Local effects of adipose tissue in psoriasis and psoriatic arthritis

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Abstract: The structure and physiological state of the local white adipose tissue (WAT) located underneath the lesional psoriatic skin and inside of the joints affected by psoriatic arthritis play an important role in the pathophysiology of these diseases. WAT pads associated with inflammatory sites in psoriasis and psoriatic arthritis are, correspondingly, dermal WAT and articular adipose tissue; these pads demonstrate inflammatory phenotypes in both diseases. Such local WAT inflammation could be the primary effect in the pathophysiology of psoriasis leading to the modification of the local expression of adipokines, a change in the structure of the basement membrane and the release of keratinocytes with consequent epidermal hyperproliferation during psoriasis. Similar articular adipose tissue inflammation can lead to the induction of structural modifications and synovial inflammation in the joints of patients with psoriatic arthritis.

Keywords: psoriasis, psoriatic arthritis, pathophysiology, adipose tissue, dermal adipocytes, articular adipose tissue

Introduction

Psoriasis and psoriatic arthritis (PsA) are actually considered to be interrelated diseases that share some pathophysiologic pathways. 1 One important argument for this is that they exhibit similarities in prevalence statistics: while inflammatory arthritis occurs in 2%–3% of the general population, its prevalence among psoriatic patients is much higher. The prevalence of PsA also shows similar ethnic variations to those of psoriasis; the prevalence of PsA is high in Caucasians from Europe and low in Asians. 2

There is growing evidence that both diseases are related to the physiologic state of the adipose tissue. 3 Whereas such a relationship was normally considered to exist at the systemic level, it was shown that some inflammatory skin diseases demonstrate a reciprocal expression of inflammatory and lipid genes in lesional skin. 4 Psoriatic patients have an altered composition of high-density lipoproteins in serum and an impaired cholesterol efflux from macrophages, 5 and antipsoriatic therapy is capable of restoring the normal balance. 6,7 Also, there is a high prevalence of metabolic syndrome (MetS) in patients with psoriasis and PsA; 8,9 furthermore, psoriasis and PsA patients with MetS have significantly higher psoriasis area and severity index (PASI) values than the patients without MetS. 8–10 These are the important arguments for the systemic involvement of adipose tissue in the pathology of psoriasis.

At the same time, skin inflammation in patients with psoriasis is restricted to psoriatic plaques, and thus, its appearance is generally spatially limited. This observation supports the primary local modification of the superficial layer of the subcutaneous...
white adipose tissue (sWAT) underneath the psoriatic plaques. AD11,12 According to this theory, adipose tissue interacts with the skin not only at a systemic level, which should be mainly connected to the function of abdominal sWAT, but also with the skin locally, producing the expansion and/or physiologic modification of dermal WAT (dWAT), which leads to the overproduction of the antimicrobial peptide (AMP) cathelicidin in dermal adipocytes.13

Very recently, the expression of the microRNA (miR) member miR-26b-5p was shown to be strongly upregulated locally in sWAT underneath the lesions of psoriatic skin. This is especially interesting since miR-26b-5p downregulates cholesterol efflux from monocytes/macrophages, adipocytes, vascular endothelial cells and fibroblasts, which is in line with the results obtained by Holzer et al.5 The upregulation of miR-26b is connected to adipocyte differentiation,13 which was associated with inflammation in human WAT. Indeed, the absolute values of miR-26b are dependent on the number of macrophages that infiltrate a given fat depot, and miR-26b was shown to be regulated by different adipokines17 known to be produced in patients with psoriasis and PsA. Importantly, the expression of miRNA is strongly modified after immune stimulation, and miRNA was demonstrated to be able to alter the expression of cell surface proteins involved in the immune response in epithelial cells.18 Although a direct correlation between miR-26b expression and cathelicidin production in adipose tissue was not investigated, such a relationship is strongly assumed to exist, especially because cathelicidin is also expressed by macrophages.

Analogous to psoriasis, it can be supposed that PsA is connected to a pathologic modification of the articular adipose tissue (AAT) in an affected joint. From this point of view, the systems epidermis–dermis–sWAT in psoriasis and the synovium–AAT in PsA should demonstrate some structural and physiologic similarities. This shifts the main emphasis from systemic to local effects of adipose tissue in psoriasis and PsA. In this review, we discuss the recent insights in this field.

Adipose tissue in psoriasis
Psoriasis is actually considered to be a systemic inflammatory disease with a heterogeneous genetic background characterized by the dysregulation of the immune system, an impaired barrier function and epidermal hyperproliferation. It is broadly accepted that various cytokines are involved in the pathophysiology of this disease, which include interleukin (IL)-17, IL-22 and IL-23.19-21 At the same time, some authors have stated that IL-17 causes no psoriasis-like morphologic changes in the skin.22 Recently, it was shown that obesity can exacerbate imiquimod-induced psoriasiform dermatitis in mice by the upregulation of IL-17A, IL-22 and regenerating islet-derived protein 3 gamma (Reg3γ) expression.23 It should be noted that Reg3γ not only enhances keratinocyte proliferation, but is also an adenosine monophosphate (AMP) that demonstrates a strong reaction against Staphylococcus aureus.24

The pathophysiology and inflammatory nature of psoriasis have been connected with the physiologic state of the systemic WAT, especially with the intensity and spectrum of secreted adipokines, resulting in the unbalanced production of pro- and anti-inflammatory signaling proteins.25 This finding supports the opinion that WAT is a key participant in the development of different skin pathologies, including psoriasis.

Systemic levels of adipokines and psoriasis
Different adipokines demonstrate various activities in patients with psoriasis. For example, the secretion of tumor necrosis factor (TNF)-α and IL-6 from keratinocytes as well as the secretion of IL-6, IL-8, IL-17, IL-22 and TNF-α from T-lymphocytes can be stimulated by leptin and inhibited by adiponectin.26 At the same time, different authors have reported very inconsistent levels of adipokines such as adiponectin and leptin in the serum of psoriatic patients.29 Whereas high serum levels of leptin were found in some clinical studies of patients with psoriasis,30,31 other studies reported significantly reduced levels of this adipokine, which were also strongly dependent on PASI.31 Adiponectin is primarily known as a metabolic regulator of insulin sensitivity and a protector against inflammation in MetS.32 Its anti-inflammatory properties were demonstrated, among others, in AdipoR1/AdipoR2-double-knockout (KO) mice.33 Serum levels of adiponectin and IL-22 were reported to be positively correlated in patients with psoriasis.34 The importance of adiponectin in the pathophysiology of psoriasis became evident after it was shown that this adipokine was highly involved in the pathophysiology of IL-17-related psoriasiform dermatitis and that the adiponectin KO mice demonstrated a severe form of this disease.35 Moreover, application of exogenous adiponectin significantly suppressed the elevated production of IL-17 in these mice and improved the cutaneous lesions. Importantly, exogenous adiponectin did not suppress IL-17 expression in wild-type mice, which means that the mechanism of such a suppression should have a threshold character. It should be taken into account that the systemic fat deposition in PsA is primarily connected to the function of abdominal sWAT, but also with the skin not only at a systemic level, which should be also strongly connected to the physiologic state of the systemic WAT, especially with the intensity and spectrum of secreted adipokines, resulting in the unbalanced production of pro- and anti-inflammatory signaling proteins. This finding supports the opinion that WAT is a key participant in the development of different skin pathologies, including psoriasis.

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account that psoriasiform dermatitis in adiponectin KO mice was induced by the topical application of imiquimod, which is known to cause an almost complete depletion of the dWAT layer in murine skin. Such a depletion can significantly reduce the local reaction of WAT underneath the lesional skin, thus reducing the local immune response of the skin to pathogens and increasing the inflammatory reaction induced by these pathogens.

The adiponectin content in patients with psoriasis was mainly measured in serum samples, which reflects the systemic level of this adipokine, and it was found to be significantly higher in PsA patients than in psoriatic patients without arthritis. This can at least partly explain the inconsistent results obtained by different authors who did not differ between these groups. Moreover, adiponectin demonstrated a negative correlation and leptin a positive correlation with body mass index, and both adipokines correlated with PASI. Interestingly, serum adiponectin was significantly decreased in patients with mild (PASI < 10) and moderate (10 < PASI < 20) psoriasis, but it almost reached control values in patients with severe (PASI > 20) psoriasis. Although antipsoriatic treatments can significantly reduce PASI values, they do not affect the serum levels of both adipokines. These results indicate that skin appearance in patients with psoriasis is not primarily connected to the systemic levels of adipokines.

Another parameter that can sufficiently influence the levels of adipokines in serum and was not properly controlled in the majority of psoriatic studies is the presence of MetS. Indeed, the concentration of serum adiponectin was found to be significantly reduced in controls with MetS and in psoriasis patients with MetS, compared to controls without MetS. At the same time, serum leptin was significantly higher in psoriasis patients with MetS than in psoriasis patients without MetS. In this study, the serum concentration of IL-6 was not significantly different from the control values. This could mean that MetS influences serum adiponectin and leptin levels to a greater extent than psoriasis, which must be taken into account in the interpretation of experimental and clinical results. It should also be noted that the coefficients of variation for all investigated adipokines in every group were very high, which normally means that these groups were not homogeneous and that there should be additional hidden parameters to define the adipokine levels in serum.

Local levels of adipokines in sWAT in patients with psoriasis
The same authors also investigated the local adipokine levels in sWAT underneath the lesional psoriatic skin. They found that the local concentrations of adiponectin and TNF-α in sWAT were not statistically different between controls and the groups with psoriasis and/or MetS. The local concentration of leptin in sWAT was not different between the psoriasis group and controls, but significantly differed between the groups of psoriasis patients with and without MetS. Also, the local concentration of IL-6 in sWAT underneath the lesional psoriatic skin was significantly higher in controls than in patients with psoriasis. Fourteen out of 18 patients were treated with topical corticosteroids and vitamin D analogs, which were interrupted before the biopsy. This could have shifted the local concentrations of adipokines in sWAT at the moment of biopsy, compared with their levels in untreated patients.

Concurrently, another group revealed that the local adiponectin levels in human skin and in sWAT underneath the skin lesions were significantly lower in patients with psoriasis than in control subjects. This is in contrast to the results obtained by Mitsuyama et al, but correlates well with the anti-inflammatory properties of adiponectin and with the hypothesis of a local, not systemic, connection between adiponectin and psoriasis.

Adiponectin in innate immunity
Adiponectin was also recognized as a regulator of innate immunity. This function of adiponectin correlates with recent observations that dermal adipocytes are involved in the innate skin protection against infection. Infection of murine skin with S. aureus induced a quick proliferation of preadipocytes and a massive expansion of dermal adipose tissue thickness. At the same time, mice with impaired adipogenesis demonstrated reduced protection against S. aureus infection. Such a defense function was mediated through the high-level production of AMPs related to cathelicidin that were released by dermal adipocytes during early adipogenesis. From the above, it can be predicted that such an immune reaction should be strongly reduced in the case of psoriasiform dermatitis induced by imiquimod, since the dWAT is almost completely depleted in this model.

Taken together, we can note the growing evidence that skin inflammation in psoriasis is connected with the function of the adipose tissue. Such a connection appears to be primarily realized through a local interaction between the epidermis and underneath the dWAT layer.

Adipose tissue in PsA
Traditionally, psoriasis and PsA are considered to be autoimmune diseases that share some pathophysiological mechanisms involving T-cell reactions and differ mainly in their targets,
which are skin and synovial tissue, respectively. Contrarily, it was proposed that enthesopathies (disorders involving the attachment of tendons or ligaments to a bone), not an autoimmune reaction, could be the primary reason for PsA. Indeed, enthesitis (together with peripheral arthritis, axial disease and dactylitis) belongs to a typical manifestation of PsA, and it was even stated that PsA was more similar to undifferentiated spondyloarthopathy than to rheumatoid arthritis. Because of this, our discussion of the role of adipose tissue in PsA will take into account both synovial tissue and entheses.

**Structure of AATs**

The main joints known to be affected by PsA contain the localized fat pads (AATs) such as the Hoffa’s (infrapatellar) fat pad (IPFP) in the knee, the heel fat pad (HFP) or the anterior and posterior fat pads in the elbow. The adipose tissue is also localized on the tendon surfaces and in the bursa.

The IPFP is the AAT within the knee joint, which was investigated more in depth than other AATs. The IPFP was recently histologically described as sWAT of the lobular type with lobules covered by thick fibrous sheaths that produced baskets around the cells. In the IPFP, the lobules appear smaller and the fibrillary structure appears thicker than in the abdominal sWAT. This structure corresponds to the “fibrous” type of adipose tissue as described by Sbarbati et al and Bertossi et al. The HFP was also described as a “fibrous” AAT with small lobules of adipocytes covered by thick distinct fibrous shells.

The “fibrous” type of WAT, which appears to be typical for AATs, has better mechanical and, thus, protective properties than the “structural” type of WAT that contains less collagen around the adipocytes. At the same time, the “fibrous” WAT normally contains smaller adipocytes and should be more prone to inflammation.

**AATs as active arthritis units**

It was proposed that the IPFP should be considered as an active osteoarthritic joint tissue that can secrete interleukins and adipokcytokines. It was also stated that the IPFP has an inflammatory phenotype in patients with osteoarthritis and rheumatoid arthritis. Indeed, the IPFP volume positively correlates with knee cartilage volume and negatively correlates with the structural abnormalities in the synovium, which indirectly supports the anti-inflammatory role of the IPFP in knee osteoarthritis.

Interestingly, resection of the juxta-articular adiposis dolorosa (lipohypertrophy of the inner or outer parts of the knee joints) significantly reduced or even fully eliminated the joint pain.

The HFP structure in rheumatoid arthritis and in spondyloarthritis was also shown to be strongly modified, whereas this modification occurs more frequently in an inflammatory-edematous and less frequently in a degenerative-atrophic pattern, which means that foot arthritis correlates with inflammation in the HFP. It is, however, still not clear whether this is a primary or secondary effect of synovial inflammation and arthritis.

**Role of adipose tissue in enthesopathies**

Adipose tissue is also a common feature of normal enthesis, where it appears in enthesis itself as well as in the angle between the tendon/ligament and the bone. One of the most prominent adipose tissue pads that are associated with enthesis is the Karger’s (retromalleolar) fat pad (KFP) in the Achilles area. The KFP is composed of unilocular adipocytes that are separated by small bundles of elastic and collagen (type I) fibers that produce a structure similar to that of the HFP.

Adipose tissue was supposed to be involved in the pathophysiology of enthesopathies, similar to the involvement of the IPFP and HFP in joint inflammation in the knee and heel, respectively. Recently, it was demonstrated that KFP has an inflammatory phenotype and an altered lipid metabolism in patients with Achilles tendinopathy, compared with healthy controls. Adipocytes from such an inflammatory fat pad exhibit reduced lipolysis and adiponectin secretion but increased fatty acid β-oxidation.

Moreover, it was proposed that the inflammatory reaction in enthesis can be the primary reason for PsA. This inflammation can be caused by microtrauma, which is similar to the Koebner phenomenon in patients with psoriasis. Also, such inflammation can be caused by a proinflammatory reaction of the surrounding adipose tissue.

**Adipokine production in AATs**

AATs can express different adipokines with significantly different concentrations in controls and in subjects with arthritis. It was shown that the IPFP from osteoarthritic patients expresses higher levels of leptin and chemerin compared with healthy controls; rheumatoid IPFP secretes both pro- (IL-6, IL-8 and TNF) and anti-inflammatory (IL-1Ra) cytokines as well as the classical adipokines, leptin and adiponectin increases with the progressing stage of osteoarthritis. Recently, it was also demonstrated that the WNT1 inducible signaling pathway protein 2 in the IPFP is significantly increased in patients with osteoarthritis compared with control subjects. This adipokine can be involved in the crosstalk between the IPFP and the synovium,
since it regulates preadipocyte commitment and activates the master adipogenic factor peroxisome proliferator-activated receptor gamma,
which is essential for the production of mature adipocytes.

The role of adiponectin in joint diseases remains contradictory. Adiponectin was thought to have a protective effect in osteoarthritis.
Adiponectin levels in plasma and synovial fluid decrease significantly with the increased severity of osteoarthritis, which can indeed suggest a protective role of adiponectin in this disease. On the other hand, it was stated that adiponectin is involved in key pathways of inflammation and in matrix degradation in the joints.

**AMPs in psoriasis and PsA**

The expression of AMPs was incorporated into the pathogenesis of different autoimmune diseases. Such expression was investigated both in patients with psoriasis and PsA and was found to be different: whereas a broad spectrum of AMPs was detected in psoriatic skin, only some of these peptides were found in the synovium of PsA patients.

Cathelicidin (LL-37) generally demonstrates a proinflammatory effect; it attracts neutrophils, monocytes, T-cells, and mast cells, and it is known to be strongly upregulated in psoriatic skin. At the same time, nonlesional skin in psoriasis demonstrates a trend toward increased expression of cathelicidin, compared to healthy skin. Moreover, nonlesional psoriatic skin also exhibits the same upregulation of cathelicidin expression after barrier disruption as the original psoriatic lesions, which means that this reaction should be of a local and not a systemic nature. In this context, topical application of calcipotriol, which leads to significant reduction of IL-17 and a decrease in cutaneous inflammation, correlates with a sufficient increase of cathelicidin expression in psoriatic plaques.

It was proposed that the cathelicidins are involved in the pathogenesis of arthritis, since they were shown to be strongly upregulated in synovial membranes and in joints from humans and rats with rheumatoid arthritis. Interestingly, there are strong indications that vitamin D induces cathelicidin production and, thus, promotes innate immunity.

The connection between cathelicidin and adipose tissue may be much more intriguing than was previously thought. Very recently it was shown that cathelicidin can suppress lipid accumulation in adipocytes by the inhibition of the CD36 receptor, which indicates that this peptide is a modulator of adipogenesis. Indeed, serum cathelicidin protein levels were found to be significantly increased in nondiabetic obese patients compared with nondiabetic controls with normal body mass index values. Since the CD36 receptor not only facilitates the transport of long-chain fatty acids into cells but also binds many ligands including collagens, the production of cathelicidin in adipocytes can modulate not only the lipid content in adipocytes but also the extracellular matrix (ECM) in WAT. This means that the pathogens can modulate the whole structure of sWAT, especially of the superficial sWAT layer, dWAT.

**Role of collagen VI in psoriasis and PsA**

The ECM contains different types of collagen, including collagen type VI (COL6), which is known to be involved in various regulatory processes in the adipose tissue, bones, cartilage and skin. Different chains of COL6 are distinctly present in the skin. Whereas COL6a5 (also known as COL29a1) is present in the epidermis, COL6a3 is not found there. However, it is distributed throughout the dermis and is particularly abundant in the basement membrane at the epidermal–dermal interface. This interface is connected with the dermal ECM through a protein network containing COL1, COL4, COL5a1, COL6a3 and laminin-111.

Proteogenomic analysis revealed that the expression levels of COL1a1, COL1a2 and COL6a3 are strongly reduced both at the mRNA and the protein levels in papillary and reticular dermis from psoriatic plaques, compared with corresponding values in the nonlesional skin of psoriatic patients. Such a reduced expression of collagens in the lesional psoriatic skin should evidently impair the mechanical stability of the basement membrane and release the keratinocytes that are anchored to its opposite side. Both the hyperproliferation of keratinocytes and the structural modifications of the basement membrane in psoriatic plaques (splitting, excessive folding and production of large gap areas with reduced collagen content) are known as typical pathologic signs of psoriatic skin.

Whereas the expression of COL6 in the skin is mainly connected with fibroblasts, it is very doubtful that this process is fully independent of the state of COL6 in the underlying sWAT. First, sWAT is the most abundant source of COL6; it produces the pericellular fibrous structures around adipocytes. Consequently, its expression should be stronger in the “fibrous” type WAT. Expression of COL6 by the adipocytes cannot be spatially restricted only to sWAT and should be noticeable in the dermis at least several cell diameters away from the dermis/sWAT interface. Moreover, while dermal adipocytes can penetrate deep into the dermis...
and in some cases, can even reach the papillary dermis, this induction of COL6 should be present in a significant part of the dermis volume.

Second, COL6 not merely exerts structural functions, but can also act as a paracrine factor. This effect was shown in the process of mammary tumorigenesis.85 It should be noted that monocyte-derived macrophages are able to produce COL6 in a nonfibrillar form, which cannot be incorporated into the ECM, but appears to mediate cell–cell interactions and cell adhesions.86

Third, there is an interaction between fibroblasts and adipocytes from the underlying sWAT, which can significantly modulate the synthetic activity of these skin cells.87 From this point of view, collagen arrangement in the dermis and in the underlying sWAT should be considered as a single network, which additionally strengthens the role of the local sWAT in psoriasis.

Also, COL6 is involved in cutaneous innate immunity and different pathogens exhibit strong affinity for this collagen.88 COL6 has a very low triple helix content and is predominantly composed of globular von Willebrand factor type A domains.89 Peptides from these domains are able to display a dose-dependent antimicrobial activity.90

Very recently, it was demonstrated that COL6a3 knockdown in adipocytes leads to inflammatory resistance by the suppression of monocyte chemoattractant protein 1, which points to an interconnection between COL6 and inflammation.91 While systemic modification of COL6 content was shown to be generally connected with MetS,92 local modification of the adipose tissue ECM can be assumed to be significant in some skin pathologies. It was also shown that cathelicidin regulates myeloid cell accumulation in WAT and can thus promote insulin resistance.93 The realization of such a reaction locally in sWAT underneath the lesional psoriatic skin could mean the occurrence of a local pathologic condition corresponding to the appearance of the local “insulin resistive area”.94 In this context, it is noteworthy that patients with PsA but not rheumatoid arthritis have a significantly higher prevalence of MetS.94 As mentioned above, this prevalence is also higher in patients with PsA than in patients with psoriasis.8

Chondrocytes are also encapsulated by pericellular fibrosis, which in normal cartilage consists mainly of COL6.95 It was shown that aged COL6a1KO mice demonstrate progressive osteoarthritic joint degeneration.96 The lack of COL6 results in a loss of stiffness of the articular cartilage, which correlates with the results obtained in a previous study92 on the mechanical modules of WAT. Remarkably, strongly dysfunctional fibrillogenesis was found in the tendons of COL6a1KO mice.97

In summary, COL6 – the most important structural component of ECM in the adipose tissue – appears to be involved in a crosstalk between superficial WAT and the epidermis/papillary dermis. This collagen also influences the structure and stability of the protein network that bridges the basement membrane and the dermal ECM. On the other side, adipocytes should be considered as cells having a double participation in cutaneous innate immunity through COL6 expression and cathelicidin production.98 Future research should examine whether these two processes are interconnected.

Interaction of epidermal and dermal cells with adipocytes

The presence of spatially limited hyperproliferative epidermal areas in patients with psoriasis that are connected to the local modification of the superficial adipocytes located near the interface of the dermis/subcutis strongly suggests that these adipocytes must have an ability to influence fibroblasts and keratinocytes and induce their proliferation.11,98

Adipocytes can interact with fibroblasts and affect their synthetic function, and this interaction appears to be dependent on the adipocyte size. It was shown that enlarged adipocytes can significantly suppress the synthetic activity of co-cultured fibroblasts, whereas small adipocytes failed to do so.97 Adiponectin expression in adipocytes is also cell size dependent and is higher in smaller adipocytes,99,100 which should be more typical for “fibrous” type WAT.44 On the other hand, such an interaction in vivo can be realized through paracrine signaling only for the neighboring areas that contain fibroblasts and adipocytes, thus making the dWAT adipocytes the first choice for such a process.

The interaction of adipose tissue with skin cells is not limited to fibroblasts. Whereas IL-22 does not affect skin fibroblasts, endothelial cells or adipocytes, it can indeed interact with keratinocytes.22 Moreover, human keratinocytes can express adiponectin receptors, and adiponectin promotes both the proliferation and migration of these cells.27 Recently, it was shown that sWAT contains keratinocyte progenitor cells.101

Thus, adipocytes from the superficial sWAT layer can interact with the epidermal and dermal cells to modulate their synthetic activity and proliferation.

Conclusion

Local inflammation in WAT is an important step in the pathophysiology of psoriasis and PsA. dWAT is the nearest
to the epidermis adipose tissue depot and is the source of adipokines, keratinocyte progenitors, COL6 and AMPs, which are involved in the pathophysiology of psoriasis. Local production of adipokines and cathelicidin in dWAT underneath the lesional psoriatic skin can stimulate and regulate the local inflammatory cutaneous reactions. The production of COL6 can modulate the structure of the protein network that connects the basement membrane with the dermal ECM; the weakening of this structure influences the anchoring of keratinocytes and their release, thus contributing to epidermal hyperproliferation and modifications of the basement membrane that are typical in psoriasis. Similar processes should take place in PsA, whereas instead of dWAT, the corresponding AATs inside of the joints serve as the local sources of adipokines, AMPs and possibly COL6.

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