



The Dual Role of the TRAIL-DR5 Signaling Axis in Cardiovascular Disease: From Molecular Mechanisms to Targeted Therapies

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Abstract: The TRAIL-DR5 signaling axis exhibits a pronounced “double-edged sword” nature in cardiovascular diseases, embodying both deleterious and protective roles. On one hand, it contributes to pathology by promoting cardiomyocyte apoptosis and enhancing inflammatory responses, thereby driving the progression of conditions such as myocardial ischemia-reperfusion injury, atherosclerotic plaque destabilization, and heart failure. On the other hand, under specific contexts, TRAIL-DR5 signaling can exert protective effects through mechanisms including the regulation of angiogenesis, suppression of inflammation, and facilitation of tissue repair. This functional dichotomy likely stems from cell-type specificity, dynamic microenvironmental changes, and crosstalk with other signaling pathways—such as NF- κ B, MAPK, and autophagy-related processes. This review systematically examines the molecular mechanisms underlying TRAIL-DR5 signaling and its multifaceted involvement in acute myocardial infarction, heart failure, atherosclerosis, and atrial fibrillation. Furthermore, it explores targeted therapeutic strategies, including: DR5 agonists (such as monoclonal antibodies and small molecule compounds) for selective clearance of pathological cells; inhibitors (for instance, soluble DR5-Fc fusion proteins and siRNAs) to block deleterious signaling; and combination therapies (eg, with kinase inhibitors) to achieve synergistic efficacy. We propose that future investigations should prioritize the development of highly specific biomarkers, the refinement of targeted delivery systems, and a deeper mechanistic understanding of cellular and disease-stage heterogeneity. Such advances will be essential to propel the field from broad-spectrum treatments toward precision interventions, offering innovative solutions for complex cardiovascular disorders.

Keywords: TRAIL-DR5 signaling axis, cardiovascular disease, inflammasome response, targeted therapy, molecular mechanisms

Introduction

Cardiovascular disease (CVD) remains the leading cause of global mortality, posing a significant burden on healthcare systems worldwide.^{1,2} Despite advances in management strategies, including revascularization and pharmacotherapy, critical challenges persist. These include: (1) Irreversible myocardial cell damage: Myocardial cell apoptosis is a key mechanism underlying myocardial injury post-infarction.^{3,4} (2) Inflammasome imbalance: Excessive inflammatory responses following cardiovascular injury, exacerbate tissue damage.^{5,6} (3) Insufficient tissue repair: Functional angiogenesis and endothelial-pericyte interactions are crucial for effective repair.⁷ This multifactorial complexity is likely linked to heterogeneous activation of the tissue microenvironment, receptor expression patterns, and downstream signaling events. So, it is highlighting the urgent need for novel therapeutic targets that can precisely modulate these pathological processes.

The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and its death receptor 5 (DR5) pathway, initially characterized for its anti-cancer potential, has emerged as a key regulatory axis in CVD. Intriguingly, current evidence reveals a complex, context-dependent “double-edged sword” role for TRAIL-DR5 signaling in the cardiovascular system.^{8–11} It can exacerbate injury by promoting apoptosis and inflammation in conditions like myocardial infarction,^{5,12} preclinical studies confirm that elevated TRAIL levels correlate with increased apoptosis, and DR5 is

upregulated in ischemic myocardium, amplifying cell death signals.¹³ Otherwise, high glucose or inflammatory cytokines boost TRAIL and DR5 expression, promoting apoptosis in cardiomyocytes and endothelial cells, accelerating plaque instability, and enhancing fibrosis.^{14,15} In Alzheimer's-related vascular impairment, TRAIL-DR5 activation may damage the neurovascular unit via apoptosis.¹⁶ Clinically, high serum TRAIL in acute stroke patients predicts poorer short-term outcomes, underscoring its pathological relevance.¹⁷

Paradoxically, however, it also demonstrates protective effects by enhancing vascular stability, resolving inflammation, and facilitating repair in other contexts.^{5,18–20} Animal studies also show that blocking TRAIL-DR5—eg, with sDR5-Fc fusion protein—attenuates viral myocarditis and COVID-19-related cardiovascular complications.^{14,21} In summary, this functional dichotomy suggests immense therapeutic potential but also underscores the risk of unintended consequences if targeted without a deep understanding of its nuanced biology.

While several reviews have extensively covered the role of TRAIL-DR5 in oncology, a comprehensive synthesis focusing on its dual and often contradictory roles across various cardiovascular diseases is notably lacking. Existing literature on this topic is fragmented, often focusing on a single disease entity, and has not adequately addressed the mechanistic basis for its opposing functions or the translational barriers specific to CVD. Therefore, this review is designed to fill this gap. We aim to provide a systematic and updated examination of the TRAIL-DR5 signaling axis, with a specific focus on: its intricate molecular mechanisms; its multifaceted and paradoxical roles in key CVDs (AMI, heart failure, atherosclerosis, atrial fibrillation); the latest advances in targeted therapeutic strategies, including agonists, inhibitors, and combination therapies.

By integrating these aspects, this review seeks to offer a foundational resource for understanding the TRAIL-DR5 pathway in CVD and to propel the development of novel, effective, and safe therapeutic interventions.

Molecular Mechanism of TRAIL-DR5

TRAIL Ligands and Their Receptor Family

TRAIL is a member of the TNF superfamily and functions as a type II transmembrane protein. This protein can be proteolytically cleaved into a soluble trimeric form. It is predominantly secreted by immune cells, such as natural killer (NK) cells and T lymphocytes, playing a critical role in immune surveillance.^{22–24} The receptor family of TRAIL comprises two types of receptors with opposing functions: death receptors (DR4/DR5) and decoy receptors (DcR1/DcR2/OPG). These receptors collectively regulate the biological activities of TRAIL.^{25,26}

Both DR4 and DR5 possess an intracellular Death Domain (DD), which upon TRAIL binding induces receptor trimerization. This process recruits Fas-associated death domain (FADD) protein and caspase-8/10 to form the death-inducing signaling complex (DISC), thereby activating the caspase cascade and ultimately leading to apoptosis.^{25,27} While the two receptors exhibit partial functional redundancy, certain tumors may preferentially rely on either DR4 or DR5 for mediating apoptosis.^{28,29}

Decoy receptors modulate the biological activity of TRAIL by binding to it without transmitting apoptotic signals. Owing to the absence of an intracellular domain, DcR1 is tethered to the cell membrane via glycosyl phosphatidylinositol (GPI) and competitively inhibits TRAIL from binding to DR4/DR5.^{30,31} DcR2, which contains an incomplete intracellular death domain, suppresses Caspase activation while activating pro-survival pathways such as NF- κ B.^{31,32} Osteoprotegerin (OPG), the sole soluble receptor, primarily binds to TRAIL, thereby preventing its interaction with membrane-bound receptors and playing a critical role in bone metabolism and the tumor microenvironment.³³

TRAIL-DR5-Mediated Signaling Pathway

At present, the signal pathways mediating apoptosis by TRAIL-DR5 can be mainly divided into three categories: exogenous apoptotic pathway, mitochondrial apoptotic pathway and other cross-signaling pathways (Figure 1).

DR5-Mediated Apoptosis Pathway

As a homotrimeric ligand, TRAIL specifically binds to the DR5 receptor on the surface of the cell membrane. This binding is highly selective, but the affinity of DR5 for TRAIL may be affected by the glycosylation status of the receptor or the cell type. TRAIL binding induces the formation of a homotrimer of the DR5 receptor, leading to a conformational

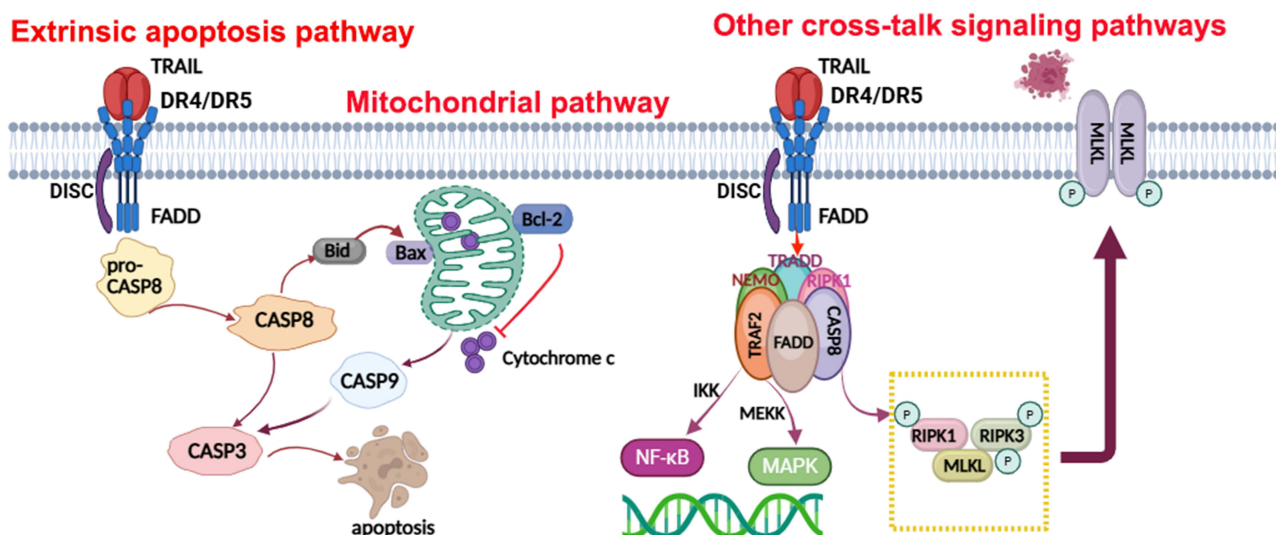


Figure 1 TRAIL-DR5-mediated apoptosis signaling pathway. Activation of DR4 and DR5 by TRAIL induces the extrinsic apoptosis pathway, which is triggered by a variety of stimuli and leads to the release of proapoptotic proteins from the mitochondria, thereby initiating the mitochondria-mediated apoptotic process. The two pathways interact upon the activation of caspase-8. Specifically, caspase-8 can activate initiator caspases such as caspase-3, which subsequently induces apoptosis. Alternatively, caspase-8 can also activate the mitochondrial mechanism of apoptosis through the cleavage and activation of Bid. In addition to the aforementioned classical apoptotic signaling pathways, the TRAIL-DR5 signaling axis also activates a range of additional signaling mechanisms that facilitate cell survival, proliferation, migration, or inflammatory responses. For instance, within the DR5 complex, the recruitment of receptor-interacting protein kinase 1 (RIPK1) constitutes a pivotal event in non-apoptotic signaling. Furthermore, non-apoptotic signals mediated by DR5 can promote inflammatory responses and cell survival via the NF- κ B pathway. In addition, there are complex cross-interactions among various signaling pathways, including protein kinase B (Akt) and mitogen-activated protein kinases (MAPK), such as extracellular signal-regulated kinase 1/2 (ERK1/2).

change in its intracellular DD, which subsequently recruits the adaptor protein FADD to interact with the DD of DR5 via its C-terminal DD. The N-terminal Death Effector Domain (DED) of FADD further recruits DED containing pro-caspase 8 or pro-caspase 10 to form the DISC complex.³⁴ In DISC, pro-caspase 8 is activated via a proximity-induced self-cleavage mechanism to generate the enzymatically active caspase 8 (or caspase 10). Activated caspase 8 clears downstream effector caspases (such as caspase 3, 6, and 7), triggering their activation, and directly degrades key cellular structural proteins (such as lamin and cytoskeletal proteins) and DNA repair enzymes (such as PARP), leading to cell apoptosis.^{35,36}

In some cases, activated caspase 8 specifically cleaves BH3-only protein Bid to generate a truncated form of tBid.³⁷ Through its BH3 domain, tBid interacts with pro-apoptotic proteins of the Bcl-2 family, such as Bax/Bak, inducing their oligomerization and formation of pores in the outer mitochondrial membrane.³⁸ Mitochondrial outer membrane permeabilization (MOMP) leads to the release of cytochrome c (Cyt c) from the mitochondrial membrane space to the cytoplasm, which may be accompanied by the release of other pro-apoptotic factors (such as Smac/DIABLO).³⁹ Cyt c in the cytoplasm binds to Apaf-1 and forms apoptosome in the presence of dATP, which recruits and activates caspase-9.⁴⁰ Activated caspase 9 further clears downstream effector caspases, such as Caspase-3/7, to execute apoptosis. This process significantly amplifies apoptotic signals through a protease cascade. In some cells, even in the absence of caspase 9, the mitochondrial pathway can induce apoptosis through other effector molecules, such as caspase 2 or the alternative pathway.⁴¹

TRAIL-DR5-Mediated Non-Apoptotic Signal Transduction Pathways

In addition to the classical apoptotic signaling pathways described above, the TRAIL-DR5 signaling axis activates a range of other signaling mechanisms that promote cell survival, proliferation, migration, or inflammatory responses. For example, in the DR5 complex, the recruitment of receptor-interacting protein kinase 1 (RIPK1) is a central event in non-apoptotic signaling. The antibody drug AMG655 (Conatumumab) could activate RIPK1 in the DR5 complex in either sensitive or resistant cells, thereby triggering pro-survival and pro-proliferation effects.⁴² NK (c-Jun N-terminal kinase) has been shown to promote the transcription of DR5 by phosphorylating transcription factors such as c-Jun. 7-methoxy-esculetin significantly up-regulates the expression of DR5 mRNA and protein by activating JNK pathway, thereby enhancing the killing effect of TRAIL on colon cancer cells.⁴³

Similarly, 6-MS, a chemotherapeutic agent, upregulates DR5 expression through JNK-dependent oxidative stress pathway and enhances TRAIL-induced apoptosis in liver cancer cells.⁴⁴ In addition, basal ERK activity can inhibit DR5 expression, while ERK inhibition (eg, PD98059) or ERK gene knockdown can significantly enhance the expression of DR4 and DR5 by relieving the negative regulation of DR5 by ERK.^{45,46} In glioblastoma, the combination of ERK inhibitor and TRAIL enhanced apoptosis by upregulating DR5.⁴⁷

DR5 non-apoptotic signaling can also mediate inflammatory responses and cell survival through the NF- κ B pathway. In DcR2 knockdown tumor cells, TRAIL stimulation significantly enhanced the activity of NF- κ B, suggesting a direct or indirect association between DR5 signaling and NF- κ B.⁴⁸ In pancreatic β cells, glucocorticoid-induced upregulation of TRAIL and DR5 expression activates NF- κ B and is accompanied by the release of pro-apoptotic proteins (such as BAX, caspase-8/3) and inflammatory mediators, which further leads to cellular dysfunction.⁴⁹ In addition, studies have shown that TRAIL-induced ERK and p38 activities are significantly enhanced after knocking down DcR2, suggesting that DR5 signaling may cooperate with other receptors to regulate the MAPK pathway.⁴⁸

Paradoxical Role of TRAIL-DR5 Signaling Axis in Cardiovascular Diseases

Recent studies have shown that circulating TRAIL may have important value in the prognosis evaluation of cardiovascular diseases. A prospective cohort study in the elderly population⁵⁰ found that plasma TRAIL level was negatively correlated with all-cause mortality, especially for cardiovascular death, while non-cardiovascular mortality did not show statistically significant association. Although the research in this field is still in the early stage, TRAIL and its death receptor DR5 have shown potential value, such as a new biomarker for cardiovascular events. However, the existing evidence mainly comes from observational studies, and it is still necessary to verify its clinical transformation value through large-scale cohorts and further clarify its specific regulatory mechanism in different cardiovascular disease subtypes (Figure 2, Table 1 and Table 2).

Dual Role of the TRAIL-DR5 Axis in Acute Myocardial Infarction (AMI)

AMI is a serious cardiovascular disease caused by acute complete or incomplete occlusion of the coronary artery, leading to myocardial ischemia and necrosis. Current studies have shown that the role of TRAIL-DR5 signaling axis in AMI involves multiple pathophysiological links, including the regulation of myocardial cell apoptosis, neutrophil-mediated inflammatory response and ischemia-reperfusion injury. A systematic screening study of 92 cardiovascular and inflammation-related biomarkers⁵⁸ found that soluble DR5 (sDR5) had the strongest predictive power for long-term all-cause mortality risk in patients with AMI. This finding suggests that high or low levels of circulating DR5 may be associated with poor prognosis. In addition, serum TRAIL levels within 72 hours after AMI onset were significantly negatively correlated with peak creatine kinase (CK-MB) and also negatively correlated with B-type natriuretic peptide (BNP), suggesting that it may play a protective role by antagonizing the ventricular remodeling process.⁵⁷ These evidences suggest that reduced serum TRAIL levels after myocardial infarction may be detrimental to prognosis. However, these changes in circulating TRAIL may not be specific to the heart and may also be associated with other ischemic events such as ischemic stroke.⁶⁹ In addition, although many studies have shown that TRAIL is down-regulated in the serum of AMI patients,^{58,59} the expression level of TRAIL in peripheral blood mononuclear cells (PBMCs) (mainly CD4⁺ and CD14⁺) is up-regulated in the acute phase of AMI patients,⁷⁰ indicating that immune cells may be an important source of TRAIL in AMI.

In addition, the high expression of DcR2 in normal cardiomyocytes may inhibit the pro-apoptotic effect of TRAIL, while the up-regulation of DR5 may enhance the sensitivity to apoptosis in I/R injury.⁷¹ During AMI, myocardial ischemia and hypoxia cause TRAIL to bind to DR5, activate the caspase cascade, induce cardiomyocyte apoptosis, and aggravate myocardial injury.⁵¹

Heart Failure (HF)

HF is a complex clinical syndrome characterized by the inability of the heart to pump blood efficiently to meet systemic metabolic demands or to maintain pumping function only when filling pressure is elevated. The causes of heart failure include coronary heart disease, hypertension, cardiomyopathy, etc. According to a clinical study on non-ischemic cardiomyopathy, the plasma TRAIL concentration of patients was increased, which was positively correlated with left

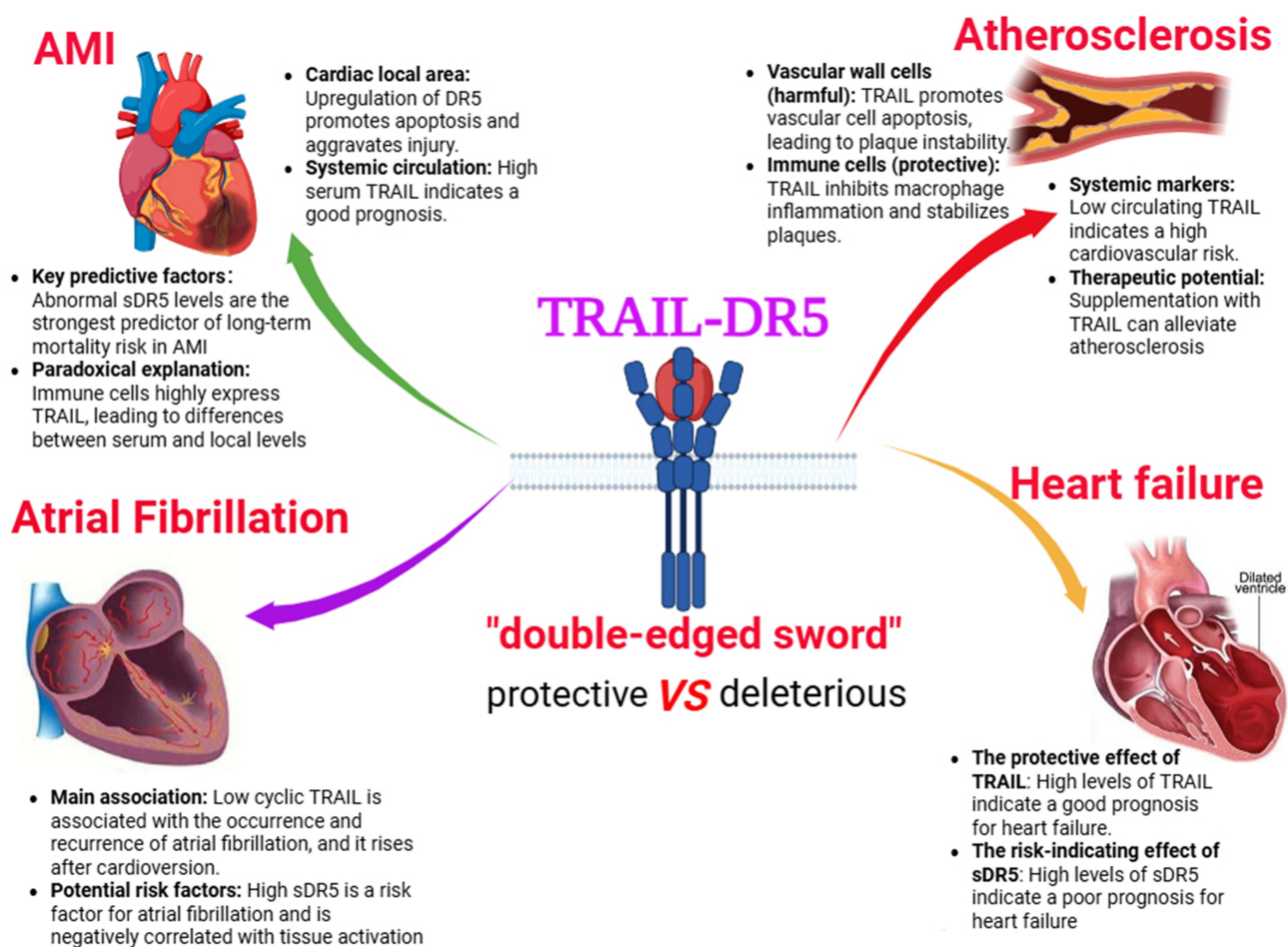


Figure 2 Paradoxical role of TRAIL-DR5 signaling axis in cardiovascular diseases. The TRAIL-DR5 signaling axis presents a complex and contradictory role in cardiovascular disease. Studies have shown that circulating TRAIL levels correlate with cardiovascular disease prognosis: reduced serum TRAIL levels in patients with acute myocardial infarction (AMI) correlate with poor prognosis, whereas soluble DR5 (sDR5) has a significant predictive potency for long-term mortality risk, suggesting its potential as a novel biomarker. Notably, peripheral blood immune cell TRAIL expression is upregulated during AMI, whereas cardiomyocyte DR5 upregulation enhances apoptosis susceptibility and exacerbates ischemia-reperfusion injury. In heart failure (HF), elevated plasma TRAIL was associated with reduced mortality and may exert a protective effect by inhibiting apoptosis or promoting cell proliferation, but elevated DR5 levels were associated with deterioration of left ventricular function, demonstrating an inverse ligand-receptor regulatory feature. In atherosclerosis, TRAIL action shows tissue specificity: in vascular endothelial/smooth muscle cells it may induce apoptosis to promote plaque instability, whereas in macrophages it inhibits inflammation and improves cholesterol metabolism. Circulating TRAIL levels are reduced after ablation in patients with atrial fibrillation (AF), and elevated sDR5 is associated with the risk of AF recurrence, suggesting its involvement in the electrical remodeling process. However, the existing evidence mainly originates from observational studies, and further validation of its clinical value through large-scale cohorts is needed in the future, as well as elucidation of the tissue-specific regulatory mechanisms and bidirectional roles of the signaling pathways (pro-apoptotic and non-apoptotic effects), to provide a theoretical basis for precision therapy.

ventricular diastolic diameter. The expression of TRAIL was detected in the ento-myocardial biopsy of patients, and the TRAIL gene in the peripheral blood leukocytes of patients was up to the surface.⁷² In addition, a study of 351 patients with advanced HF found that elevated sTRAIL levels were associated with a 70% reduction in all-cause mortality, possibly by exerting a protective effect through inhibition of apoptosis or promotion of cell proliferation, associated with β -blocker use.⁶⁰ Other studies using proteomics in two community-based elderly cohorts, PIVUS cohort (n=901, median age 70.2 years) and ULSAM cohort (n=685, median age 77.8 years), found that soluble DR5 was associated with deterioration of left ventricular systolic function. It is a risk factor for the development of heart failure, but the specific mechanism is not clear.⁶¹ However, the study had a limitation that the sample size was not large enough to determine causality. A clinical study on heart failure with preserved ejection fraction (HFpEF) found that plasma TRAIL was determined to be negatively correlated with prognosis, while soluble DR5 was positively correlated.⁶² Circulating DR5 is elevated in heart failure patients with poor left ventricular ejection fraction and diastolic function, but it is positively correlated with disease incidence.⁶¹ In contrast, a prospective observational study showed no difference in TRAIL levels

Table 1 Summary of the Roles in Various Cardiovascular Cells

Cell Type	Detrimental Role	Protective Role	Key Mechanisms
Cardiomyocytes	Inducing apoptosis and exacerbating myocardial injury (such as in AMI or I/R) ^{5,12,51}	It may induce physiological hypertrophy and improve contractile function by activating non-apoptotic signals (such as EGFR/ERK1/2) ⁵²	Apoptosis: Activation of Caspase-8/3 cascade. ^{35,36} Protection: ERK1/2 activation, EGFR transactivation ⁵²
Endothelial Cells	Promotes apoptosis and impairs vascular function in a high-glucose environment ^{13,18}	It is the main source of TRAIL in the healthy cycle and is crucial for generating stable microvessels under ischemic conditions. ¹⁸	Apoptosis: Apoptosis mediated by the classic DISC. Protection: Promoting vascular stability and repair.
Macrophages	May promote the formation and apoptosis of foam cells and exacerbate the formation of plaque necrotic cores ¹³	Anti-inflammatory: TRAIL-deficient macrophages are more inflammatory, with poor exocytosis and cholesterol handling capabilities; TRAIL can inhibit intra-plaque inflammation. ⁵³ Pro-clearance: Monocytes/macrophages expressing TRAIL are crucial for alleviating atherosclerosis ⁵³	Apoptosis: Receptor activation leads to apoptosis. Protection: Inhibit the release of inflammatory factors, improve cholesterol metabolism, and enhance migration ability.
Neutrophils	Promote neutrophil infiltration and the formation of neutrophil extracellular traps (NETs), exacerbating I/R injury ⁵	/	Activation of DR5 exacerbates the inflammatory response, leading to more neutrophil recruitment and NETosis ⁵
Vascular smooth muscle cells (VSMCs)	/	Promote survival, migration and proliferation, contribute to neointimal hyperplasia pathological hyperplasia ⁵⁴⁻⁵⁶	Non-apoptotic signals: driving proliferation through the NF-κB and insulin-like growth factor-I receptor (IGF-IR) pathways ⁵⁶

Table 2 The Paradoxical Role of the TRAIL-DR5 Signaling Axis in Cardiovascular Diseases

Type of diseases	Protective Role	Detrimental Role	Molecular mechanisms	Clinical significance/ Biomarkers
Acute myocardial infarction (AMI)	Serum TRAIL levels are negatively correlated with peak CK-MB and BNP, and may antagonize ventricular remodeling, which is beneficial for prognosis ⁵⁷	Myocardial ischemia and hypoxia promote the binding of TRAIL to DR5, activate the Caspase cascade, induce myocardial cell apoptosis, and aggravate the damage ⁵¹	Harmful: Increased DR5 in cardiomyocytes activates the extrinsic apoptotic pathway	sDR5: The strongest predictor of long-term all-cause mortality. ⁵⁸ Serum TRAIL: Associated with poor prognosis. ^{58,59}
Heart failure (HF)	Increased plasma TRAIL concentration is associated with a 70% reduction in all-cause mortality, possibly related to inhibiting apoptosis or promoting proliferation, and with beta-blocker use. ⁶⁰	The level of soluble DR5 (sDR5) is positively correlated with the deterioration of left ventricular systolic function and the risk of heart failure. ⁶¹	Protective: May act through non-apoptotic signals (such as promoting survival and proliferation). Harmful: DR5 activates the pro-apoptotic pathway.	TRAIL / sDR5: May be associated with a better prognosis. ^{60,62} sDR5: Risk factor for heart failure ⁶¹
Atherosclerosis (AS)	TRAIL-deficient macrophages exhibit enhanced inflammation and impaired function; exogenous TRAIL alleviates atherosclerosis, reduces macrophage content in plaques, and diminishes inflammation ^{53,63}	TRAIL induces neointimal hyperplasia by promoting the proliferation and migration of vascular smooth muscle cells (VSMCs); ^{55,56} it may induce apoptosis of endothelial cells/ VSMCs and promote plaque instability.	Protection: Macrophages inhibit inflammation, improve cholesterol metabolism. Harmful effects: VSMCs/ endothelial cells promote proliferation/apoptosis, induce inflammation.	Circulating TRAIL levels: associated with newly formed AS plaques in patients with chronic kidney disease. ⁶⁴ It may serve as a potential biomarker. ¹⁵
Atrial Fibrillation (AF)	The circulating TRAIL level decreases after successful ablation of AF; ⁶⁵ the TRAIL level is lower during the acute attack phase and increases after the maintenance of sinus rhythm ⁶⁶	sDR5 is a biological marker related to AF, and its elevated level is considered a risk factor for AF ⁶⁷	Abnormal expression of TRAIL receptors may impair the immune system's ability to clear damaged cardiomyocytes, leading to abnormal electrical and structural remodeling. ²⁴	TRAIL cardiac gradient (coronary sinus - aortic root): negatively correlated with AF recurrence ⁶⁸ sDR5: associated with AF risk ⁶⁷

in heart failure patients treated with cardiac resynchronization therapy, and TRAIL levels did not predict mortality.⁷³ These studies indicate that decreased ligand levels and increased nuclear receptor levels may be associated with worse prognosis in the disease, suggesting a possible beneficial role for TRAIL signaling.

The activation of TRAIL pathway has been implicated in the development and progression of HF, but the mechanism by which TRAIL exerts cardio-protection has not been fully elucidated. One idea is that higher levels of TRAIL may reflect the need to resolve inflammation due to TRAIL-induced apoptosis,⁶² but data from animal models actually suggest the opposite. Injection of recombinant TRAIL significantly reduced myocardial fibrosis and apoptosis and, therefore, prevented more relevant cardiac structural changes in a mouse model of cardiomyopathy.⁷⁴ In this study, it was proposed that, in contrast to its pro-apoptotic effect, it may be the result of triggering non-apoptotic signals in normal cells (promoting survival, migration, and proliferation of primary vascular smooth muscle cells.^{54,75} Therefore, TRAIL and TRAIL receptors may serve as potential biomarkers for HF and predict the prognosis and mortality of patients; However, more studies are needed to confirm these.

Atherosclerosis

Atherosclerosis refers to the thickening and hardening of the arterial wall, loss of elasticity and narrowing of the lumen, and the appearance of yellow atheroma of lipids accumulated on the intima of the artery. TRAIL and its receptors, such as DR5, are closely related to the pathological process of atherosclerosis. In response to perivascular cuff injury, *Trail*^{-/-} mice had reduced neointimal hyperplasia compared with *Trail*^{+/+} mice, and recombinant TRAIL delivery restored neointimal thickening,⁵⁵ a finding supported by in vitro studies using human VSMCS.⁵⁶ These findings suggest that TRAIL may contribute to the development of early atherosclerosis. In addition, meta-analysis showed that changes in circulating TRAIL or DR5 levels may be associated with mortality or risk of cardiovascular events in patients with atherosclerosis, suggesting its possibility as a potential biomarker.¹⁵ In patients with chronic kidney disease, a 24-month follow-up study found that low levels of circulating TRAIL were associated with the emergence of new atherosclerotic plaques.⁶⁴ However, TRAIL levels measured in coronary arteries from patients with stable angina or a positive noninvasive ischemia test showed an inverse correlation with TRAIL levels in the necrotic core of atherosclerotic plaques, and TRAIL levels were also reduced in the fibrofatty component of atherosclerotic plaques, although the decrease was small.⁷⁶ Preclinical studies have also shown that TRAIL may play a protective role in atherosclerosis by inhibiting intra-plaque inflammation or regulating cell survival, such as reducing intra-plaque macrophage infiltration or enhancing fibrous cap stability.¹³ DcR1 and DcR2 may regulate TRAIL signaling through competitive binding and affect the balance between cell survival and death in the plaque.³⁵ TRAIL-deficient macrophages are more inflammatory, have poor exocytosis, impaired cholesterol processing, and reduced migration, which are hallmarks of macrophage dysfunction in lesions and accelerate atherosclerosis.⁵³ In contrast, pretreatment with exogenous TRAIL increased lipid uptake and foam cell formation, and resulted in macrophage apoptosis. There may be cross-regulation of TRAIL receptor signaling with other inflammatory pathways, such as NF-κB or TLR pathways. For example, TRAIL-activated FADD complex can promote NF-κB signaling, which in turn affects the expression of inflammatory factors (such as IL-6 and TNF-α) and aggravates the progression of atherosclerosis.⁷⁷ At the same time, TRAIL may affect monocyte infiltration by regulating endothelial cell function (such as adhesion molecule expression) and participate in early plaque formation.⁷⁸ In diabetic *Apoe*^{-/-} or *Trail*^{-/-} *apoe*^{-/-} mice, TRAIL protein, TRAIL gene therapy, or TRAIL bone marrow transplantation attenuated the development of atherosclerosis, reduced the content of macrophages in the vessel wall, and reduced inflammation.^{53,63} In conclusion, TRAIL activates the apoptotic signaling pathway by binding to death receptors, but its role in atherosclerosis may be tissue specific. In vascular endothelial cells or smooth muscle cells, TRAIL may promote plaque instability (such as fibrous cap thinning) by inducing apoptosis; While in immune cells (such as macrophages), TRAIL may inhibit the release of proinflammatory factors, thereby reducing the local inflammatory response.

Atrial Fibrillation (AF)

AF refers to the loss of regular and orderly atrial electrical activity, which is replaced by rapid and disordered fibrillation waves. It is a serious disorder of atrial electrical activity. At this time, the atrium loses effective contraction and relaxation, and blood is easy to stasis in the atrium, which increases the risk of thrombosis. AF promotes tissue fibrosis and is an important cause of AF recurrence, drug resistance and complications.^{79,80} A prospective observational study

found that circulating TRAIL levels were reduced in patients with successful ablation of AF,⁶⁵ in contrast, patients with acute episodes of AF had lower circulating TRAIL levels and increased TRAIL levels after sinus rhythm maintenance.⁶⁶ In addition, abnormal TRAIL receptor expression may impair the immune system's ability to clear damaged cardiomyocytes, leading to abnormal electrical and structural remodeling.²⁴ Some clinical studies have reported that TRAIL levels were decreased in patients with AF after electrical cardioversion and during six-month follow-up when TRAIL concentrations were measured on the cardiac gradient (coronary sinus concentration minus aortic root concentration), indicating that the gradient was negatively correlated with AF recurrence, but there was no difference in plasma TRAIL levels.⁶⁸ In addition, a cardiovascular biomarker screening study found that sDR5 is one of the markers associated with AF in patients with AF. DR5 lacks the intracellular domain required for initiating signaling, so circulating DR5 levels are considered to be negatively correlated with DR5 activation at the tissue level. Therefore, DR5 is considered as a risk factor for AF.⁶⁷ However, based on the current research, whether TRAIL and its receptors can be used as prognostic factors or biomarkers needs to be further elucidated.

Intervention Strategies Targeting TRAIL-DR5 Signaling Axis in Cardiovascular Related Diseases

The clinical relevance of many of the current studies on the cardiovascular effects of TRAIL-DR suggests both protective and detrimental effects depending on the study and the disease. This may vary depending on the type of cardiovascular disease being studied. Interventional strategies targeting the TRAIL-DR5 axis have potential for multidirectional regulation in cardiovascular disease, such as agonists to remove diseased cells through selective activation of apoptotic pathways; inhibitory interventions to protect the myocardium by blocking pathological signaling; and combination therapies to enhance the efficacy of therapy through multi-target synergy. However, there are no drugs on the market for this target yet (Figure 3 and Table 3).

Agonist Development - Enhancing Pro-Apoptotic Signaling

Monoclonal antibodies against DR5, such as Drozitumab, induce apoptosis by activating death receptor signaling pathways and have shown selective killing potential especially in cancer therapy, but their application in cardiovascular diseases still needs to be optimized for improved efficacy.⁸¹ Multivalent ligands, such as MEDI3039. MEDI3039 is a multivalent ligand. By enhancing the cross-linking efficiency of the DR5 receptor, it significantly improves its activation ability, thereby demonstrating stronger pro-apoptotic activity in preclinical models. Its effect does not depend on the classic FADD/caspase-8 pathway, but promotes apoptosis through an atypical RIPK1-dependent signaling pathway, and can still effectively activate DR5 especially in drug-resistant cells.⁸² This class of drugs can selectively remove inflammatory cells in atherosclerotic plaques and reduce plaque instability. In addition, the bifunctional protein SRH-DR5-B achieves the synergistic effect of DR5 receptor-mediated tumor cell apoptosis and vascular targeting by fusing the specific peptide of VEGFR2, providing a new idea for the treatment of abnormal vascular proliferation in cardiovascular diseases.⁸²

Small-molecule DR5 agonists, such as Bioymifi, selectively activate DR5 and promote cell apoptosis by mimicking the natural TRAIL domain-activated receptor. Their advantages are high oral bioavailability and strong penetration, and they have shown the potential to enhance stem cell activity in intestinal organoid models.⁸⁸ In addition, studies have shown that the combination of Bioymifi and chemotherapy drugs (such as doxorubicin) can synergistically enhance the sensitivity of vascular endothelial cells and smooth muscle cells to apoptosis, especially in inhibiting vascular remodeling.^{13,15} Studies have demonstrated that the treatment of cardiomyocytes with TRAIL or Bioymifi can promote cardiomyocyte hypertrophy through the activation of the ERK1/2 signaling pathway and transactivation of the epidermal growth factor receptor (EGFR). This form of hypertrophy is characterized in animal models by increased heart weight, thickened ventricular walls, and improved contractile function, which suggests that it may represent a physiological compensatory response rather than a pathological condition. Nevertheless, further research is required to determine whether prolonged activation of these pathways leads to pathological cardiac remodeling.⁵² Treatment of wild-type mice with MD5-1 (agonizing mDR5 mAb) resulted in an increase in heart weight and cardiomyocyte area, in part through

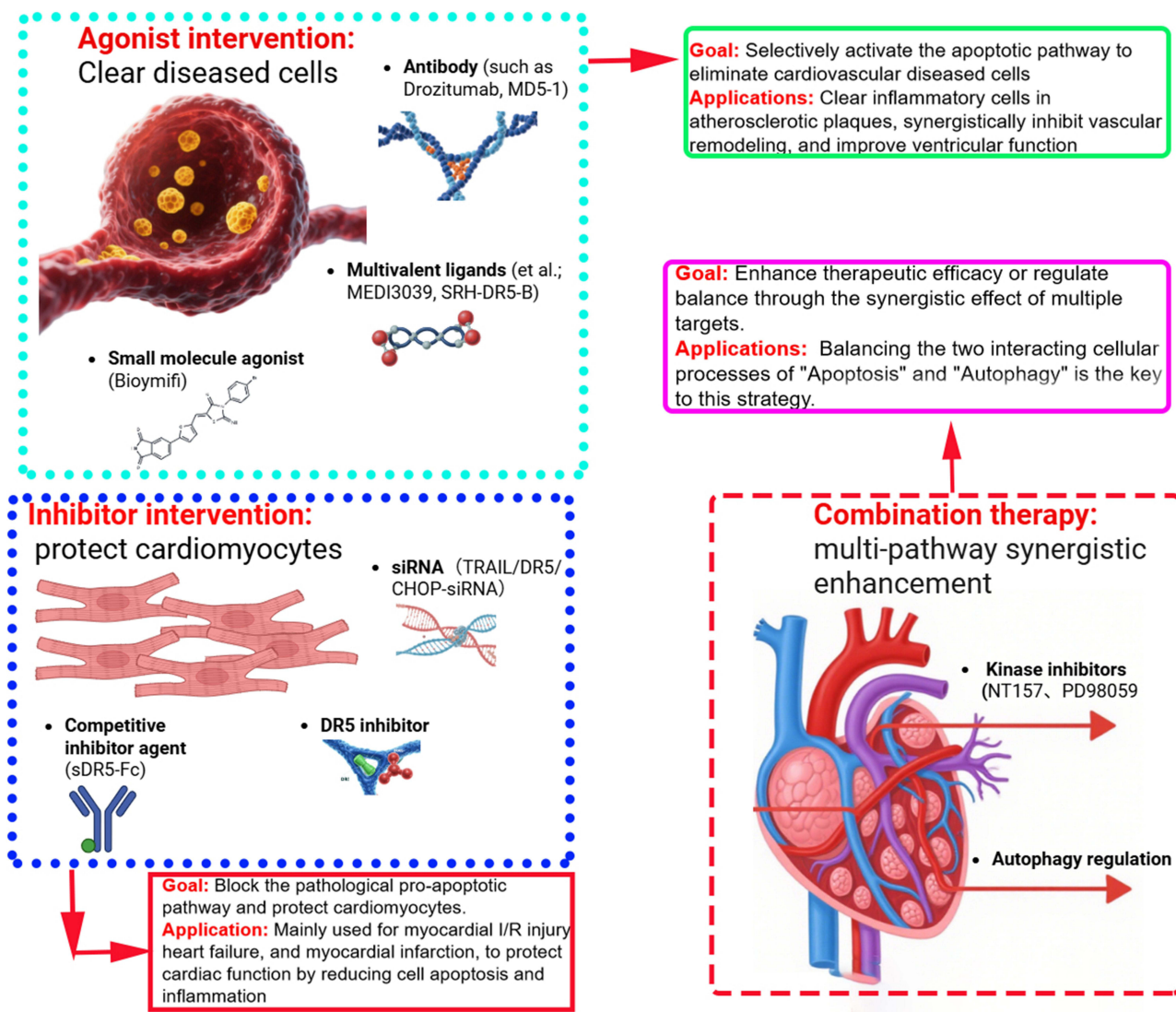


Figure 3 Intervention strategies targeting TRAIL-DR5 signaling axis in cardiovascular related diseases. Targeting the TRAIL-DR5 signaling axis has demonstrated multidimensional intervention potential in cardiovascular disease therapy, with strategies that can be categorized into agonist activation, inhibitory blockade, and combination therapies, which need to be combined with the stage of the disease and the cell type to achieve precise modulation. Agonist development focuses on selective clearance of diseased cells: monoclonal antibodies (eg, Drozitumab) and multivalent ligands (eg, MEDI3039) induce apoptosis in inflammatory cells by enhancing DR5 cross-linking, but cardiac targeting needs to be optimized to minimize off-target effects; small-molecule agonists (eg, Bioymifi) are highly utilized orally but may activate the ERK1/2 pathway and lead to myocardial hypertrophy; engineered DR5-scFv sEVs clear pro-inflammatory macrophages by targeted delivery, but clinical translation requires validation of specificity. Inhibitory interventions protect the myocardium by blocking TRAIL-DR5 signaling in myocardial ischemia or heart failure, eg, sDR5-Fc competitive binding of TRAIL improves cardiac function, and DR5 inhibitors reduce apoptosis in the infarct zone by 45%, but timing of blockade needs to be weighed to avoid impaired inflammatory clearance. Combination therapy enhances efficacy by synergistically modulating multiple pathways such as apoptosis and autophagy, eg, the kinase inhibitor NT157 enhances the apoptotic effect of TRAIL, and chloroquine inhibits autophagy and synergistically promotes apoptosis, but the threshold of intervention needs to be finely tuned.

activation of the epidermal growth factor receptor.⁵² Increased ventricular fractional shortening was also observed with DR5 activation.⁵² Engineered DR5 agonists, such as DR5-scFv sEVs, can specifically induce apoptosis in DR5-positive cells, and this targeting has been validated in cancer therapy.⁸³ In cardiovascular disease, this technology may have applications to eliminate pathologic cells, such as proatherogenic macrophages or hyperproliferating vascular smooth-muscle cells, thereby slowing plaque progression. Small molecule DR5 agonists have shown many therapeutic potentials in cardiovascular diseases, but their translational application still needs further mechanistic studies and clinical trials.

Table 3 Intervention Strategies Targeting the TRAIL-DR5 Signaling Axis

Strategy Type	Representative Agents/Methods	Mechanism of Action	Potential Applications /Effects	Challenges/Risks
Agonists (Enhancing pro-apoptotic signaling)	Drozitumab (mAb)	Activates DR5 death receptor signaling pathway to induce apoptosis.	Selective clearance of pathological cells (eg, inflammatory cells in atherosclerotic plaques), reduces plaque instability.	Application in CVD requires optimization for efficacy; minimization of off-target effect. ⁸¹
	MEDI3039 (Multivalent ligand)	Enhances DR5 receptor cross-linking efficiency; promotes apoptosis via an atypical RIPK1-dependent pathway, effective even in resistant cells.	Demonstrates potent pro-apoptotic activity in preclinical models.	Mechanism is independent of the classic FADD/caspase-8 pathway. ⁸²
	Biomifi (Small molecule)	Mimics the TRAIL domain to selectively activate DR5 and promote apoptosis.	High oral bioavailability and strong penetration; synergizes with chemotherapeutic agents (eg, doxorubicin) to enhance apoptosis sensitivity in vascular endothelial/smooth muscle cells, inhibits vascular remodeling. ^{13,15}	May activate the ERK1/2 pathway, leading to cardiomyocyte hypertrophy; long-term effects require further study. ⁵²
	DR5-scFv sEVs (Engineered extracellular vesicles)	Specifically induces apoptosis in DR5-positive cells.	Eliminates pathological cells (eg, pro-atherogenic macrophages or hyperproliferative VSMCs), slowing plaque progression.	Clinical translation requires validation of specificity. ⁸³
Inhibitor (Blocking pro-apoptotic pathway)	sDR5-Fc	Competitively binds TRAIL, blocking its interaction with membrane-bound DR5.	In models of myocardial I/R injury and heart failure, it reduces cardiomyocyte apoptosis and inflammation, improving cardiac function; ^{5,59} inhibits excessive inflammatory responses in severe COVID-19. ²¹	The timing of blockade must be carefully weighed to avoid impairing necessary inflammatory clearance.
	siRNA (Targeted silencing)	Delivered via liposomes or viral vectors to silence TRAIL or DR5 mRNA, downregulating pro-apoptotic protein levels.	Alleviates high glucose-induced podocyte injury in diabetic nephropathy models; ¹⁴ increases cell survival in cardiac apoptosis models. ⁸⁴	Delivery system efficiency and targeting need optimization.
Combination Therapy (Multi-pathway synergistic regulation)	Kinase Inhibitors (eg, NT157, PD98059)	NT157 enhances TRAIL-induced apoptosis by upregulating DR5 expression; ⁴⁷ MAPK pathway inhibitors (eg, PD98059) amplify TRAIL-DR5 apoptotic effects by regulating ERK/JNK phosphorylation levels. ^{46,85}	Synergistically inhibits tumor growth in models like glioblastoma; potential application to enhance clearance of pathological cells in CVD.	MAPK inhibitors can have a “double-edged sword” effect (eg, downregulating DR4/5), potentially requiring combination with DR5 stabilizers (eg, tetrandrine). ⁸⁶
	Autophagy Modulators (eg, Chloroquine)	Cross-regulation exists between TRAIL-DR5 and autophagy. Late-stage autophagy inhibitors (eg, chloroquine) can enhance the pro-apoptotic effect of TRAIL-DR5.	Suitable for cardiovascular pathological states with apoptosis resistance. ⁸⁷	The threshold for apoptosis and autophagy varies by cell type and disease stage; excessive autophagy inhibition may aggravate cell death.

Inhibitory Intervention: Blocking the Pro-Apoptotic Pathway

sDR5-Fc inhibits apoptotic signaling by competitively binding TRAIL and blocking its interaction with membrane-bound DR5. In a model of myocardial I/R injury, sDR5-Fc exerts cardioprotective effects by reducing cardiomyocyte apoptosis and inflammatory responses.^{5,59} Similar strategies have also shown potential to inhibit excessive inflammatory responses in the treatment of severe COVID-19 patients.²¹ In addition, targeted silencing of TRAIL or DR5 mRNA by siRNA delivered by liposomes or viral vectors can down-regulate the levels of pro-apoptotic proteins. For example, silencing TRAIL or DR5 significantly alleviated podocyte injury induced by high glucose in diabetic nephropathy models.¹⁴ Similarly, administration of recombinant TRAIL or adenoviral TRAIL resulted in a significant reduction in cardiac fibrosis and apoptosis compared with control diabetic animals.⁷⁴ Knockdown of CHOP by siRNA resulted in a 60% decrease in DR5 expression and a 2.3-fold increase in cell survival in a model of cardiac apoptosis induced by eugenol combined with TRAIL.⁸⁴ In the rat model of acute myocardial infarction, treatment with DR5 inhibitor reduced the apoptotic cells in the infarct area by 45%, while improving the left ventricular ejection fraction by 28%.¹² Blockade of

DR5 using sDR5-fc in heart failure models prevents myocardial cell death and inflammation, preserves ejection fraction and fractional shortening, reduces fibrosis, and prevents ventricular wall thinning, as observed in rodents, pigs, and monkeys.⁵⁹ In addition, inhibition of the TRAIL-DR5 pathway improved cardiac function by reducing neutrophil infiltration and inflammatory factor release in a myocardial ischemia model.⁵ This implies that the activation of TRAIL signaling in the heart may be detrimental under certain circumstances, and that blocking TRAIL signaling may be used as a potential therapeutic approach.

Combined Therapeutic Strategy: Multi-Pathway Synergistic Regulation

Recent studies have shown that kinase inhibitors, such as NT157, enhance TRAIL-induced apoptosis by up-regulating DR5 expression. In the glioblastoma model, NT157 combined with TRAIL significantly activated caspase-3 and inhibited tumor growth, suggesting that it may enhance apoptosis sensitivity through a similar mechanism in cardiovascular diseases.⁴⁷ In addition, MAPK pathway inhibitors (such as PD98059) further amplify TRAIL-DR5 signaling-mediated apoptotic effects by regulating ERK and JNK phosphorylation levels.^{46,85} In the atherosclerosis model, MAPK signaling affects plaque stability by regulating DR5 expression, suggesting that combined targeting of autophagy and apoptosis pathways may become a new therapeutic strategy.⁸⁹ However, MAPK inhibitors may present a “double-edged sword” effect. For example, in KRAS-mutant pancreatic cancer, although MAPK inhibition up-regulates TRAIL, but down-regulates DR4/DR5, it is necessary to combine DR5 stabilizer (such as tetrandrine) to enhance the efficacy.⁸⁶ In addition, JNK pathway activation can up-regulate the expression of DR5 and enhance TRAIL-induced apoptosis. For example, 7-methoxy-aesculin enhances DR5 expression through the JNK pathway and promotes tumor cell death in combination with TRAIL. A similar mechanism may be applied to myocardial protection.⁴³ In addition, the RAS-RAF-MEK-ERK pathway is associated with the progression of cardiovascular diseases, and the combination of MEK inhibitors and TRAIL-DR5 activators may synergistically inhibit pathological cell proliferation or inflammation.⁹⁰ Although combination with kinase inhibitors (eg, JNK, ERK, or MEK inhibitors) can enhance efficacy by regulating DR5 expression or signal transduction, it is necessary to balance pro-apoptotic and cytoprotective effects. Future studies need to further explore tissue-specific mechanisms and develop precise combined treatment regimens.

There is a cross-regulation mechanism between TRAIL-DR5 signaling pathway and autophagy. For example, activated caspase-8 can cleave autophagy-related proteins (such as Beclin-1) and inhibit autophagy to promote apoptosis-led cell death.¹⁹ TRAIL-DR5 activation may up-regulate autophagy-related genes (such as LC3) through JNK or p38 MAPK signaling to induce protective autophagy to antagonized apoptosis.⁴⁵ DR5 activation partly promotes the expression of anti-apoptotic proteins (such as Bcl-2) through NF- κ B, while Bcl-2 can bind to Beclin-1 to inhibit autophagy, forming an apoptosis-autophagy negative feedback loop.⁹¹ It is worth noting that TRAIL-DR5 also interacts with autophagy in some disease models. For example, in the atherosclerotic model, excessive activation of TRAIL-DR5 in intraplaque macrophages leads to increased apoptosis, while autophagy inhibition (eg, mTOR activation) exacerbates lipid accumulation and inflammation; Conversely, enhanced autophagy may remove oxidized LDL and stabilize the plaque,⁹² suggesting that combined regulation of the two may be more effective in stabilizing the plaque. During myocardial ischemia-reperfusion injury, autophagy enhances the removal of damaged mitochondria and protects the myocardium. Excessive activation of TRAIL-DR5 during reperfusion leads to apoptosis, while autophagy may alleviate injury by inhibiting ROS production.^{5,21} In advanced cardiovascular diseases, such as heart failure, excessive autophagy may lead to excessive degradation of cardiomyocytes and impaired contractile function. For example, autophagy-related genes (such as SPAG5) affect endothelial cell survival by regulating the PI3K/Akt/mTOR pathway, and their abnormal expression may accelerate the process of atherosclerosis,⁹³ suggesting that myocardial cell autophagy dysregulation (excessive or insufficient) and TRAIL-DR5-mediated apoptosis synergistically promote myocardial fibrosis and deterioration of systolic function. Late autophagy inhibitors (such as chloroquine) can enhance the pro-apoptotic effect of TRAIL-DR5, which is also suitable for cardiovascular pathological states with apoptosis resistance.⁸⁷ Of course, the threshold of apoptosis and autophagy varies with cell type and disease stage. Excessive inhibition of autophagy may aggravate cell death, while excessive activation of TRAIL-DR5 may induce unexpected inflammatory responses. Most of the existing studies are based on animal models. It is necessary to further explore the interaction mechanism and therapeutic window of apoptosis and autophagy in human tissues.

In conclusion, the intervention strategy targeting TRAIL-DR5 signaling axis has multi-directional regulatory potential in cardiovascular diseases: agonists eliminate diseased cells by selectively activating apoptotic pathways; Inhibitory intervention protects myocardium by blocking pathological signals. Combination therapy enhances the efficacy through multi-target synergy. In the future, it is necessary to further explore the specific mechanism of DR5 signaling in cardiovascular cell types and optimize drug delivery systems to improve targeting.

Challenges and Future Directions

Currently, serum DR5/TRAIL levels are associated with outcomes of cardiovascular events, such as atherosclerotic plaque stability or degree of myocardial damage, but there are significant individual differences in sensitivity and specificity. Although pre-clinical studies have suggested that TRAIL concentration may be a prognostic indicator of CVD,¹³ actual clinical data are still contradictory. The pathological mechanisms of different cardiovascular diseases (for example, myocardial infarction, heart failure, and arrhythmia) are different, and the role of TRAIL signaling may be opposite. Age, gender, and comorbidities (such as diabetes and hypertension) can also affect the level of TRAIL and its biological effects. For example, inhibition of the TRAIL-DR5 pathway can reduce cardiac ischemia-reperfusion injury,⁵ but there is a lack of consistency in the association of TRAIL levels with disease severity or short-term prognosis in different patients. In addition, biomarkers such as TRAIL, sDR5, and OPG exhibit alterations across various diseases—including cancer, autoimmune disorders, and infections—and therefore lack cardiac specificity. Currently, there are no standardized methods or threshold values for their detection, limiting their utility in clinical classification and prognosis. Existing biomarker discovery approaches predominantly rely on single-omics data (eg, genomics or proteomics) and lack integration across multiple omics layers, which compromises the specificity of identified biomarkers.^{27,94} In the future, large-scale longitudinal studies combined with multi-omics technologies (such as proteomics, metabolomics and epio-omics, etc) are needed to screen dynamic marker combinations to accurately evaluate the relationship between pathway activity and disease progression, so as to verify the clinical value of TRAIL/DR5 related markers.⁹⁵

TRAIL or DR5 agonists and antagonists require precise targeting of cardiac tissues to minimize systemic side effects, such as immunosuppression and hepatotoxicity. Conventional systemic administration methods are susceptible to off-target effects, including the activation of apoptotic pathways in non-cardiac tissues. Furthermore, current delivery systems, such as recombinant proteins, antibodies, and small molecules, face challenges related to stability, half-life, and tissue permeability.^{34,51} For example, TRAIL can be combined with chemotherapeutic agents to enhance anti-apoptotic effects, but the penetration efficiency of nanocrystals in ischemic myocardium is insufficient.⁵ In the future, responsive nanocarriers, such as pH or ROS-sensitive, can be developed for precise release of TRAIL agonists in the cardiac microenvironment^{34,51} or combined with single-cell imaging techniques to optimize delivery pathways, such as enhancing vascular stability through endothelial-pericyte interactions.^{18,96}

In addition to the above-mentioned obstacles in clinical translation, there is also a need for research on specific mechanisms. There are multiple TRAIL receptors (DR4, DR5, DcR1, DcR2, OPG), with different affinities, expression levels and downstream signaling pathways. A single-targeting strategy may be ineffective or even harmful. Different cell subsets in the cardiovascular system (such as cardiomyocytes, endothelial cells, fibroblasts, and immune cells) have significant heterogeneity in response to TRAIL-DR5 signaling. For example, endothelial cells are the main source of TRAIL in the healthy circulation, but their ability to secrete is impaired under ischemic conditions.¹⁸ DR5 activation may promote macrophage apoptosis to reduce inflammation, but induce myocardial cell apoptosis to aggravate cardiac function damage. Currently, single-cell transcriptome, epio-omics and spatial omics techniques can be used to reveal ① the epigenetic regulation mechanism of DR5 expression in specific cell subsets (such as diabetes-associated inflammatory macrophages).^{13,97} ② the interaction network between TRAIL signaling and key angiogenic pathways (such as VEGF or Notch) during cardiac repair.^{18,98} However, the integration of existing single-cell data still faces the challenge of insufficient standardization, and it is necessary to establish cross-platform analysis methods.

The function of TRAIL-DR5 pathway is also regulated by post-translational modifications such as ubiquitination and phosphorylation. For example, ASB3-mediated ubiquitination of DR5 may affect its apoptotic signaling efficiency, but the specificity of this mechanism in cardiovascular cells has not been tested.⁴⁵ Gene editing technologies such as CRISPR-Cas9 or base editing can be applied to construct cardiovascular disease models such as cardiomyocyte-

specific DR5 knockout mice, to resolve the dual role of TRAIL signaling in pathological conditions (pro-apoptotic or pro-repair) or to screen for key factors regulating DR5 stability (such as de-ubiquitinating enzyme USP9X), and to explore the role of TRAIL signaling in the pathogenesis of cardiovascular disease. Providing new targets for drug design.^{26,81} In addition, the role of non-coding Rnas (such as miR-155) in the regulation of TRAIL-DR5 pathway is also worth further exploration.⁹⁹

The efficacy of TRAIL-DR5 pathway is significantly affected by patients' comorbidities, such as diabetes and chronic kidney disease. For example, high glucose environment in diabetic patients with CVD can enhance TRAIL-DR5-mediated endothelial cell apoptosis while inhibiting its proangiogenic function.^{13,18} In the future, it is necessary to establish a patient stratification system based on multi-dimensional biomarkers (genetic variation, metabolic characteristics, imaging phenotypes), and develop concomitant diagnostic tools (such as circulating tumor necrosis factor receptor detection) to guide individualized medicine.

In addition, TRAIL-DR5 has a “double-edge sword” effect in the cardiovascular system: moderate activation in the early stage can clear diseased cells (such as pro-inflammatory macrophages), but excessive activation leads to myocardial cell loss and aggravation of injury, and promotes repair and improves angiogenesis in the later stage.^{18,26} Spatiotemporal specific intervention strategies (such as the use of DR5 neutralizing antibodies to reduce myocardial apoptosis in the acute phase, and gene editing or small molecule activators to enhance the pro-angiogenic function of TRAIL in the recovery phase) can be used to achieve local signaling regulation.^{100,101} In addition, combination therapies (eg, TRAIL agonists combined with antifibrotic agents) may synergistically improve cardiac remodeling. Artificial intelligent-driven multi-omics models can predict a patient's individualized treatment window.⁹⁴

In conclusion, the potential of TRAIL-DR5 pathway in the treatment of cardiovascular diseases has not been fully released, and the translational barriers need to be overcome through the interdisciplinary (such as biomaterials, computational biology, and clinical medicine). Future research should focus on: (1) developing highly sensitive biomarkers and targeted delivery systems; (2) Unraveling the mechanisms of cell subpopulation-specificity and validating novel targets; (3) Constructing a dynamic intervention strategy to achieve the balance between efficacy and safety. The ultimate goal is to achieve a paradigm shift from “broad spectrum treatment” to “precision intervention” and provide innovative solutions for complex cardiovascular diseases.

Conclusions

The TRAIL-DR5 signaling axis exhibits a context-dependent dual role in cardiovascular diseases, acting both as a promoter of apoptosis/injury and a mediator of anti-inflammatory/protective effects. This functional dichotomy is influenced by cell-type specificity, dynamic microenvironmental changes, and crosstalk with other signaling pathways such as NF- κ B, MAPK, and autophagy. Throughout this review, we have highlighted its complex involvement in key cardiovascular conditions—including acute myocardial infarction, heart failure, atherosclerosis, and atrial fibrillation—where TRAIL and DR5 levels often serve as prognostic biomarkers with contradictory implications.

Therapeutic strategies targeting this axis are multifaceted: DR5 agonists (such as, monoclonal antibodies, multivalent ligands, and small molecules) show promise in selectively eliminating pathological cells; inhibitory approaches (such as, sDR5-Fc, siRNA) protect against excessive apoptosis and inflammation; and combination therapies (eg, with kinase or autophagy inhibitors) enhance efficacy through synergistic pathway modulation. However, the clinical translation of these interventions remains challenging due to issues of specificity, delivery, and contextual signaling outcomes. Future research should prioritize: (1) Elucidating the mechanisms underlying cell-type-specific responses to TRAIL-DR5 signaling; (2) Exploring its interactions with immune homeostasis and alternative cell death modalities; (3) Developing spatiotemporally controlled delivery systems to balance therapeutic efficacy with safety. Advances in multi-omics profiling, single-cell technologies, and biomarker validation will be essential to transition from broad-spectrum treatments toward precision interventions, ultimately enabling individualized therapeutic strategies for complex cardiovascular diseases.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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