | 3.83E-02 | 0.707   | IGF1,MMP1,MMP14,MMP3,MMP8,MMP9,SERPINE1,VEGFA   |
| Myr-Mediated Apoptosis Signaling                                      | 5.79E00           | 9.8E-02  | -1.342  | BCL2,BCL2L1,FAS,FASLG,TNF   |
| Signaling by Rho Family GTPases                                       | 5.61E00           | 3.23E-02 | NaN     | ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5   |
| p53 Signaling   | 4.52E00           | 5.26E-02 | -0.447  | BCL2,BCL2L1,CTNNB1,FAS,THBS1  |
| Apoptosis Signaling   | 4.41E00           | 5E-02    | -1.342  | BCL2,BCL2L1,FAS,FASLG,TNF   |
| Phospholipase C Signaling   | 3.89E00           | 1.82E-02 | NaN     | ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5   |
| PDGF Signaling  | 3.49E00           | 4.76E-02 | -1.000  | BCL2,BCL2L1,FAS,FASLG   |
| Death Receptor Signaling  | 3.34E00           | 4.3E-02  | -1.000  | BCL2,FAS,FASLG,TNF  |
| Acute Phase Response Signaling  | 3.3E00            | 2.79E-02 | -1.342  | AGT,FN1,IL1B,SERPINE1,TNF   |
| Inhibition of Angiogenesis by TSP1                                    | 3.3E00            | 8.11E-02 | NaN     | MMP9,THBS1,VEGFA  |
| Docosahexaenoic Acid (DHA) Signaling                                  | 3.13E00           | 6.98E-02 | NaN     | BCL2,BCL2L1,IL1B  |
| p38 MAPK Signaling  | 3.02E00           | 3.48E-02 | -2.000  | FAS,FASLG,IL1B,TNF  |
| Renin-Angiotensin Signaling   | 2.87E00           | 3.15E-02 | -1.000  | AGT,CCL2,CCL5,TNF   |
| FXR/RXR Activation  | 2.85E00           | 3.1E-02  | NaN     | AGT,APOE,IL1B,TNF   |
| STAT3 Pathway   | 2.78E00           | 2.94E-02 | 0.000   | BCL2,IGF1,IL1B,VEGFA  |
| Prostanoid Biosynthesis   | 2.67E00           | 1.33E-01 | NaN     | PTGIS,PTGS2   |
| VDR/RXR Activation  | 2.49E00           | 4E-02    | NaN     | CCL5,SP1,THBD   |
| VEGF Signaling  | 2.15E00           | 2.94E-02 | NaN     | BCL2,BCL2L1,VEGFA   |
| PPAR Signaling  | 2.12E00           | 2.91E-02 | NaN     | IL1B,PTGS2,TNF  |
| Autophagy   | 2.09E00           | 1.85E-02 | -1.000  | BCL2,IGF1,TNF,VEGFA   |
| IL-6 Signaling  | 1.89E00           | 2.36E-02 | NaN     | IL1B,TNF,VEGFA  |
| Communication between Innate and Adaptive Immune Cells                | 1.83E00           | 1.52E-02 | NaN     | CCL5,IL1B,IL3,TNF   |
| Necroptosis Signaling Pathway   | 1.7E00            | 1.97E-02 | NaN     | FAS,FASLG,TNF   |
| Tight Junction Signaling  | 1.61E00           | 1.82E-02 | NaN     | CTNNB1,OCLN,TNF   |
| IL-10 Signaling   | 1.43E00           | 2.7E-02  | NaN     | IL1B,TNF  |
| Angiotensin Signaling   | 1.42E00           | 2.63E-02 | NaN     | ANGPT1,TEK  |
| Chemokine Signaling   | 1.38E00           | 2.5E-02  | NaN     | CCL2,CCL5   |
| TGF-β Signaling   | 1.25E00           | 2.08E-02 | NaN     | BCL2,SERPINE1   |
| IGF-1 Signaling   | 1.19E00           | 1.9E-02  | NaN     | CCN2,IGF1   |
| Glycogen Degradation II   | 1.11E00           | 5.88E-02 | NaN     | TYMP  |
| Fatty Acid α-oxidation  | 1.11E00           | 5.88E-02 | NaN     | PTGS2   |
| Glycogen Degradation III  | 1.06E00           | 5.26E-02 | NaN     | TYMP  |
| Salvage Pathways of Pyrimidine Deoxyribonucleotides                   | 1.04E00           | 5E-02    | NaN     | TYMP  |
| TNFR2 Signaling   | 8.86E-01          | 3.23E-02 | NaN     | TNF   |
| PPARα/RXRα Activation   | 8.45E-01          | 1.1E-02  | NaN     | IL1B,ITGB5  |
| Production of Nitric Oxide and Reactive Oxygen Species in Macrophages | 8.18E-01          | 1.04E-02 | NaN     | APOE,TNF  |
| RAR Activation  | 8.12E-01          | 1.03E-02 | NaN     | MMP1,VEGFA  |
| Endothelin-1 Signaling  | 8.1E-01           | 1.02E-02 | NaN     | EDNRA,PTGS2   |
| TNFR1 Signaling   | 7.42E-01          | 2.04E-02 | NaN     | TNF   |
| PXR/RXR Activation  | 6.52E-01          | 1.49E-02 | NaN     | TNF   |
| JAK/Stat Signaling  | 6.02E-01          | 1.22E-02 | NaN     | BCL2L1  |
| Unfolded protein response   | 5.82E-01          | 1.15E-02 | NaN     | BCL2  |
| VEGF Family Ligand-Receptor Interactions                              | 5.8E-01           | 1.14E-02 | NaN     | VEGFA   |
| UVA-Induced MAPK Signaling  | 5.51E-01          | 1.04E-02 | NaN     | BCL2L1  |
| NF-κB Signaling   | 5.24E-01          | 5.81E-03 | NaN     | IL1B,TNF  |
| RhoA Signaling  | 5.03E-01          | 8.93E-03 | NaN     | IGF1  |
| Protein Kinase A Signaling  | 4.79E-01          | 5.26E-03 | NaN     | CTNNB1,PTGS2  |
| Nitric Oxide Signaling in the Cardiovascular System                   | 4.74E-01          | 8E-03    | NaN     | VEGFA   |
| Epithelial Adherens Junction Signaling                                | 4.23E-01          | 6.62E-03 | NaN     | CTNNB1  |
| eNOS Signaling  | 4.03E-01          | 6.13E-03 | NaN     | VEGFA   |
| Mitochondrial Dysfunction   | 3.76E-01          | 5.62E-03 | NaN     | BCL2  |
| Gap Junction Signaling  | 3.37E-01          | 4.93E-03 | NaN     | CTNNB1  |
| mTOR Signaling  | 3.32E-01          | 4.81E-03 | NaN     | VEGFA   |
| Sensence Pathway  | 2.4E-01           | 3.42E-03 | NaN     | SERPINE1  |
| Sirtuin Signaling Pathway   | 2.33E-01          | 3.32E-03 | NaN     | TNF   |

**Supplementary Table 4 ( S4): Molecular Functions and Diseases**

| Category                               | B-H p-value       | Molecules  |
|--|-------------------|--|
| Cellular Movement                      | 3E-45-3E-10       | ADAM17,AGT,ANG,ANGPT1,APOE,BCL2,CCL2,CCL5,CCN2,CD44,COL4A2,CTNNB1,CX3CL1,CXCL1,CXCL5,ECM1,EDNRA,F3,FAS,FASLG,FN1,ICAM1,IGF1,IL11,IL1B,IL3,ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5,MMP1,MMP14,MMP3,MMP8,MMP9,NCAM1,OCLN,PECAM1,PTGS2,SELE,SELP,SERPINE1,SPP1,TEK,THBD,THBS1,THBS2,TIMP2,TNC,TNF,VCAM1,VCAN,VEGFA                          |
| Inflammatory Response                  | 1.88E-42-3E-10    | ADAM17,AGT,ANG,ANGPT1,APOE,BCL2,BCL2L1,CCL2,CCL5,CCN2,CD44,CTNNB1,CX3CL1,CXCL1,CXCL5,ECM1,EDNRA,F3,FAS,FASLG,FN1,ICAM1,IGF1,IL11,IL1B,IL3,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,MMP1,MMP14,MMP3,MMP8,MMP9,OCLN,PECAM1,PTGIS,PTGS2,SELE,SELP,SERPINE1,SPP1,TEK,THBD,THBS1,THBS2,TIMP2,TNC,TNF,TYMP,VCAM1,VCAN,VEGFA                                 |
| Tissue Development                     | 5.14E-35-2.68E-10 | ADAM17,AGT,ANG,ANGPT1,APOE,BCL2,BCL2L1,CCL2,CCL5,CCN2,CD44,COL4A2,COL8A1,CTNNB1,CXCL1,CXCL5,ECM1,F3,FAS,FASLG,FN1,ICAM1,IGF1,IL11,IL1B,IL3,ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5,MMP1,MMP14,MMP3,MMP8,MMP9,PECAM1,PTGS2,SELE,SELP,SERPINE1,SPP1,TEK,THBS1,THBS2,TIMP2,TNC,TNF,VCAM1,VCAN,VEGFA   |
| Cell-To-Cell Signaling and Interaction | 4.38E-33-3E-10    | AGT,ANG,ANGPT1,APOE,BCL2,BCL2L1,CCL2,CCL5,CCN2,CD44,CTNNB1,CX3CL1,CXCL1,CXCL5,F3,FAS,FASLG,FN1,ICAM1,IGF1,IL11,IL1B,IL3,ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5,MMP1,MMP14,MMP3,MMP9,NCAM1,PECAM1,PTGS2,SELE,SELP,SERPINE1,SPP1,THBD,THBS1,THBS2,TNC,TNF,TYMP,VCAM1,VCAN,VEGFA   |
| Cell Death and Survival                | 3.2E-31-3.54E-10  | ADAM17,AGT,ANG,ANGPT1,APOE,BCL2,BCL2L1,CCL2,CCL5,CCN2,CD44,COL4A2,CTNNB1,CX3CL1,CXCL1,F3,FAS,FASLG,FN1,ICAM1,IGF1,IL11,IL1B,IL3,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5,MMP1,MMP3,MMP9,NCAM1,OCLN,PECAM1,PTGIS,PTGS2,SERPINE1,SPP1,TEK,THBD,THBS1,THBS2,TIMP2,TNC,TNF,TYMP,VCAM1,VCAN,VEGFA  |
| Cellular Development                   | 5.3E-30-2.45E-10  | ADAM17,AGT,ANG,ANGPT1,APOE,BCL2,BCL2L1,CCL2,CCL5,CCN2,CD44,COL4A2,CTNNB1,CXCL1,CXCL5,ECM1,F3,FAS,FASLG,FN1,ICAM1,IGF1,IL11,IL1B,IL3,ITGA5,ITGB1,ITGB2,ITGB3,MMP1,MMP14,MMP8,MMP9,NCAM1,PECAM1,PTGS2,SERPINE1,SPP1,TEK,THBS1,THBS2,TIMP2,TNC,TNF,VCAM1,VCAN,VEGFA   |
| Cellular Function and Maintenance      | 5.3E-30-2.86E-10  | ADAM17,AGT,ANG,ANGPT1,APOE,BCL2,BCL2L1,CCL2,CCL5,CCN2,CD44,COL4A2,CTNNB1,CX3CL1,CXCL1,CXCL5,ECM1,EDNRA,F3,FAS,FN1,ICAM1,IGF1,IL1B,IL3,ITGA5,ITGB1,ITGB2,ITGB3,ITGB5,MMP1,MMP14,MMP9,OCLN,PECAM1,PTGS2,SELE,SERPINE1,SPP1,TEK,THBS1,THBS2,TIMP2,TNC,TNF,VCAM1,VEGFA   |
| Cellular Growth and Proliferation      | 5.3E-30-1.65E-10  | ADAM17,AGT,ANG,ANGPT1,APOE,BCL2,BCL2L1,CCL2,CCL5,CCN2,CD44,COL4A2,CTNNB1,CXCL1,CXCL5,ECM1,F3,FAS,FASLG,FN1,ICAM1,IGF1,IL11,IL1B,IL3,ITGA5,ITGB1,ITGB2,ITGB3,MMP1,MMP14,MMP8,MMP9,NCAM1,PECAM1,PTGS2,SERPINE1,SPP1,TEK,THBS1,THBS2,TIMP2,TNC,TNF,TYMP,VCAM1,VCAN,VEGFA  |
| Organismal Injury and Abnormalities    | 4.69E-29-3.4E-10  | ADAM17,AGT,ANG,ANGPT1,APOE,BCL2,BCL2L1,CCL2,CCL5,CCN2,CD44,COL4A2,COL8A1,CTNNB1,CX3CL1,CXCL1,CXCL5,ECM1,EDNRA,F3,FAS,FASLG,FN1,ICAM1,IGF1,IL11,IL1B,IL3,ITGA1,ITGA5,ITGA6,ITGAV,ITGB1,ITGB2,ITGB3,ITGB5,MMP1,MMP14,MMP3,MMP8,MMP9,NCAM1,OCLN,PECAM1,PTGIS,PTGS2,SELE,SELP,SERPINE1,SPP1,TEK,THBD,THBS1,THBS2,TIMP2,TNC,TNF,TYMP,VCAM1,VCAN,VEGFA |
| Cardiovascular Disease                 | 5.07E-28-2.51E-10 | AGT,ANGPT1,APOE,BCL2,BCL2L1,CCL2,CCL5,CCN2,COL4A2,COL8A1,CTNNB1,CX3CL1,CXCL1,CXCL5,EDNRA,F3,FAS,FN1,ICAM1,IGF1,IL11,IL1B,ITGAV,ITGB2,ITGB3,MMP1,MMP14,MMP3,MMP8,MMP9,PECAM1,PTGIS,PTGS2,SELE,SELP,SERPINE1,SPP1,TEK,THBD,THBS1,THBS2,TIMP2,TNC,TNF,TYMP,VCAM1,VCAN,VEGFA   |
| Endocrine System Disorders             | 1.6E-27-1.62E-10  | ADAM17,AGT,ANG,ANGPT1,APOE,BCL2,BCL2L1,CCL2,CCN2,CD44,COL4A2,COL8A1,CTNNB1,CXCL1,ECM1,EDNRA,F3,FAS,FASLG,FN1,IGF1,IL1B,ITGAV,ITGB3,ITGB5,MMP1,MMP14,MMP3,MMP9,NCAM1,OCLN,PECAM1,PTGIS,PTGS2,SELE,SELP,SERPINE1,SPP1,TEK,THBD,THBS1,THBS2,TNC,TNF,VCAM1,VCAN,VEGFA  |
| Metabolic Disease                      | 4.64E-27-8.24E-13 | AGT,APOE,BCL2,BCL2L1,CCL2,CD44,COL4A2,COL8A1,CTNNB1,CXCL1,EDNRA,F3,FAS,FASLG,FN1,IGF1,IL1B,ITGAV,ITGB3,ITGB5,MMP9,PECAM1,PTGIS,PTGS2,SELE,SELP,SERPINE1,SPP1,TEK,THBD,THBS1,THBS2,TNC,TNF,VCAM1,VEGFA  |

|  |  |   |
|--|--|---|
| Cell Signaling                             | 5.1 <sup>E-27</sup> -4.77 <sup>E-15</sup>  | AGT,APOE,BCL2,BCL2L1,CCL2,CCL5,CD44,CX3CL1,CXCL1,CXCL5,EDNRA,F3,FAS,FASLG, FN1, ICAM1, IGF1, IL11, IL1B, IL3, ITGA5, ITGB1, ITGB2, ITGB3, ITGB5, MMP1, MMP3, MMP9, NCAM1, PECAM1, PTGS2, SELE, SELP, SPP1, TEK, THBS1, TNF, VCAM1, VEGFA  |
| Free Radical Scavenging                    | 8.89 <sup>E-27</sup> -2.14 <sup>E-10</sup> | AGT, ANGPT1, APOE, BCL2, BCL2L1, CCL2, CCL5, CD44, CX3CL1, F3, FAS, FN1, ICAM1, IGF1, IL11, IL1B, IL3, ITGA5, ITGB1, ITGB2, ITGB3, MMP14, MMP8, PECAM1, PTGS2, SELE, SELP, SPP1, TNF, VCAM1, VEGFA  |
| Connective Tissue Disorders                | 1.2 <sup>E-23</sup> -4.92 <sup>E-11</sup>  | ADAM17, ANG, ANGPT1, APOE, BCL2, BCL2L1, CCL2, CCL5, CD44, CTNNB1, CX3CL1, CXCL1, CXCL5, EDNRA, FAS, FASLG, FN1, ICAM1, IGF1, IL11, IL1B, IL3, ITGA5, ITGB2, ITGB3, MMP1, MMP14, MMP3, MMP8, MMP9, PECAM1, PTGIS, PTGS2, SELE, SELP, SERPINE1, SPP1, TEK, THBS1, TNC, TNF, TYMP, VCAM1, VEGFA |
| Cell-mediated Immune Response              | 2.54 <sup>E-23</sup> -3.3 <sup>E-14</sup>  | ADAM17, CCL2, CCL5, CD44, CX3CL1, CXCL1, FAS, FN1, ICAM1, IL1B, ITGA1, ITGA5, ITGA6, ITGB1, ITGB2, ITGB3, MMP9, PECAM1, SELE, SELP, SPP1, THBS1, THBS2, TIMP2, TNF, VCAM1   |
| Cellular Assembly and Organization         | 1.79 <sup>E-19</sup> -1.51 <sup>E-10</sup> | AGT, ANG, ANGPT1, APOE, CCL2, CCL5, CCN2, CD44, CTNNB1, CX3CL1, CXCL1, F3, FAS, FN1, ICAM1, IGF1, IL1B, IL3, ITGA1, ITGAV, ITGB1, ITGB2, ITGB3, ITGB5, NCAM1, PECAM1, SELE, SELP, THBD, THBS1, THBS2, TNC, TNF, VCAM1, VEGFA  |
| Organ Development                          | 5.11 <sup>E-19</sup> -6.75 <sup>E-11</sup> | ADAM17, AGT, ANG, APOE, BCL2, CCL2, CCL5, CTNNB1, CXCL5, F3, FAS, ICAM1, IGF1, IL1B, IL3, ITGB2, MMP14, MMP8, MMP9, SERPINE1, SPP1, THBS1, TNC, TNF, VCAN, VEGFA  |
| Organismal Survival                        | 2.26 <sup>E-18</sup> -2.93 <sup>E-13</sup> | ANGPT1, APOE, BCL2, BCL2L1, CCL2, CCN2, CD44, CTNNB1, CXCL5, FAS, FASLG, FN1, ICAM1, IL1B, ITGA5, ITGB3, MMP9, NCAM1, PTGS2, SERPINE1, SPP1, TEK, THBD, THBS2, TIMP2, TNC, TNF, TYMP, VCAN, VEGFA   |
| Cell Morphology                            | 1.28 <sup>E-17</sup> -7.91 <sup>E-13</sup> | ANG, ANGPT1, BCL2, CCL2, CCL5, CD44, CX3CL1, FN1, IGF1, IL1B, ITGA1, ITGA5, ITGAV, ITGB1, ITGB2, ITGB3, MMP9, SELE, SPP1, TEK, TIMP2, TNC, TNF, VEGFA   |
| Post-Translational Modification            | 2.7 <sup>E-17</sup> -2.17 <sup>E-13</sup>  | ADAM17, AGT, ANG, ANGPT1, CCL2, CCL5, CD44, FAS, FN1, IGF1, IL11, IL1B, ITGA5, ITGA6, ITGB2, ITGB3, MMP9, OCLN, PECAM1, SPP1, TEK, THBS1, TNF, VEGFA  |
| Connective Tissue Development and Function | 9.06 <sup>E-17</sup> -2.45 <sup>E-10</sup> | ADAM17, AGT, ANGPT1, APOE, BCL2, BCL2L1, CCL2, CCN2, CD44, CTNNB1, ECM1, FAS, FASLG, FN1, ICAM1, IGF1, IL11, IL1B, IL3, ITGA5, ITGAV, ITGB1, ITGB3, MMP1, MMP9, SERPINE1, SPP1, THBS1, TNC, TNF, VCAN   |
| Molecular Transport                        | 2.58 <sup>E-15</sup> -2.14 <sup>E-10</sup> | AGT, ANG, APOE, BCL2, CCL2, CCL5, CTNNB1, CX3CL1, CXCL1, CXCL5, EDNRA, F3, FAS, FN1, IGF1, IL11, IL1B, IL3, ITGB2, MMP1, NCAM1, PECAM1, PTGS2, SELE, SELP, THBS1, TNC, TNF, VCAM1, VEGFA  |
| Amino Acid Metabolism                      | 2.17 <sup>E-13</sup> -2.17 <sup>E-13</sup> | AGT, ANGPT1, CD44, IGF1, IL11, ITGA5, ITGB2, ITGB3, PECAM1, TEK, VEGFA  |
| Small Molecule Biochemistry                | 2.17 <sup>E-13</sup> -3.17 <sup>E-10</sup> | AGT, ANG, ANGPT1, APOE, BCL2, BCL2L1, CCL2, CCL5, CD44, CX3CL1, CXCL1, FAS, FN1, IGF1, IL11, IL1B, IL3, ITGA5, ITGAV, ITGB2, ITGB3, MMP3, NCAM1, PECAM1, PTGIS, PTGS2, TEK, TNC, TNF, VEGFA   |
| Tissue Morphology                          | 2.61 <sup>E-13</sup> -2.61 <sup>E-13</sup> | BCL2, BCL2L1, CCL2, FAS, FN1, IGF1, IL11, IL1B, IL3, MMP3, MMP9, PTGS2, THBS1, THBS2, TNF, VCAN, VEGFA  |
| DNA Replication, Recombination, and Repair | 3.78 <sup>E-13</sup> -3.78 <sup>E-13</sup> | AGT, APOE, CCL5, CTNNB1, FN1, IGF1, IL1B, ITGA5, ITGB1, MMP14, PTGS2, THBS2, TNC, TNF, VEGFA  |
| Lipid Metabolism                           | 1.26 <sup>E-11</sup> -3.17 <sup>E-10</sup> | AGT, ANG, ANGPT1, APOE, BCL2, BCL2L1, CCL2, CCL5, CX3CL1, CXCL1, FAS, FN1, IGF1, IL1B, IL3, ITGAV, ITGB2, ITGB3, MMP3, NCAM1, PTGIS, PTGS2, TNC, TNF, VEGFA   |
| Protein Synthesis                          | 7.25 <sup>E-11</sup> -7.25 <sup>E-11</sup> | ADAM17, AGT, ANG, APOE, BCL2L1, FAS, FN1, IGF1, IL1B, IL3, ITGB1, MMP1, MMP14, MMP3, MMP8, MMP9, SERPINE1, SPP1, THBS1, TNC, TNF, VCAN  |
| Cell Cycle                                 | 8.41 <sup>E-11</sup> -8.41 <sup>E-11</sup> | AGT, BCL2, FASLG, FN1, IGF1, IL11, IL1B, IL3, ITGB2, ITGB3, TNF, VEGFA  |
| Gene Expression                            | 8.41 <sup>E-11</sup> -8.41 <sup>E-11</sup> | AGT, BCL2, FASLG, FN1, IGF1, IL11, IL1B, IL3, ITGB2, ITGB3, TNF, VEGFA  |
| Carbohydrate Metabolism                    | 1.85 <sup>E-10</sup> -1.85 <sup>E-10</sup> | ANGPT1, APOE, CCL5, CCN2, CD44, CTNNB1, CX3CL1, IGF1, IL1B, THBD, TNF, VCAN   |

**Supplementary Table 5 (S5)****Mapping of the DEGs**

| num<br>ber | Gene symbol | Transcript      | annotation  |
|------------|-------------|-----------------|---|
| 1          | ADAM17      | ENSP00000309968 | Disintegrin and metalloproteinase domain-containing protein 17; Cleaves the membrane-bound precursor of TNF-alpha to its mature soluble form. Responsible for the proteolytical release of soluble JAM3 from endothelial cells surface. Responsible for the proteolytical release of several other cell-surface proteins, including p75 TNF-receptor, interleukin 1 receptor type II, p55 TNF-receptor, transforming growth factor-alpha, L-selectin, growth hormone receptor, MUC1 and the amyloid precursor protein. Acts as an activator of Notch pathway by mediating cleavage of Notch.  |
| 2          | AGT         | ENSP00000355627 | Angiotensinogen; Essential component of the renin-angiotensin system (RAS), a potent regulator of blood pressure, body fluid and electrolyte homeostasis; Endogenous ligands  |
| 3          | ANG         | ENSP00000336762 | Angiogenin; Binds to actin on the surface of endothelial cells; once bound, angiogenin is endocytosed and translocated to the nucleus. Stimulates ribosomal RNA synthesis including that containing the initiation site sequences of 45S rRNA. Cleaves tRNA within anticodon loops to produce tRNA-derived stress-induced fragments (tiRNAs) which inhibit protein synthesis and triggers the assembly of stress granules (SGs). Angiogenin induces vascularization of normal and malignant tissues. Angiogenic activity is regulated by interaction with RNH1 in vivo; Ribonuclease A family |
| 4          | ANGPT1      | ENSP00000428340 | Angiopoietin-1; Binds and activates TEK/TIE2 receptor by inducing its dimerization and tyrosine phosphorylation. Plays an important role in the regulation of angiogenesis, endothelial cell survival, proliferation, migration, adhesion, and cell spreading, reorganization of the actin cytoskeleton, but also maintenance of vascular quiescence. Required for normal angiogenesis and heart development during embryogenesis. After birth, activates or inhibits angiogenesis, depending on the context. Inhibits angiogenesis and promotes vascular stability in quiescent vessels.     |
| 5          | APOE        | ENSP00000252486 | Apolipoprotein E; Mediates the binding, internalization, and catabolism of lipoprotein particles. It can serve as a ligand for the LDL (apo B/E) receptor and for the specific apo-E receptor (chylomicron remnant) of hepatic tissues; Apolipoproteins   |
| 6          | BCL2        | ENSP00000381185 | Apoptosis regulator Bcl-2; Suppresses apoptosis in a variety of cell systems including factor-dependent lymphohematopoietic and neural cells. Regulates cell death by controlling the mitochondrial membrane permeability. Appears to function in a feedback loop system with caspases. Inhibits caspase activity either by preventing the release of cytochrome c from the mitochondria and/or by binding to the apoptosis-activating factor (APAF-1). May attenuate inflammation by impairing NLRP1-inflammasome activation, hence CASP1 activation and IL1B release; BCL2 family           |
| 7          | BCL2L1      | ENSP00000302564 | Bcl-2-like protein 1; Potent inhibitor of cell death. Inhibits activation of caspases. Appears to regulate cell death by blocking the voltage-dependent anion channel (VDAC) by binding to it and preventing the release of the caspase activator, CYC1, from the mitochondrial membrane. Also acts as a regulator of G2 checkpoint and progression to cytokinesis during mitosis; Belongs to the Bcl-2 family  |
| 8          | CCL2        | ENSP00000225831 | C-C motif chemokine 2; Chemotactic factor that attracts monocytes and basophils but not neutrophils or eosinophils. Augments monocyte anti-tumor activity. Has been implicated in the pathogenesis of diseases characterized by monocytic infiltrates, like psoriasis, rheumatoid arthritis or atherosclerosis. May be involved in the recruitment of monocytes into the arterial wall during the disease process of atherosclerosis; Belongs to the intercrine beta (chemokine CC) family  |

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|----|--------|-----------------|--|
| 9  | CCL5   | ENSP00000474412 | C-C motif chemokine 5; Chemoattractant for blood monocytes, memory T-helper cells and eosinophils. Causes the release of histamine from basophils and activates eosinophils. May activate several chemokine receptors including CCR1, CCR3, CCR4 and CCR5. One of the major HIV-suppressive factors produced by CD8+ T-cells. Recombinant RANTES protein induces a dose-dependent inhibition of different strains of HIV-1, HIV-2, and simian immunodeficiency virus (SIV). The processed form RANTES(3-68) acts as a natural chemotaxis inhibitor and is a more potent inhibitor of HIV-1- infection. |
| 10 | CCN2   | ENSP00000356954 | Cellular communication network factor 2; Connective tissue growth factor; Major connective tissue chemoattractant secreted by vascular endothelial cells. Promotes proliferation and differentiation of chondrocytes. Mediates heparin- and divalent cation-dependent cell adhesion in many cell types including fibroblasts, myofibroblasts, endothelial and epithelial cells. Enhances fibroblast growth factor-induced DNA synthesis; Belongs to the CCN family   |
| 11 | CD44   | ENSP00000398632 | CD44 antigen; Receptor for hyaluronic acid (HA). Mediates cell-cell and cell-matrix interactions through its affinity for HA, and possibly also through its affinity for other ligands such as osteopontin, collagens, and matrix metalloproteinases (MMPs). Adhesion with HA plays an important role in cell migration, tumor growth and progression. In cancer cells, may play an important role in invadopodia formation. Also involved in lymphocyte activation, recirculation and homing, and in hematopoiesis. Altered expression or dysfunction causes numerous pathogenic phenotypes.          |
| 12 | COL4A2 | ENSP00000353654 | Collagen alpha-2(IV) chain; Type IV collagen is the major structural component of glomerular basement membranes (GBM), forming a 'chicken-wire' meshwork together with laminins, proteoglycans and entactin/nidogen  |
| 13 | COL8A1 | ENSP00000261037 | Collagen alpha-1(VIII) chain; Macromolecular component of the subendothelium. Major component of the Descemet's membrane (basement membrane) of corneal endothelial cells. Also, component of the endothelia of blood vessels. Necessary for migration and proliferation of vascular smooth muscle cells and thus, has a potential role in the maintenance of vessel wall integrity and structure, in particular in atherogenesis; Collagens   |
| 14 | CTNNB1 | ENSP00000344456 | Catenin beta-1; Key downstream component of the canonical Wnt signaling pathway. In the absence of Wnt, forms a complex with AXIN1, AXIN2, APC, CSNK1A1 and GSK3B that promotes phosphorylation on N-terminal Ser and Thr residues and ubiquitination of CTNNB1 via BTRC and its subsequent degradation by the proteasome. In the presence of Wnt ligand, CTNNB1 is not ubiquitinated and accumulates in the nucleus, where it acts as a coactivator for transcription factors of the TCF/LEF family, leading to activate Wnt responsive genes. Involved in the regulation of cell adhesion.           |
| 15 | CX3CL1 | ENSP00000006053 | C-X3-C motif chemokine ligand 1; Fractalkine; Acts as a ligand for both CX3CR1 and integrins. Binds to CX3CR1. Binds to integrins ITGA5:ITGB3 and ITGA4:ITGB1. Can activate integrins in both a CX3CR1-dependent and CX3CR1-independent manner. In the presence of CX3CR1, activates integrins by binding to the classical ligand-binding site (site 1) in integrins. In the absence of CX3CR1, binds to a second site (site 2) in integrins which is distinct from site 1 and enhances the binding of other integrin ligands to site 1. The soluble form is chemotactic for T-cells and monocytes     |
| 16 | CXCL1  | ENSP00000379110 | Growth-regulated alpha protein; Has chemotactic activity for neutrophils. May play a role in inflammation and exerts its effects on endothelial cells in an autocrine fashion. In vitro, the processed forms GRO- alpha(4-73), GRO-alpha(5-73) and GRO-alpha(6-73) show a 30-fold higher chemotactic activity; Chemokine ligands   |
| 17 | CXCL5  | ENSP00000296027 | C-X-C motif chemokine 5; Involved in neutrophil activation. In vitro, ENA-78(8-78) and ENA-78(9-78) show a threefold higher chemotactic activity for neutrophil granulocytes; Chemokine ligands  |

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|----|-------|-----------------|--|
| 18 | ECM1  | ENSP00000358045 | Extracellular matrix protein 1; Involved in endochondral bone formation as negative regulator of bone mineralization. Stimulates the proliferation of endothelial cells and promotes angiogenesis. Inhibits MMP9 proteolytic activity  |
| 19 | EDNRA | ENSP00000315011 | Endothelin receptor type a; Endothelin-1 receptor; Receptor for endothelin-1. Mediates its action by association with G proteins that activate a phosphatidylinositol- calcium second messenger system. The rank order of binding affinities for ET-A is: ET1 > ET2 >> ET3   |
| 20 | F3    | ENSP00000334145 | Coagulation factor iii (tissue factor); Tissue factor; Initiates blood coagulation by forming a complex with circulating factor VII or VIIa. The [TF:VIIa] complex activates factors IX or X by specific limited proteolysis. TF plays a role in normal hemostasis by initiating the cell-surface assembly and propagation of the coagulation protease cascade   |
| 21 | FAS   | ENSP00000347979 | Tumor necrosis factor receptor superfamily member 6; Receptor for TNFSF6/FASLG. The adapter molecule FADD recruits caspase-8 to the activated receptor. The resulting death- inducing signaling complex (DISC) performs caspase-8 proteolytic activation which initiates the subsequent cascade of caspases (aspartate-specific cysteine proteases) mediating apoptosis. FAS- mediated apoptosis may have a role in the induction of peripheral tolerance, in the antigen-stimulated suicide of mature T-cells, or both. The secreted isoforms 2 to 6 block apoptosis (in vitro); CD molecules |
| 22 | FASLG | ENSP00000356694 | Tumor necrosis factor ligand superfamily member 6; Cytokine that binds to TNFRSF6/FAS, a receptor that transduces the apoptotic signal into cells. Involved in cytotoxic T-cell-mediated apoptosis, natural killer cell-mediated apoptosis and in T-cell development. Initiates fratricidal/suicidal activation-induced cell death (AICD) in antigen-activated T-cells contributing to the termination of immune responses (By similarity). TNFRSF6/FAS-mediated apoptosis has also a role in the induction of peripheral tolerance (By similarity).   |
| 23 | FN1   | ENSP00000346839 | Fibronectin 1; Fibronectin type III domain containing; Endogenous ligands  |
| 24 | ICAM1 | ENSP00000264832 | Intercellular adhesion molecule 1; ICAM proteins are ligands for the leukocyte adhesion protein LFA-1 (integrin alpha-L/beta-2). During leukocyte trans- endothelial migration, ICAM1 engagement promotes the assembly of endothelial apical cups through ARHGEF26/SGEF and RHOG activation; CD molecules  |
| 25 | IGF1  | ENSP00000302665 | Insulin-like growth factor I; The insulin-like growth factors, isolated from plasma, are structurally and functionally related to insulin but have a much higher growth-promoting activity. May be a physiological regulator of [1-14C]-2-deoxy-D-glucose (2DG) transport and glycogen synthesis in osteoblasts. Stimulates glucose transport in bone-derived osteoblastic (PyMS) cells and is effective at much lower concentrations than insulin, not only regarding glycogen and DNA synthesis but also with regard to enhancing glucose uptake.  |
| 26 | IL11  | ENSP00000264563 | Interleukin-11; Cytokine that stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and induces megakaryocyte maturation resulting in increased platelet production. Also promotes the proliferation of hepatocytes in response to liver damage. Binding to its receptor formed by IL6ST and either IL11RA1 or IL11RA2 activates a signaling cascade that promotes cell proliferation. Signaling leads to the activation of intracellular protein kinases and the phosphorylation of STAT3; Belongs to the IL-6 superfamily                              |
| 27 | IL1B  | ENSP00000263341 | Interleukin-1 beta; Potent proinflammatory cytokine. Initially discovered as the major endogenous pyrogen, induces prostaglandin synthesis, neutrophil influx and activation, T-cell activation and cytokine production, B-cell activation and antibody production, and fibroblast proliferation and collagen production. Promotes Th17 differentiation of T-cells   |
| 28 | IL3   | ENSP00000296870 | Interleukin-3; Granulocyte/macrophage colony-stimulating factors are cytokines that act in hematopoiesis by controlling the production,  |



|    |       |                 |   |
|----|-------|-----------------|---|
|    |       |                 | differentiation, and function of 2 related white cell populations of the blood, the granulocytes and the monocytes-macrophages;<br>Interleukins   |
| 29 | ITGA1 | ENSP00000282588 | Integrin alpha-1; Integrin alpha-1/beta-1 is a receptor for laminin and collagen. It recognizes the proline-hydroxylated sequence G-F-P-G- E-R in collagen. Involved in anchorage-dependent, negative regulation of EGF-stimulated cell growth; CD molecules  |
| 30 | ITGA5 | ENSP00000293379 | Integrin alpha-5; Integrin alpha-5/beta-1 is a receptor for fibronectin and fibrinogen. It recognizes the sequence R-G-D in its ligands. ITGA5:ITGB1 binds to PLA2G2A via a site (site 2) which is distinct from the classical ligand-binding site (site 1) and this induces integrin conformational changes and enhanced ligand binding to site 1. ITGA5:ITGB1 acts as a receptor for fibrillin-1 (FBN1) and mediates R-G-D-dependent cell adhesion to FBN1; CD molecules  |
| 31 | ITGA6 | ENSP00000386896 | Integrin subunit alpha 6; Integrin alpha-6; Integrin alpha-6/beta-1 is a receptor for laminin on platelets. Integrin alpha-6/beta-4 is a receptor for laminin in epithelial cells and it plays a critical structural role in the hemidesmosome (By similarity). ITGA6:ITGB4 binds to NRG1 (via EGF domain) and this binding is essential for NRG1-ERBB signaling. ITGA6:ITGB4 binds to IGF1, and this binding is essential for IGF1 signaling   |
| 32 | ITGAV | ENSP00000261023 | Integrin alpha-V; The alpha-V (ITGAV) integrins are receptors for vitronectin, cytotactin, fibronectin, fibrinogen, laminin, matrix metalloproteinase-2, osteopontin, osteomodulin, prothrombin, thrombospondin and vWF. They recognize the sequence R-G-D in a wide array of ligands. ITGAV:ITGB3 binds to fractalkine (CX3CL1) and may act as its coreceptor in CX3CR1-dependent fractalkine signaling. ITGAV:ITGB3 binds to NRG1 (via EGF domain) and this binding is essential for NRG1-ERBB signaling. ITGAV:ITGB3 binds to FGF1 and this binding is essential for FGF1 signaling. ITGAV:ITGB3 binds to IGF. |
| 33 | ITGB1 | ENSP00000379350 | Integrin beta-1; Integrins alpha-1/beta-1, alpha-2/beta-1, alpha-10/beta-1 and alpha-11/beta-1 are receptors for collagen. Integrins alpha-1/beta-1 and alpha-2/beta-2 recognize the proline-hydroxylated sequence G-F-P-G-E-R in collagen. Integrins alpha-2/beta-1, alpha-3/beta-1, alpha-4/beta-1, alpha-5/beta-1, alpha-8/beta-1, alpha-10/beta-1, alpha-11/beta-1 and alpha-V/beta-1 are receptors for fibronectin. Alpha-4/beta-1 recognizes one or more domains within the alternatively spliced CS-1 and CS-5 regions of fibronectin. Integrin alpha-5/beta-1 is a receptor for fibrinogen.               |
| 34 | ITGB2 | ENSP00000380948 | Integrin beta-2; Integrin ITGAL/ITGB2 is a receptor for ICAM1, ICAM2, ICAM3 and ICAM4. Integrins ITGAM/ITGB2 and ITGAX/ITGB2 are receptors for the iC3b fragment of the third complement component and for fibrinogen. Integrin ITGAX/ITGB2 recognizes the sequence G-P-R in fibrinogen alpha-chain. Integrin ITGAM/ITGB2 recognizes P1 and P2 peptides of fibrinogen gamma chain. Integrin ITGAM/ITGB2 is also a receptor for factor X. Integrin ITGAD/ITGB2 is a receptor for ICAM3 and VCAM1. Contributes to natural killer cell cytotoxicity. Involved in leukocyte adhesion and transmigration of leukocyte. |
| 35 | ITGB3 | ENSP00000452786 | Integrin beta-3; Integrin alpha-V/beta-3 (ITGAV:ITGB3) is a receptor for cytotactin, fibronectin, laminin, matrix metalloproteinase-2, osteopontin, osteomodulin, prothrombin, thrombospondin, vitronectin and von Willebrand factor. Integrin alpha-IIb/beta-3 (ITGA2B:ITGB3) is a receptor for fibronectin, fibrinogen, plasminogen, prothrombin, thrombospondin and vitronectin. Integrins alpha-IIb/beta-3 and alpha-V/beta-3 recognize the sequence R-G-D in a wide array of ligands. Integrin alpha-IIb/beta-3 recognizes the sequence H-H-L-G-G-A-K-Q-A-G-D-V in fibrinogen gamma chain.                   |
| 36 | ITGB5 | ENSP00000296181 | Integrin subunit beta 5; Integrin beta-5; Integrin alpha-V/beta-5 (ITGAV:ITGB5) is a receptor for fibronectin. It recognizes the sequence R-G-D in its ligand   |

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| 37 | MMP1   | ENSP00000322788 | Matrix metalloproteinase-1 (interstitial collagenase); Interstitial collagenase; Cleaves collagens of types I, II, and III at one site in the helical domain. Also cleaves collagens of types VII and X. In case of HIV infection, interacts and cleaves the secreted viral Tat protein, leading to a decrease in neuronal Tat's mediated neurotoxicity; Endogenous ligands   |
| 38 | MMP14  | ENSP00000308208 | Matrix metalloproteinase-14; Endopeptidase that degrades various components of the extracellular matrix such as collagen. Activates progelatinase A. Essential for pericellular collagenolysis and modeling of skeletal and extracellular connective tissues during development (By similarity). May be involved in actin cytoskeleton reorganization by cleaving PTK7. Acts as a positive regulator of cell growth and migration via activation of MMP15. Involved in the formation of the fibrovascular tissues in association with pro-MMP2. |
| 39 | MMP3   | ENSP00000299855 | Matrix metalloproteinase-3 (stromelysin 1, progelatinase); Stromelysin-1; Can degrade fibronectin, laminin, gelatins of type I, III, IV, and V; collagens III, IV, X, and IX, and cartilage proteoglycans. Activates procollagenase; Belongs to the peptidase M10A family   |
| 40 | MMP8   | ENSP00000236826 | Matrix metalloproteinase-8 (neutrophil collagenase); Neutrophil collagenase; Can degrade fibrillar type I, II, and III collagens; Belongs to the peptidase M10A family  |
| 41 | MMP9   | ENSP00000361405 | Matrix metalloproteinase 9; May play an essential role in local proteolysis of the extracellular matrix and in leukocyte migration. Could play a role in bone osteoclastic resorption. Cleaves KiSS1 at a Gly- -Leu bond. Cleaves type IV and type V collagen into large C-terminal three quarter fragments and shorter N-terminal one quarter fragments. Degrades fibronectin but not laminin or Pz-peptide; M10 matrix metallopeptidases  |
| 42 | NCAM1  | ENSP00000480132 | Neural cell adhesion molecule 1; This protein is a cell adhesion molecule involved in neuron-neuron adhesion, neurite fasciculation, outgrowth of neurites, etc; CD molecules   |
| 43 | OCLN   | ENSP00000347379 | Occludin; May play a role in the formation and regulation of the tight junction (TJ) paracellular permeability barrier. It is able to induce adhesion when expressed in cells lacking tight junctions; Protein phosphatase 1 regulatory subunits  |
| 44 | PECAM1 | ENSP00000457421 | Platelet endothelial cell adhesion molecule: Cell adhesion molecule which is required for leukocyte transendothelial migration (TEM) under most inflammatory conditions. Tyr-690 plays a critical role in TEM and is required for efficient trafficking of PECAM1 to and from the lateral border recycling compartment (LBRC) and is also essential for the LBRC membrane to be targeted around migrating leukocytes. Heterophilic interaction with CD177 plays a role in transendothelial migration of neutrophils.                            |
| 45 | PTGIS  | ENSP00000244043 | Prostacyclin synthase; Catalyzes the isomerization of prostaglandin H2 to prostacyclin (= prostaglandin I2); Cytochrome P450 family 8   |
| 46 | PTGS2  | ENSP00000356438 | Prostaglandin G/H synthase 2; Converts arachidonate to prostaglandin H2 (PGH2), a committed step in prostanoid synthesis. Constitutively expressed in some tissues in physiological conditions, such as the endothelium, kidney, and brain, and in pathological conditions, such as in cancer. PTGS2 is responsible for production of inflammatory prostaglandins. Up-regulation of PTGS2 is also associated with increased cell adhesion, phenotypic changes, resistance to apoptosis and tumor angiogenesis.                                  |
| 47 | SELE   | ENSP00000331736 | E-selectin; Cell-surface glycoprotein having a role in immunoadhesion. Mediates in the adhesion of blood neutrophils in cytokine-activated endothelium through interaction with PSGL1/SELPLG. May have a role in capillary morphogenesis; Belongs to the selectin/LECAM family  |
| 48 | SELP   | ENSP00000263686 | P-selectin; Ca (2+)-dependent receptor for myeloid cells that binds to carbohydrates on neutrophils and monocytes. Mediates the interaction of activated endothelial cells or platelets with leukocytes. The ligand recognized is sialyl-Lewis X. Mediates rapid rolling of leukocyte rolling over vascular surfaces during the initial steps in  |

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|    |          |                 | inflammation through interaction with PSGL1; Belongs to the selectin/LECAM family  |
| 49 | SERPINE1 | ENSP00000223095 | Plasminogen activator inhibitor 1; Serine protease inhibitor. This inhibitor acts as 'bait' for tissue plasminogen activator, urokinase, protein C and matrilysin-3/TMPRSS7. Its rapid interaction with PLAT may function as a major control point in the regulation of fibrinolysis; Serpin peptidase inhibitors  |
| 50 | SPP1     | ENSP00000378517 | Secreted phosphoprotein 1; Osteopontin; Binds tightly to hydroxyapatite. Appears to form an integral part of the mineralized matrix. Probably important to cell-matrix interaction; Endogenous ligands   |
| 51 | TEK      | ENSP00000369375 | Angiopoietin-1 receptor; Tyrosine-protein kinase that acts as cell-surface receptor for ANGPT1, ANGPT2 and ANGPT4 and regulates angiogenesis, endothelial cell survival, proliferation, migration, adhesion and cell spreading, reorganization of the actin cytoskeleton, but also maintenance of vascular quiescence. Has anti-inflammatory effects by preventing the leakage of proinflammatory plasma proteins and leukocytes from blood vessels. Required for normal angiogenesis and heart development during embryogenesis. Required for post- natal hematopoiesis.  |
| 52 | TGFB1    | ENSP00000221930 | Transforming growth factor beta-1; Multifunctional protein that controls proliferation, differentiation, and other functions in many cell types. Many cells synthesize TGFB1 and have specific receptors for it. It positively and negatively regulates many other growth factors. It plays an important role in bone remodeling as it is a potent stimulator of osteoblastic bone formation, causing chemotaxis, proliferation, and differentiation in committed osteoblasts (By similarity). Stimulates sustained production of collagen through the activation of CREB3L1 by regulated intramembrane proteolysis. |
| 53 | THBD     | ENSP00000366307 | Thrombomodulin; Thrombomodulin is a specific endothelial cell receptor that forms a 1:1 stoichiometric complex with thrombin. This complex is responsible for the conversion of protein C to the activated protein C (protein Ca). Once evolved, protein Ca scissions the activated cofactors of the coagulation mechanism, factor Va and factor VIIIa, and thereby reduces the amount of thrombin generated; C-type lectin domain containing  |
| 54 | THBS1    | ENSP00000260356 | Thrombospondin-1; Adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions. Binds heparin. May play a role in dentinogenesis and/or maintenance of dentin and dental pulp (By similarity). Ligand for CD36 mediating antiangiogenic properties. Plays a role in ER stress response, via its interaction with the activating transcription factor 6 alpha (ATF6) which produces adaptive ER stress response factors (By similarity)   |
| 55 | THBS2    | ENSP00000355751 | Thrombospondin 2/3/4/5; Thrombospondin-2; Adhesive glycoprotein that mediates cell-to-cell and cell-to-matrix interactions. Ligand for CD36 mediating antiangiogenic properties  |
| 56 | TIMP2    | ENSP00000262768 | Metalloproteinase inhibitor 2; Complexes with metalloproteinases (such as collagenases) and irreversibly inactivates them by binding to their catalytic zinc cofactor. Known to act on MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-13, MMP-14, MMP-15, MMP-16 and MMP-19; Belongs to the protease inhibitor I35 (TIMP) family  |
| 57 | TNC      | ENSP00000265131 | Tenascin; Extracellular matrix protein implicated in guidance of migrating neurons as well as axons during development, synaptic plasticity as well as neuronal regeneration. Promotes neurite outgrowth from cortical neurons grown on a monolayer of astrocytes. Ligand for integrins alpha-8/beta-1, alpha-9/beta-1, alpha-V/beta-3 and alpha-V/beta-6. In tumors, stimulates angiogenesis by elongation, migration and sprouting of endothelial cells; Belongs to the tenascin family  |
| 58 | TNF      | ENSP00000398698 | Tumor necrosis factor; Cytokine that binds to TNFRSF1A/TNFR1 and TNFRSF1B/TNFR2. It is mainly secreted by macrophages and can induce cell death of certain tumor cell lines. It is potent pyrogen causing fever by direct action or by stimulation of interleukin-1  |

|    |       |                 |   |
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|    |       |                 | secretion and is implicated in the induction of cachexia, under certain conditions it can stimulate cell proliferation and induce cell differentiation. Impairs regulatory T-cells (Treg) function in individuals with rheumatoid arthritis via FOXP3 dephosphorylation.  |
| 59 | TYMP  | ENSP00000379038 | Thymidine phosphorylase; May have a role in maintaining the integrity of the blood vessels. Has growth promoting activity on endothelial cells, angiogenic activity in vivo and chemotactic activity on endothelial cells in vitro; Minor histocompatibility antigens   |
| 60 | VCAM1 | ENSP00000294728 | Vascular cell adhesion protein 1; Important in cell-cell recognition. Appears to function in leukocyte-endothelial cell adhesion. Interacts with integrin alpha-4/beta-1 (ITGA4/ITGB1) on leukocytes, and mediates both adhesion and signal transduction. The VCAM1/ITGA4/ITGB1 interaction may play a pathophysiologic role both in immune responses and in leukocyte emigration to sites of inflammation; C2-set domain containing  |
| 61 | VCAN  | ENSP00000265077 | Versican core protein; May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid; C-type lectin domain containing   |
| 62 | VEGFA | ENSP00000478570 | Vascular endothelial growth factor A; Growth factor active in angiogenesis, vasculogenesis and endothelial cell growth. Induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces permeabilization of blood vessels. Binds to the FLT1/VEGFR1 and KDR/VEGFR2 receptors, heparan sulfate and heparin. NRP1/Neuropilin-1 binds isoforms VEGF-165 and VEGF-145. Isoform VEGF165B binds to KDR but does not activate downstream signaling pathways, does not activate angiogenesis and inhibits tumor growth. |

**Supplementary Table 6 (S6). Illustrates DEGs involved in angiogenesis- Fig 6F**

| Symbol | Entrez Gene Name                        | Gene Symbol - human (HUGO / HGNC / Entrez Gene)/Gene Symbol - human (HUGO / HGNC / Entrez Gene) | Expr Fold Change | Expr p-value | Location            |
|--------|---|---|------------------|--------------|---------------------|
| ADAM17 | ADAM metallopeptidase domain 17         | ADAM17  | -2.66            | 0.025        | Plasma Membrane     |
| AGT    | angiotensinogen                         | AGT   | -2.26            | 0.025        | Extracellular Space |
| ANG    | angiogenin                              | ANG   | 4.03             | 0.00203      | Extracellular Space |
| ANGPT1 | angiopoietin 1                          | ANGPT1  | -5.93            | 0.0002       | Extracellular Space |
| APOE   | apolipoprotein E                        | APOE  | -5.96            | 0.0001       | Extracellular Space |
| BCL2   | BCL2 apoptosis regulator                | BCL2  | -2.72            | 0.035        | Cytoplasm           |
| CCL2   | C-C motif chemokine ligand 2            | CCL2  | 4.06             | 0.000001     | Extracellular Space |
| CCN2   | cellular communication network factor 2 | CCN2  | -4.801           | 0.0002       | Extracellular Space |
| CD44   | CD44 molecule (Indian blood group)      | CD44  | -7.23            | 0.035        | Plasma Membrane     |
| COL4A2 | collagen type IV alpha 2 chain          | COL4A2  | -3.443           | 0.00001      | Extracellular Space |
| CTNNB1 | catenin beta 1                          | CTNNB1  | -8.332           | 0.00004      | Nucleus             |
| CXCL1  | C-X-C motif chemokine ligand 1          | CXCL1   | 7.57             | 0.000395     | Extracellular Space |

|          |   |          |         |          |                     |
|----------|---|----------|---------|----------|---------------------|
| CXCL5    | C-X-C motif chemokine ligand 5                    | CXCL5    | 3.41    | 0.00251  | Extracellular Space |
| ECM1     | extracellular matrix protein 1                    | ECM1     | -10.162 | 0.035    | Extracellular Space |
| F3       | coagulation factor III, tissue factor             | F3       | -2.26   | 0.035    | Plasma Membrane     |
| FASLG    | Fas ligand  | FASLG    | -2.26   | 0.035    | Extracellular Space |
| FN1      | fibronectin 1                                     | FN1      | -4.415  | 0.035    | Extracellular Space |
| ICAM1    | intercellular adhesion molecule 1                 | ICAM1    | -1.58   | 0.040    | Plasma Membrane     |
| IGF1     | insulin like growth factor 1                      | IGF1     | 2.42    | 0.000104 | Extracellular Space |
| IL1B     | interleukin 1 beta                                | IL1B     | -2.26   | 0.035    | Extracellular Space |
| ITGA5    | integrin subunit alpha 5                          | ITGA5    | -3.927  | 0.00001  | Plasma Membrane     |
| ITGAV    | integrin subunit alpha V                          | ITGAV    | -2.694  | 0.035    | Plasma Membrane     |
| ITGB1    | integrin subunit beta 1                           | ITGB1    | -3.974  | 0.0002   | Plasma Membrane     |
| ITGB3    | integrin subunit beta 3                           | ITGB3    | -3.845  | 0.0005   | Plasma Membrane     |
| MMP1     | matrix metalloproteinase 1                        | MMP1     | -5.855  | 0.00001  | Extracellular Space |
| MMP14    | matrix metalloproteinase 14                       | MMP14    | -9.666  | 1E-07    | Extracellular Space |
| MMP3     | matrix metalloproteinase 3                        | MMP3     | 3.257   | 0.0002   | Extracellular Space |
| MMP8     | matrix metalloproteinase 8                        | MMP8     | 7.657   | 0.00001  | Extracellular Space |
| MMP9     | matrix metalloproteinase 9                        | MMP9     | -3.96   | 0.0428   | Extracellular Space |
| PECAM1   | platelet and endothelial cell adhesion molecule 1 | PECAM1   | -4.938  | 0.00001  | Plasma Membrane     |
| PTGIS    | prostaglandin I2 synthase                         | PTGIS    | -2.26   | 0.035    | Cytoplasm           |
| PTGS2    | prostaglandin-endoperoxide synthase 2             | PTGS2    | 2.96    | 0.027    | Cytoplasm           |
| SELE     | selectin E  | SELE     | -2.79   | 1E-14    | Plasma Membrane     |
| SERPINE1 | serpin family E member 1                          | SERPINE1 | 2.1     | 0.0328   | Extracellular Space |
| SPP1     | secreted phosphoprotein 1                         | SPP1     | -2.257  | 0.0021   | Extracellular Space |
| TEK      | TEK receptor tyrosine kinase                      | TEK      | 3.07    | 0.0142   | Plasma Membrane     |
| THBS1    | thrombospondin 1                                  | THBS1    | -2.156  | 0.031    | Extracellular Space |
| THBS2    | thrombospondin 2                                  | THBS2    | -4.91   | 0.0313   | Extracellular Space |
| TIMP2    | TIMP metalloproteinase inhibitor 2                | TIMP2    | -3.391  | 0.0002   | Extracellular Space |
| TNC      | tenascin C  | TNC      | 3.257   | 0.0002   | Extracellular Space |
| TNF      | tumor necrosis factor                             | TNF      | -2.65   | 0.0378   | Extracellular Space |
| VCAM1    | vascular cell adhesion molecule 1                 | VCAM1    | -2.758  | 1E-07    | Plasma Membrane     |
| VEGFA    | vascular endothelial growth factor A              | VEGFA    | 2.08    | 0.0217   | Extracellular Space |

Supplementary Table 7. (S7). Top upstream molecules

| Top upstream molecules | P value   | Predicted activation/ target and action  |
|------------------------|-----------|--|
| 1- TGFB1               | 2.22 E-46 | NA   |
| 2- TNF                 | 2.87 E-46 | NA   |
| 3- SP600125            | 3.30 E-44 | Activated/ a broad-spectrum JNK inhibitor for JNK1, JNK2 and JNK3/ Inhibits the expression of inflammatory genes COX-2, IL-2, IL-10, IFN- $\gamma$ , and TNF- $\alpha$ |
| 4- IL-1B               | 3.75 E-42 | NA   |
| 5- P38 MAPK            | 4.90 E-42 | NA   |

Supplementary Table 8. (S8). Targets of TNF as upstream regulator

| Target   | Expr Fold Change | Molecule Type           | TNF effect |
|----------|------------------|-------------------------|------------|
| IL3      | -8.96            | cytokine                | Inhibited  |
| ITGAV    | -2.694           | transmembrane receptor  | Affected   |
| CCN2     | -4.801           | growth factor           | Activated  |
| ITGB2    | -9.102           | transmembrane receptor  | Inhibited  |
| THBS1    | -2.156           | other                   | Inhibited  |
| TEK      | 3.07             | kinase                  | Activated  |
| CXCL1    | 7.57             | cytokine                | Activated  |
| TNC      | 3.257            | other                   | Activated  |
| ANGPT1   | -5.93            | growth factor           | Affected   |
| SPP1     | -2.257           | cytokine                | Inhibited  |
| OCLN     | -11.37           | other                   | Activated  |
| IL1B     | -2.26            | cytokine                | Inhibited  |
| CCL5     | -2.26            | cytokine                | Inhibited  |
| TYMP     | -2.8             | growth factor           | Inhibited  |
| VEGFA    | 2.08             | growth factor           | Activated  |
| CTNNB1   | -8.332           | transcription regulator | Activated  |
| IGF1     | 2.42             | growth factor           | Activated  |
| MMP3     | 3.257            | peptidase               | Activated  |
| SELP     | -4.139           | transmembrane receptor  | Inhibited  |
| MMP8     | 7.657            | peptidase               | Activated  |
| SERPINE1 | 2.1              | other                   | Activated  |
| BCL2L1   | 2.65             | other                   | Activated  |
| FAS      | -3.31            | transmembrane receptor  | Inhibited  |
| MMP1     | -5.855           | peptidase               | Inhibited  |
| PECAM1   | -4.938           | other                   | Activated  |
| ITGA5    | -3.927           | transmembrane receptor  | Inhibited  |
| MMP9     | -3.96            | peptidase               | Inhibited  |
| SELE     | -2.79            | transmembrane receptor  | Inhibited  |
| VCAM1    | -2.758           | transmembrane receptor  | Inhibited  |
| CX3CL1   | -5.08            | cytokine                | Inhibited  |
| IL11     | -2.26            | cytokine                | Inhibited  |
| FN1      | -4.415           | enzyme                  | Activated  |
| TNF      | -2.65            | cytokine                | Inhibited  |
| ITGB3    | -3.845           | transmembrane receptor  | Affected   |
| CXCL5    | 3.41             | cytokine                | Activated  |

|       |        |                        |           |
|-------|--------|------------------------|-----------|
| FASLG | -2.26  | cytokine               | Inhibited |
| ITGB5 | -6.178 | other                  | Inhibited |
| CD44  | -7.23  | other                  | Inhibited |
| AGT   | -2.26  | growth factor          | Activated |
| THBD  | 2.36   | transmembrane receptor | Inhibited |
| CCL2  | 4.06   | cytokine               | Activated |
| PTGS2 | 2.96   | enzyme                 | Activated |
| BCL2  | -2.72  | transporter            | Inhibited |
| F3    | -2.26  | transmembrane receptor | Inhibited |
| APOE  | -5.96  | transporter            | Affected  |
| ICAM1 | -1.58  | transmembrane receptor | Inhibited |
| MMP14 | -9.666 | peptidase              | Inhibited |

Supplementary Table9 (S9). Targets of TGFB1 as upstream regulator and relationship

| TGFB1 | relationship                 | Target    |
|-------|------------------------------|-----------|
| TGFB1 | activation                   | STAT3     |
| TGFB1 | expression                   | ADIPOQ    |
| TGFB1 | expression                   | D-glucose |
| TGFB1 | expression                   | EDN1      |
| TGFB1 | expression                   | IFNG      |
| TGFB1 | expression                   | IL1B      |
| TGFB1 | expression                   | IL6       |
| TGFB1 | expression                   | STAT3     |
| TGFB1 | expression                   | VCAM1     |
| TGFB1 | localization                 | EDN1      |
| TGFB1 | localization                 | IFNG      |
| TGFB1 | localization                 | IL6       |
| TGFB1 | phosphorylation              | STAT3     |
| TGFB1 | protein-protein interactions | STAT3     |
| TGFB1 | regulation of binding        | IL6       |
| TGFB1 | regulation of binding        | STAT3     |
| TGFB1 | transcription                | EDN1      |
| TGFB1 | transcription                | IL6       |

Supplementary Table 10 (S10). NW1 target molecules( focus and non-focus)

| Symbol                | Entrez Gene Name                | Gene Symbol | Expr Fold Change | Expr p-value | Location            | Type(s)                |
|-----------------------|---------------------------------|-------------|------------------|--------------|---------------------|------------------------|
| BCL2                  | BCL2 apoptosis regulator        | BCL2        | -2.72            | 0.035        | Cytoplasm           | transporter            |
| COL4A2                | collagen type IV alpha 2 chain  | COL4A2      | -3.443           | 0.00001      | Extracellular Space | other                  |
| FAS                   | Fas cell surface death receptor | FAS         | -3.31            | 0.001        | Plasma Membrane     | transmembrane receptor |
| FASLG                 | Fas ligand                      | FASLG       | -2.26            | 0.035        | Extracellular Space | cytokine               |
| FN1                   | fibronectin 1                   | FN1         | -4.415           | 0.035        | Extracellular Space | enzyme                 |
| Focal adhesion kinase | --                              | --          |                  |              | Cytoplasm           | group                  |

|                  |   |        |        |         |                     |                        |
|------------------|---|--------|--------|---------|---------------------|------------------------|
| IL1B             | interleukin 1 beta                                | IL1B   | -2.26  | 0.035   | Extracellular Space | cytokine               |
| Interferon alpha | --  | --     |        |         | Extracellular Space | group                  |
| MMP14            | matrix metalloproteinase 14                       | MMP14  | -9.666 | 1E-07   | Extracellular Space | peptidase              |
| Nfat (family)    | --  | --     |        |         | Cytoplasm           | group                  |
| NFkB (complex)   | --  | --     |        |         | Nucleus             | complex                |
| P38 MAPK         | --  | --     |        |         | Cytoplasm           | group                  |
| PECAM1           | platelet and endothelial cell adhesion molecule 1 | PECAM1 | -4.938 | 0.00001 | Plasma Membrane     | other                  |
| PTGIS            | prostaglandin I2 synthase                         | PTGIS  | -2.26  | 0.035   | Cytoplasm           | enzyme                 |
| PTGS2            | prostaglandin-endoperoxide synthase 2             | PTGS2  | 2.96   | 0.027   | Cytoplasm           | enzyme                 |
| RAS              | --  | --     |        |         | Cytoplasm           | group                  |
| SYK/ ZAP         | --  | --     |        |         | Cytoplasm           | group                  |
| TEK              | TEK receptor tyrosine kinase                      | TEK    | 3.07   | 0.0142  | Plasma Membrane     | kinase                 |
| THBS1            | thrombospondin 1                                  | THBS1  | -2.156 | 0.031   | Extracellular Space | other                  |
| VCAM1            | vascular cell adhesion molecule 1                 | VCAM1  | -2.758 | 1E-07   | Plasma Membrane     | transmembrane receptor |
| VEGFA            | vascular endothelial growth factor A              | VEGFA  | 2.08   | 0.0217  | Extracellular Space | growth factor          |

Supplementary Table 11 (S11). Hypothetical action of APN on HMVRECs cells. Fig S8/Relationships

| From Molecule(s) | Relationship Type     | To Molecule(s)                        |
|------------------|-----------------------|---------------------------------------|
| ADIPOQ           | activation            | Jnk                                   |
| ADIPOQ           | activation            | NFKB1                                 |
| ADIPOQ           | activation            | NFkB (complex)                        |
| ADIPOQ           | activation            | P38 MAPK                              |
| ADIPOQ           | activation            | RELA                                  |
| ADIPOQ           | activation            | Vegf                                  |
| ADIPOQ           | causation             | Inflammatory response                 |
| ADIPOQ           | causation             | PPARα/RXRα Activation                 |
| ADIPOQ           | causation             | Production of reactive oxygen species |
| ADIPOQ           | expression            | ICAM1                                 |
| ADIPOQ           | expression            | NFkB (complex)                        |
| ADIPOQ           | expression            | NPPA                                  |
| ADIPOQ           | expression            | TGFB1                                 |
| ADIPOQ           | expression            | TNF                                   |
| ADIPOQ           | expression            | VCAM1                                 |
| ADIPOQ           | expression            | Vegf                                  |
| ADIPOQ           | expression            | adhesion molecule                     |
| ADIPOQ           | inhibition            | TNF                                   |
| ADIPOQ           | localization          | Collagen Alpha1                       |
| ADIPOQ           | localization          | IL1B                                  |
| ADIPOQ           | localization          | TNF                                   |
| ADIPOQ           | localization          | Vegf                                  |
| ADIPOQ           | phosphorylation       | Jnk                                   |
| ADIPOQ           | phosphorylation       | P38 MAPK                              |
| ADIPOQ           | phosphorylation       | RELA                                  |
| ADIPOQ           | regulation of binding | NFKB1                                 |
| ADIPOQ           | regulation of binding | RELA                                  |
| ADIPOQ           | transcription         | TNF                                   |
| ADIPOQ           | translocation         | NFKB1                                 |
| ADIPOQ           | translocation         | RELA                                  |
| Collagen Alpha1  | causation             | Adhesion of neutrophils               |
| ICAM1            | causation             | Adhesion of neutrophils               |



|                |                              |  |
|----------------|------------------------------|--|
| ICAM1          | causation                    | Adhesion of vascular endothelial cells |
| ICAM1          | causation                    | Chemotaxis of leukocytes               |
| ICAM1          | causation                    | Extravasation                          |
| ICAM1          | causation                    | Production of reactive oxygen species  |
| ICAM1          | correlation                  | Retinal vasculopathy                   |
| IL1B           | activation                   | NFkB (complex)                         |
| IL1B           | causation                    | Adhesion of vascular endothelial cells |
| IL1B           | causation                    | Chemotaxis of leukocytes               |
| IL1B           | causation                    | Extravasation                          |
| IL1B           | causation                    | Inflammatory response                  |
| IL1B           | causation                    | Production of reactive oxygen species  |
| IL1B           | correlation                  | Inflammatory response                  |
| IL1B           | expression                   | NFkB (complex)                         |
| IL1B           | inhibition                   | NFkB (complex)                         |
| IL1B           | localization                 | ADIPOQ                                 |
| IL1B           | localization                 | NFkB (complex)                         |
| IL1B           | molecular cleavage           | NFkB (complex)                         |
| IL1B           | regulation of binding        | NFkB (complex)                         |
| IL1B           | translocation                | NFkB (complex)                         |
| Jnk            | causation                    | Adhesion of vascular endothelial cells |
| Jnk            | causation                    | Chemotaxis of leukocytes               |
| Jnk            | causation                    | Production of reactive oxygen species  |
| NFKB1          | expression                   | RELA                                   |
| NFKB1          | expression                   | TNF                                    |
| NFKB1          | localization                 | TNF                                    |
| NFKB1          | protein-DNA interactions     | RELA                                   |
| NFKB1          | protein-DNA interactions     | TNF                                    |
| NFKB1          | protein-protein interactions | RELA                                   |
| NFKB1          | regulation of binding        | RELA                                   |
| NFKB1          | transcription                | TNF                                    |
| NFKB1          | translocation                | RELA                                   |
| NFKBIE         | correlation                  | PPAR $\alpha$ /RXR $\alpha$ Activation |
| NFKBIE         | expression                   | ICAM1                                  |
| NFKBIE         | expression                   | SELE                                   |
| NFKBIE         | expression                   | TNF                                    |
| NFKBIE         | expression                   | VCAM1                                  |
| NFKBIE         | protein-protein interactions | NFKB1                                  |
| NFKBIE         | protein-protein interactions | NFKBIE                                 |
| NFKBIE         | regulation of binding        | NFKB1                                  |
| NFkB (complex) | activation                   | IL1B                                   |
| NFkB (complex) | causation                    | Adhesion of vascular endothelial cells |
| NFkB (complex) | causation                    | Production of reactive oxygen species  |
| NFkB (complex) | expression                   | IL1B                                   |
| NFkB (complex) | expression                   | TNF                                    |
| NFkB (complex) | expression                   | VEGFA                                  |

|                |                              |  |
|----------------|------------------------------|--|
| NFkB (complex) | localization                 | IL1B                                   |
| NFkB (complex) | localization                 | TNF                                    |
| NFkB (complex) | protein-DNA interactions     | TNF                                    |
| NFkB (complex) | transcription                | IL1B                                   |
| NFkB (complex) | transcription                | TNF                                    |
| NFkB (complex) | transcription                | VEGFA                                  |
| NPPA           | causation                    | Adhesion of neutrophils                |
| NPPA           | causation                    | Production of reactive oxygen species  |
| P38 MAPK       | causation                    | Adhesion of vascular endothelial cells |
| P38 MAPK       | causation                    | Chemotaxis of leukocytes               |
| P38 MAPK       | causation                    | Production of reactive oxygen species  |
| P38 MAPK       | expression                   | ADIPOQ                                 |
| P38 MAPK       | expression                   | TNF                                    |
| P38 MAPK       | localization                 | TNF                                    |
| P38 MAPK       | modification                 | TNF                                    |
| P38 MAPK       | regulation of binding        | TNF                                    |
| P38 MAPK       | transcription                | TNF                                    |
| RELA           | causation                    | Adhesion of vascular endothelial cells |
| RELA           | causation                    | Inflammatory response                  |
| RELA           | expression                   | NFKB1                                  |
| RELA           | expression                   | TNF                                    |
| RELA           | localization                 | TNF                                    |
| RELA           | protein-DNA interactions     | NFKB1                                  |
| RELA           | protein-DNA interactions     | TNF                                    |
| RELA           | protein-protein interactions | NFKB1                                  |
| RELA           | protein-protein interactions | TNF                                    |
| RELA           | regulation of binding        | NFKB1                                  |
| RELA           | regulation of binding        | TNF                                    |
| RELA           | transcription                | NFKB1                                  |
| RELA           | transcription                | TNF                                    |
| RELA           | translocation                | NFKB1                                  |
| SELE           | causation                    | Adhesion of neutrophils                |
| SELE           | causation                    | Adhesion of vascular endothelial cells |
| SELE           | causation                    | Chemotaxis of leukocytes               |
| SELE           | causation                    | Extravasation                          |
| SELE           | causation                    | Production of reactive oxygen species  |
| SELE           | correlation                  | Retinal vasculopathy                   |
| TGFB1          | causation                    | Adhesion of neutrophils                |
| TGFB1          | causation                    | Adhesion of vascular endothelial cells |
| TGFB1          | causation                    | Chemotaxis of leukocytes               |
| TGFB1          | causation                    | Extravasation                          |
| TGFB1          | causation                    | Production of reactive oxygen species  |
| TGFB1          | expression                   | ADIPOQ                                 |

|       |                              |  |
|-------|------------------------------|--|
| TNF   | activation                   | NFKB1                                  |
| TNF   | activation                   | NFkB (complex)                         |
| TNF   | activation                   | P38 MAPK                               |
| TNF   | activation                   | RELA                                   |
| TNF   | causation                    | Adhesion of neutrophils                |
| TNF   | causation                    | Adhesion of vascular endothelial cells |
| TNF   | causation                    | Chemotaxis of leukocytes               |
| TNF   | causation                    | Extravasation                          |
| TNF   | causation                    | Inflammatory response                  |
| TNF   | causation                    | Production of reactive oxygen species  |
| TNF   | causation                    | Retinal vasculopathy                   |
| TNF   | expression                   | ADIPOQ                                 |
| TNF   | expression                   | NFKB1                                  |
| TNF   | expression                   | NFKBIE                                 |
| TNF   | expression                   | NFkB (complex)                         |
| TNF   | expression                   | P38 MAPK                               |
| TNF   | expression                   | RELA                                   |
| TNF   | inhibition                   | ADIPOQ                                 |
| TNF   | inhibition                   | NFkB (complex)                         |
| TNF   | localization                 | NFKB1                                  |
| TNF   | localization                 | NFkB (complex)                         |
| TNF   | localization                 | P38 MAPK                               |
| TNF   | localization                 | RELA                                   |
| TNF   | modification                 | NFKB1                                  |
| TNF   | modification                 | RELA                                   |
| TNF   | molecular cleavage           | NFKB1                                  |
| TNF   | molecular cleavage           | NFKBIE                                 |
| TNF   | molecular cleavage           | RELA                                   |
| TNF   | phosphorylation              | NFKB1                                  |
| TNF   | phosphorylation              | NFkB (complex)                         |
| TNF   | phosphorylation              | P38 MAPK                               |
| TNF   | phosphorylation              | RELA                                   |
| TNF   | protein-protein interactions | RELA                                   |
| TNF   | regulation of binding        | NFKB1                                  |
| TNF   | regulation of binding        | NFKBIE                                 |
| TNF   | regulation of binding        | NFkB (complex)                         |
| TNF   | regulation of binding        | RELA                                   |
| TNF   | transcription                | NFKB1                                  |
| TNF   | transcription                | NFKBIE                                 |
| TNF   | transcription                | NFkB (complex)                         |
| TNF   | transcription                | RELA                                   |
| TNF   | translocation                | NFKB1                                  |
| TNF   | translocation                | NFkB (complex)                         |
| TNF   | translocation                | RELA                                   |
| TNF   | ubiquitination               | NFKB1                                  |
| TNF   | ubiquitination               | RELA                                   |
| VCAM1 | causation                    | Adhesion of neutrophils                |
| VCAM1 | causation                    | Adhesion of vascular endothelial cells |
| VCAM1 | causation                    | Chemotaxis of leukocytes               |
| VCAM1 | causation                    | Production of reactive oxygen species  |
| VCAM1 | correlation                  | Retinal vasculopathy                   |
| VEGFA | activation                   | NFkB (complex)                         |

|                   |             |  |
|-------------------|-------------|--|
| VEGFA             | causation   | Adhesion of vascular endothelial cells |
| VEGFA             | causation   | Chemotaxis of leukocytes               |
| VEGFA             | causation   | Inflammatory response                  |
| VEGFA             | causation   | Production of reactive oxygen species  |
| VEGFA             | causation   | Retinal vasculopathy                   |
| VEGFA             | correlation | Retinal vasculopathy                   |
| Vegf              | causation   | Adhesion of vascular endothelial cells |
| Vegf              | causation   | Chemotaxis of leukocytes               |
| Vegf              | causation   | Extravasation                          |
| Vegf              | causation   | Production of reactive oxygen species  |
| Vegf              | correlation | Retinal vasculopathy                   |
| adhesion molecule | causation   | Extravasation                          |

Data describes the relationship between adiponectin and other molecules.

Supplementary Table 12 (S12). Hypothetical actions of APN on HG cells fig S8: type of molecules

| Symbol                                 | Synonym(s)  | Entrez Gene Name                                | Location            | Family                 |
|--|---|---|---------------------|------------------------|
| adhesion molecule                      | ADHESION MOLECULES  |   | Plasma Membrane     | group                  |
| Adhesion of neutrophils                |   |   | Other               | function               |
| Adhesion of vascular endothelial cells |   |   | Other               | function               |
| ADIPOQ                                 | a, Acd, ACDC, Acr, ACRP30, Ad, Adid, adip, adipo, Adipocyte complement related protein of 30 kda, ADIPOD, ADIPONECTIN, adiponectin, C1Q and collagen domain containing, ADIPQTL1, Adn, ADPN, ap, APM-1, APN, GBP2, GBP28  | adiponectin, C1Q and collagen domain containing | Extracellular Space | other                  |
| Chemotaxis of leukocytes               |   |   | Other               | function               |
| Collagen Alpha1                        | Alpha1 collagen, COL1, Col1 alpha, Col1 $\alpha$ , Collage I, Collage Type I, Collagen I, COLLAGEN type I, PROCOLLAGEN (I), PROCOLLAGEN alpha I, Procollagen alpha type i, Procollagen Type 1, PROCOLLAGEN $\alpha$ I, Procollagen $\alpha$ type i, Type 1 collagen, type I PROCOLLAGEN |   | Other               | group                  |
| Extravasation                          |   |   | Other               | function               |
| ICAM1                                  | BB2, CD54, ICAM, INTERCELLULAR ADHESION MOLECULE 1, Ly-4, Ly-47, M90551, MAL, MALA-2, Melanoma Progression  | intercellular adhesion molecule 1               | Plasma Membrane     | transmembrane receptor |

|                       |  |                                  |                     |                         |
|-----------------------|--|----------------------------------|---------------------|-------------------------|
|                       | Associated Antigen, P3.58  |                                  |                     |                         |
| IL1B                  | IL-1, IL-, IL-1 β, IL-1F2, IL1-BETA, interleukin 1 beta, Interleukin 1 β, OAF, Osteoclast-Activating Factor, Pro-IL-1beta, Pro-IL-1β   | interleukin 1 beta               | Extracellular Space | cytokine                |
| Inflammatory response |  |                                  | Other               | function                |
| Jnk                   | JNK 54/46, Jnk p56, JNK/SAPK, JUN KINASE, p40, p47, Sapk/Jnk   |                                  | Cytoplasm           | group                   |
| NFkB (complex)        | NF-KAPPA B, NF-κ B, nuclear factor-κ b, transcription factor nuclear factor κ b  |                                  | Nucleus             | complex                 |
| NFKB1                 | CVID12, EBP-1, KBF1, Nf kappa b DNA binding subunit, NF KAPPA B subunit P50, Nf κ b DNA binding subunit, NF κ B subunit P50, NF-κ, NF-kappa-B1, NF-kappa-B, NF-kappabeta, NF-kB, NF-κ-B1, NF-κ-B, NFKappaB-p50, NFKappaB1 p105, NFKB subunit P105/P50, NFKB-p105, NFκB-p50, NFκB1 p105, NUCLEAR FACTOR KAPPA B DNA binding subunit, nuclear factor kappa B subunit 1, nuclear factor of kappa light polypeptide gene enhancer in B cells 1, p105, nuclear factor of κ light polypeptide gene enhancer in B cells 1, p105, NUCLEAR FACTOR κ B DNA binding subunit, nuclear factor κ B subunit 1, p5, p105 Nfkb, P50 nf κ b, p50 NF-kappaB, p50/p1, P50/P105 | nuclear factor kappa B subunit 1 | Nucleus             | transcription regulator |
| NFKBIE                | I-kappa-B-epsilon, I-κ-B-ε, ikB-epsilon, ikB-ε, IKBE, NF-kappa-BIE, NF-κ-BIE, NFKB inhibitor epsilon, NFKB inhibitor ε, nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, epsilon, nuclear factor of κ light polypeptide gene enhancer in B cells inhibitor, ε, Slc35b2  | NFKB inhibitor epsilon           | Nucleus             | transcription regulator |
| NPPA                  | A, ANF, ANP, ATFB6, Atrial natriuretic factor, Atrial Natriuretic Peptide Prohormone, ATRST2, CDD, CDD-ANF, natriuretic peptide A, natriuretic peptide type A, P,  | natriuretic peptide A            | Extracellular Space | other                   |

|  |   |  |                        |                            |
|--|---|--|------------------------|----------------------------|
|  | PND,<br>Prepronatriodilatin,<br>RATANF  |  |                        |                            |
| P38 MAPK                                       | P38, p38 MAP<br>KINASE, P38<br>MITOGEN-<br>ACTIVATED<br>protein KINASE  |  | Cytoplasm              | group                      |
| PPARα/RXRα<br>Activation                       |   |  | Other                  | canonical<br>pathway       |
| Production of<br>reactive<br>oxygen<br>species |   |  | Other                  | function                   |
| RELA   | CMCU, NF KAPPA<br>B subunit P65, NF κ<br>B subunit P65, NF-κ<br>B (p65), NF-kappa B,<br>NF-kappa B (p65),<br>NF-κ B, NF-κ B<br>(p65), NF-κB p65,<br>NFKB3, NfκB,<br>NFKB/p65, nos2, p6,<br>p65, p65 NF-kappa<br>B, p65 NF-κ B, p65<br>NfκB, p65/Rela,<br>RELA proto-<br>oncogene, NF-kB<br>subunit, v-rel<br>reticuloendotheliosis<br>viral oncogene<br>homolog A (avian) | RELA proto-<br>oncogene,<br>NF-kB<br>subunit | Nucleus                | transcription<br>regulator |
| Retinal<br>vasculopathy                        |   |  | Other                  | disease                    |
| SELE   | CD62E, E-sele, E-<br>selectin, EL, ELAM,<br>ELAM-1, ESEL,<br>LECAM2, selectin E,<br>SELECTIN E<br>precursor, selectin,<br>endothelial cell  | selectin E                                   | Plasma<br>Membrane     | transmembrane<br>receptor  |
| TGFB1  | Beta Ig-h3, CED,<br>DPD1, IBDIMDE,<br>LAP, TGF-beta1,<br>TGF-beta, TGF-β1,<br>TGF-β, tgf-β(1),<br>TGFB, transforming<br>growth factor beta 1,<br>transforming<br>growth factor, beta<br>1, transforming<br>growth factor, β 1,<br>transforming<br>growth factor-β 1,<br>Transforming<br>growth factor-β(1), β<br>Ig-h3  | transforming<br>growth<br>factor beta 1      | Extracellular<br>Space | growth factor              |
| TNF  | AT-TNF, DI, DIF,<br>RATTNE, TMTNE,<br>Tn, TNF-α, TNF-<br>alpha, TNF-α, Tnfs,<br>TNFSF2, Tnfsf1a,<br>TNLG1F, tumor<br>necrosis factor,<br>Tumor Necrosis<br>Factor α, tumor<br>necrosis factor, α,<br>tumour necrosis<br>factor, tumour<br>Necrosis Factor<br>Alpha, tumour<br>Necrosis Factor α,<br>tumour necrosis<br>factor, alpha,<br>tumour necrosis<br>factor, α     | tumor<br>necrosis<br>factor                  | Extracellular<br>Space | cytokine                   |
| VCAM1  | CD106, INCAM-100,<br>vascular cell<br>adhesion molecule<br>1, Vcam, VCAM1B,<br>VECAM1   | vascular cell<br>adhesion<br>molecule 1      | Plasma<br>Membrane     | transmembrane<br>receptor  |
| Vegf   |   |  | Extracellular<br>Space | group                      |
| VEGFA  | Gd-vegf, MVCD1,<br>V, vascular<br>endothelial growth  | vascular<br>endothelial                      | Extracellular<br>Space | growth factor              |

|  |  |                    |  |  |
|--|--|--------------------|--|--|
|  | factor A, Veg,<br>VEGF12, VEGF16,<br>VEGF18, VEGF111,<br>VEGF, Vegf-3, VPF | growth<br>factor A |  |  |
|--|--|--------------------|--|--|

Data describes the type of the molecules .

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## **Biology category**

### **Angiogenic Growth Factors**

#### **Growth Factors & Receptors**

ANG,ANGPT1,ANGPT2,ANPEP,FGF1,FGF2 (BFGF),FLT1 (VEGFR1),JAG1,KDR (VEGFR3),NRP1,NRP2,PGF,TYMP,VEGFA,VEGFB,VEGFC,VEGFD (VEGFD).

#### **Cell Adhesion Molecules**

ADGRB1 (BAI1), COL4A3, CXCL8 (IL8), NRP1, NRP2.

#### **Extracellular Matrix (ECM) Molecules**

ANGPTL4,F3,PECAM1,PF4,PROK2,SERPINE1 (PAI-1),SERPINF1.

#### **Other Angiogenic Factors**

HIF1A,NOS3 (eNOS),SPHK1.

#### **Other Angiogenic Factors**

### **Cytokines**

CCL11 (Eotaxin), CCL2 (MCP-1),CXCL1 (GRO1, GROa, SCYB1),CXCL10 (INP10),CXCL5 (ENA-78, LIX),CXCL6 (GCP-2),CXCL9 (MIG),EDN1,IFNA1,IFNG,IL1B,IL6,MDK,TNF.

### **Growth Factors & Receptors**

CCN2,EFNA1,EFNB2,EGF,EPHB4,FGFR3,HGF,IGF1,ITGB3,PDGFA,S1PR1,TEK (TIE-2, TIE2),TGFA,TGFB1,TGFB2,TGFBR1 (ALK5).

### **Cell Adhesion Molecules**

CCL11 (Eotaxin),CCL2 (MCP-1),CCN2,CDH5,COL18A1,ENG (EVI-1),ERBB2 (HER-2, NEU),FN1,ITGAV,ITGB3,S1PR1,THBS1 (TSP-1),THBS2.

### **Extracellular Matrix (ECM) Molecules**

CNMD,LEP (Leptin),MMP14,MMP2,MMP9,PLAU (UPA),PLG,TIMP1,TIMP2,TIMP3.

### **Other Angiogenic Factors**

AKT1,HPSE,ID1,NOTCH4,PTGS1 (COX1),TIE1.

## **Human angiogenesis**

### **Angiogenic Growth Factors**

#### **Growth Factors & Receptors**

ANG,ANGPT1,ANGPT2,ANPEP,FGF1,FGF2,FIGF,FLT1,JAG1,KDR,NRP1,NRP2,PGF,TYMP,VEGFA,VEGFB,VEGFC.

#### **Cell Adhesion Molecules**

ADGRB1,COL4A3,CXCL8,NRP1,NRP2.

#### **Extracellular Matrix (ECM) Molecules**

ANGPTL4,F3,PECAM1,PF4,PROK2,SERPINE1 (SERPINE1),SERPINF1.

#### **Other Angiogenic Factors**

EPAS1,HIF1A,NOS3,SPHK1.

### **Cytokines**

CCL11 (Eotaxin),CCL2 (MCP-1),CXCL1,CXCL10 (INP10),CXCL2,CXCL6 (GCP-2),CXCL9 (MIG),EDN1,IFNB1,IFNG,IL1B,IL6,TNF.

### **Growth Factors & Receptors**

CTGF,EFNA1,EFNB2,EGF,EPHB4,FGFR3,HGF,IGF1,ITGB3,PDGFA,S1PR1,TEK,TGFA,TGFB1,TGFB2,TGFBR1.

### **Cell Adhesion Molecules**



CCL11 (Eotaxin),CCL2 (MCP-1),CDH5,COL18A1,CTGF,ENG (EVI-1),ERBB2,FN1,ITGAV,ITGB3,S1PR1,THBS1 (TSP-1),THBS2.

Extracellular Matrix (ECM) Molecules

LECT1,LEP,MMP14,MMP2,MMP9,PLAU,PLG (PLG),TIMP1,TIMP2,TIMP3.

Other Angiogenic Factors AKT1,HPSE,ID1,NOTCH4,PTGS1,TIE1.

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Endothelial Cell Biology

Angiogenesis

ANGPT1,CCL2 (MCP-1),CCL5 (RANTES),CX3CL1,EDN1,EDNRA,ENG (EVI-1),F3,FASLG (TNFSF6),FGF1,FGF2 (BFGF),FLT1

(VEGFR1),FN1,HIF1A,HMOX1,IL1B,IL6,ITGA5,ITGAV,ITGB1,ITGB3,KDR (VEGFR3),KIT (CD117),KLK3,MMP2,MMP9,NOS3 (eNOS),NPPB,NPR1,PF4,PGF,PLAU (UPA),PTGS2 (COX2),SERPINE1 (PAI-1),SPHK1,TEK (TIE-2, TIE2),THBS1 (TSP-1),TYMP,VEGFA.

Vasoconstriction & Vasodilation

ACE,AGT,AGTR1,ALOX5,APOE,CALCA,CAV1,CX3CL1,EDN1,EDN2,EDNRA,F2R (PAR1),HMOX1,ICAM1,NOS3 (eNOS),NPPB,NPR1,PTGIS,PTGS2 (COX2),SOD1.

Inflammatory Response

ACE,AGT,AGTR1,ALOX5,APOE,CALCA,CCL2 (MCP-1),CCL5 (RANTES),CX3CL1,EDNRA,F2R (PAR1),F3,FN1,HIF1A,HMOX1,IL1B,IL6,NPPB,PTGS2 (COX2),SELE,SPHK1,TGFB1,THBS1 (TSP-1),TNF,VCAM1.

Apoptosis

ANXA5,BAX,BCL2,BCL2L1 (BCLXL),CASP1 (ICE),CASP3,CAV1,CCL2 (MCP-1),CCL5 (RANTES),CFLAR (CASPER),CX3CL1,EDN1,EDNRA,FAS,FASLG (TNFSF6),FGF2 (BFGF),HIF1A,HMOX1,IL1B,IL3,IL6,IL7,OCLN,PF4,PTK2 (FAK),SPHK1,TEK (TIE-2, TIE2),THBS1 (TSP-1),TNF,TNFSF10 (TRAIL).

Cell Adhesion Molecules

ADAM17 (CD156B),AGT,BCL2,CALCA,CDH5,COL18A1,CX3CL1,ENG (EVI-1),FGF1,FN1,ICAM1,IL1B,ITGA5,ITGAV,ITGB1,ITGB3,KDR (VEGFR3),PDGFRA,PECAM1,PLAU (UPA),PLG,PTK2 (FAK),SELE,SELL (LECAM-1),SELPLG (P-Selectin),SERPINE1 (PAI-1),TGFB1,THBS1 (TSP-1),TNF,VCAM1,VEGFA,VWF.

Coagulation

ANXA5,CAV1,EDN1,F2R (PAR1),F3,FN1,MMP1,PECAM1,PF4,PLAT (TPA),PLAU (UPA),PLG,PROCR (EPCR),PTK2 (FAK),SELL (LECAM-1),SELPLG (P-Selectin),SERPINE1 (PAI-1),TEK (TIE-2, TIE2),TFPI,THBD,THBS1 (TSP-1),TIMP1,VWF.

## Platelet Activation

APOE,CX3CL1,F2R (PAR1),FN1,IL11,IL6,ITGB3,NOS3  
(eNOS),PDGFRA,PECAM1,PF4,PLG,SERPINE1 (PAI-1),SOD1,TGFB1,THBD,THBS1 (TSP-1),TIMP1,VEGFA,VWF.

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## Extracellular Matrix and Adhesion Molecules

### Cell Adhesion Molecules

#### Transmembrane Receptors

CD44,CDH1 (ECadherin),HAS1,ICAM1,ITGA1,ITGA2,ITGA3,ITGA4 (CD49D),ITGA5,ITGA6,ITGA7,ITGA8,ITGAL,ITGAM,ITGAV,ITGB1,ITGB2,ITGB3,ITGB4,ITGB5,MMP14,MMP15,MMP16,NCAM1,PECAM1,SELE,SELL (LECAM-1),SELP,SGCE,SPG7,VCAM1.

#### Cell-Cell Adhesion

CD44,CDH1 (ECadherin),COL11A1,COL14A1,COL6A2,CTNND1,ICAM1,ITGA8,VCAM1

#### Cell-Extracellular Matrix (ECM)

AdhesionADAMTS13,CD44,ITGA1,ITGA2,ITGA3,ITGA4 (CD49D),ITGA5,ITGA6,ITGA7,ITGA8,ITGAL,ITGAM,ITGAV,ITGB1,ITGB2,ITGB3,ITGB4,ITGB5,SGCE,SPP1,THBS3.

#### Other Cell Adhesion Molecules

ANOS1,CCN2,CLEC3B,CNTN1,COL12A1,COL15A1,COL16A1,COL5A1,COL6A1,COL7A1,COL8A1,CTNNA1,CTNNB1,CTNND2,FN1,LAMA1,LAMA2,LAMA3,LAMB1,LAMB3,LAMC1,THBS1 (TSP-1),THBS2,TNC,VCAN,VTN.

## Extracellular Matrix (ECM) Molecules

### Basement Membrane Constituents

COL4A2,COL7A1,LAMA1,LAMA2,LAMA3,LAMB1,LAMB3,LAMC1,SPARC.

### Collagens & ECM Structural Constituents

ANOS1,COL11A1,COL12A1,COL14A1,COL15A1,COL16A1,COL1A1,COL4A2,COL5A1,COL6A1,COL6A2,COL7A1,COL8A1,FN1.

### Extracellular Matrix (ECM) Proteases

ADAMTS1,ADAMTS13,ADAMTS8,MMP1,MMP10,MMP11,MMP12,MMP13,MMP14,MMP15,MMP16,MMP2,MMP3,MMP7,MMP8,MMP9,SPG7,TIMP1.

### Extracellular Matrix (ECM) Protease Inhibitors

ANOS1,COL7A1,THBS1 (TSP-1),TIMP1,TIMP2,TIMP3.

### Other Extracellular Matrix (ECM) Molecules

CCN2,CLEC3B,ECM1,HAS1,SPP1,TGFB1,THBS2,THBS3,TNC,VCAN,VTN.