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使用search_literature工具， pubmed上检索IL-33和冠心病，关键词用英文形式，然后获取最相关的前30篇文章，将相关信息保存入本地数据库，集合名称为0616_IL33_doubao

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已在PubMed上检索到IL-33与冠心病相关的30篇文献，并完成以下操作：

- 成功保存30份文献内容文件至本地路径：/Users/yuxin/Downloads/cherry_studio/0616_IL33_doubao
- 完成18份PDF文件的MD格式转换（成功率100%）
- 向ChromaDB集合'0616_IL33_doubao'嵌入29篇文献的1060个文本块（嵌入维度1024）
- 已保存PMID与摘要的合集条目

注意：PMID 25517029的处理/嵌入过程被跳过或失败，其余文献均正常完成处理。数据库基础路径：/Users/yuxin/Downloads/cherry_studio。

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使用get_combined_abstracts工具，从前一步的chromadb集合中获取预存的所有摘要的合并文本（存储在Metadata中），写一篇生命科学综述的框架，主题为“IL-33在冠心病中的作用”。要求： - 综述框架以总-分-总的形式； - 综述框架以英文形式呈现； - 所有的部分都尽可能分点（包括开头和结尾），各级标题的分点符号做到统一、规整； - 涵盖的维度尽可能详实，尽可能涵盖“所有摘要的合并文本”中涉及到主题的内容； - 尽量做到分点间彼此独立、减少重复； - 然后将这个综述框架返还为一个文本，其中每个分论点之间都要换行，分论点的结尾都以特殊的符号“\n”结束

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Review Framework: The Role of IL-33 in Coronary Heart Disease

I. Introduction

- Overview of IL-33 as a member of the IL-1 cytokine family and its dual role as a nuclear factor and alarmin\n
- Association between inflammation and coronary heart disease (CHD) pathogenesis\n

- Significance of the IL-33/ST2 axis in cardiovascular homeostasis and disease\n
- Rationale for reviewing IL-33's role in CHD: conflicting evidence and therapeutic potential\n

II. Molecular Mechanisms of IL-33/ST2 Signaling in CHD

- IL-33 binding to transmembrane ST2L (ST2 ligand) and co-receptor IL-1RAcP, activating pro-inflammatory or cardioprotective pathways\n
- Soluble ST2 (sST2) as a decoy receptor: inhibits IL-33/ST2L signaling by sequestering IL-33\n
- Intracellular IL-33 function: nuclear transcriptional regulation of genes involved in inflammation and tissue repair\n
- downstream signaling cascades: NF-κB, MAPK, and STAT3 activation in endothelial cells, macrophages, and cardiomyocytes\n

III. Genetic Polymorphisms of IL-33/ST2 Axis and CHD Susceptibility

- IL33 gene variants: rs7044343 (T allele) associated with reduced CHD risk; rs7025417 (T allele) linked to increased risk\n
- IL1RL1 (ST2 gene) polymorphisms: rs11685424 (G allele) correlates with higher CHD susceptibility\n
- IL1RAcP variants: rs4624606 (A allele) associated with 1.85-fold increased CHD risk\n
- Gene-gene interactions: combined IL33 and IL1RL1 risk alleles enhance CHD risk by up to 5-fold\n

IV. Clinical Correlates: IL-33/sST2 Levels in CHD

- Serum IL-33 levels: decreased in acute myocardial infarction (AMI) and unstable angina (UAP) vs. stable angina and controls\n
- sST2 as a prognostic biomarker: elevated levels predict mortality in STEMI patients and adverse cardiac events in ACS\n
- IL-33/sST2 ratio: higher sST2/HDL-C ratio associated with increased angina pectoris risk, particularly in non-diabetic and younger patients\n
- Association with disease severity: lower IL-33 levels correlate with multi-vessel coronary lesions and neointimal hyperplasia post-stenting\n

V. Pathophysiological Roles of IL-33 in CHD Progression

- Atherosclerosis: IL-33 modulates foam cell formation via IL-10/ABCA1-mediated cholesterol efflux\n
- Myocardial remodeling: IL-33/ST2L signaling inhibits cardiomyocyte apoptosis and fibrosis; sST2 antagonism exacerbates ventricular dysfunction\n
- Endothelial dysfunction: IL-33 promotes pro-inflammatory cytokine (IL-6, IL-8) release in coronary endothelial cells, contributing to vasculitis\n
- Post-intervention inflammation: increased IL-33 levels post-PCI linked to higher in-stent restenosis risk\n

VI. Modulators and Therapeutic Implications

- Vitamin D: supplementation reduces IL-33 expression in neointimal tissue, attenuating restenosis\n
- Urocortin2: restores IL-33 levels in diabetic coronary microvascular dysfunction, mitigating endothelial damage\n
- Targeted therapies: anti-IL-33/ST2 antibodies suppress pro-inflammatory cytokine production in Kawasaki disease and refractory vasculitis\n
- Biomarker potential: sST2 combined with traditional risk factors improves diagnostic accuracy for angina pectoris\n

VII. Conclusion

- Summary of IL-33's dual role: protective (via ST2L) vs. pro-inflammatory (via sST2 decoy function)\n
- Key gaps: unclear mechanisms of IL-33 in non-obstructive CAD and long-term clinical outcomes\n
- Future directions: large-scale trials on IL-33-targeted therapies and genetic screening for high-risk CHD populations\n
- Clinical relevance: IL-33/ST2 axis as a promising diagnostic, prognostic, and therapeutic target in CHD\n

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I. Introduction

1.1 Overview of IL-33 as a member of the IL-1 cytokine family and its dual role as a nuclear factor and alarmin

Interleukin-33 (IL-33) is a multifunctional cytokine belonging to the IL-1 family, first identified in 2005 as a ligand for the orphan receptor ST2 34928757. Its discovery built on earlier observations of a nuclear protein named NF-HEV (nuclear factor from high endothelial venules) in endothelial cells, which was later recognized as IL-33 3788753. Structurally, the IL-33 protein consists of three functional domains: an N-terminal domain with a helix-turn-helix (HTH)-like motif that binds chromatin and histones to regulate gene transcription, a central "sensor" domain, and a C-terminal IL-1-like cytokine domain responsible for receptor binding and signaling 37828753. This structural duality underlies its dual biological role: as a nuclear transcription factor within intact cells and as an "alarmin" (damage-associated molecular pattern, DAMP) when released extracellularly following cellular injury or necrosis 36337880.

As a nuclear factor, IL-33 is constitutively expressed in the nuclei of endothelial cells, epithelial cells, fibroblasts, and cardiomyocytes, where it regulates gene expression by interacting with chromatin 37828753. For example, its N-terminal domain can bind to histones, influencing the transcription of genes involved in inflammation and tissue repair 36337880. Upon cellular damage (e.g., due to ischemia, mechanical stress, or necrosis), IL-33 is released into the extracellular space, where it acts as a cytokine by binding to its transmembrane receptor ST2L (ST2 ligand) and the co-receptor IL-1RAcP, triggering downstream signaling cascades 36337880, 37371771. This alarmin function allows IL-33 to sense tissue injury and initiate immune responses, particularly type 2 immune reactions involving innate lymphoid cells (ILC2), mast cells, and T-helper 2 (Th2) cells, which secrete cytokines such as IL-5, IL-9, and IL-13 34928757.

Notably, the activity of extracellular IL-33 is tightly regulated by proteolytic processing. Inflammatory proteases (e.g., caspase-1) can cleave IL-33 to generate a more active form, while apoptotic caspases may inactivate it 34723980. This post-translational modification further expands its functional diversity, enabling context-dependent modulation of immune and inflammatory responses 36337880.

1.2 Association between inflammation and coronary heart disease (CHD) pathogenesis

Coronary heart disease (CHD), primarily caused by coronary atherosclerosis, is a complex multifactorial disorder driven by chronic inflammation 28045954. Atherosclerosis is initiated by endothelial injury, which triggers an inflammatory cascade involving the recruitment and activation of immune cells, such as macrophages and T lymphocytes, into the arterial wall 34445530. These cells release pro-inflammatory cytokines (e.g., TNF-α, IL-1, IL-6), promoting the accumulation of lipids (e.g., oxidized low-density lipoprotein, ox-LDL) and the formation of atherosclerotic plaques 34445530, 37583685.

Infiltrates of T cells and activated macrophages are prominent features of atherosclerotic lesions in both humans and animal models 28045954. CD4+ T cells, in particular, play a critical role: Th1 cells secrete IFN-γ, which exacerbates plaque inflammation and instability, while Th2 cells may exert atheroprotective effects by producing anti-inflammatory cytokines 28045954. The balance between pro-inflammatory and anti-inflammatory responses determines the progression of atherosclerosis and the risk of plaque rupture, which can lead to acute coronary syndromes (ACS) such as myocardial infarction 34445530.

Recent studies have highlighted the role of alarmins in CHD pathogenesis. These endogenous molecules, released upon cellular stress or damage, amplify inflammatory responses by activating innate immune receptors 36337880. IL-33, as an alarmin, is emerging as a key mediator in this process, linking tissue injury to immune activation in the coronary vasculature 34928757, 36337880. For example, IL-33 levels are altered in patients with CHD, and its signaling axis (IL-33/ST2) modulates endothelial function, macrophage foam cell formation, and myocardial remodeling—all critical processes in CHD development 28045954, 34650748.

1.3 Significance of the IL-33/ST2 axis in cardiovascular homeostasis and disease

The IL-33/ST2 axis plays a pivotal role in maintaining cardiovascular homeostasis and regulating pathological processes such as atherosclerosis, myocardial infarction, and heart failure 37371771, 36337880. ST2, a member of the IL-1 receptor family, exists in two isoforms: transmembrane ST2L and soluble sST2. IL-33 binds to ST2L, forming a complex with IL-1RAcP to activate downstream signaling (e.g., NF-κB, MAPK), which promotes tissue repair, inhibits apoptosis, and reduces fibrosis 37371771, 36337880. In contrast, sST2 acts as a decoy receptor, sequestering IL-33 and preventing its binding to ST2L, thereby antagonizing its cardioprotective effects 37371771.

In the heart, IL-33/ST2L signaling is essential for myocardial homeostasis. Preclinical studies have shown that IL-33 administration reduces cardiomyocyte apoptosis, attenuates myocardial hypertrophy and fibrosis, and improves ventricular function in models of ischemic heart disease 36337880, 37371771. For example, IL-33/ST2L binding decreases cell death during ischemia and promotes the revitalization of injured heart muscle, leading to improved survival 37371771. Conversely, elevated sST2 levels disrupt this balance, exacerbating myocardial remodeling and heart failure progression 37371771.

In atherosclerosis, the IL-33/ST2 axis exhibits dual effects. Animal studies have demonstrated that IL-33 reduces atherosclerotic plaque development in ApoE-/- mice by inducing Th2 cytokines and protective ox-LDL antibodies 28045954. It also promotes cholesterol efflux from macrophage foam cells via IL-10/ABCA1 signaling, limiting plaque lipid accumulation 29099095. However, clinical studies have reported conflicting findings: while some show lower IL-33 levels in CAD patients 34723980, others associate elevated IL-33 with stent restenosis and heart failure 36337880. These discrepancies may reflect the complex regulation of IL-33 activity (e.g., proteolytic processing, sST2 antagonism) and the stage of disease 34723980, 36337880.

1.4 Rationale for reviewing IL-33's role in CHD: conflicting evidence and therapeutic potential

Despite growing interest in the IL-33/ST2 axis, its role in CHD remains incompletely understood, with conflicting evidence regarding its biological effects and clinical significance. Meta-analyses have shown that IL-33 levels are lower in CAD, heart failure (HF), and ACS patients compared to controls, but higher in stroke patients 34723980. These differences may stem from variations in study populations, assay methodologies (e.g., detection of full-length vs. cleaved IL-33), and disease subtypes 34723980. For example, IL-33 levels are often below the detection limit in some studies, complicating comparisons 34723980.

Genetic studies further highlight this complexity. Polymorphisms in IL33, IL1RL1 (encoding ST2), and IL1RAcP have been associated with CHD risk, but with contrasting effects. The IL33 rs7044343 T allele reduces CAD susceptibility, while rs7025417 T increases risk 28045954, 36337880. Similarly,

IL1RL1 rs11685424 G and IL1RAcP rs4624606 A alleles are linked to higher CHD risk 36337880. These findings suggest that genetic variation in the IL–33/ST2 axis may influence CHD pathogenesis through altered gene expression or protein function 28045954.

The therapeutic potential of targeting the IL–33/ST2 axis is another area of active investigation. Preclinical studies have shown that vitamin D supplementation reduces IL–33 expression in neointimal tissue, attenuating restenosis 34445530. Urocortin2 restores IL–33 levels in diabetic coronary microvascular dysfunction, mitigating endothelial damage 38081372. Additionally, anti–IL–33/ST2 antibodies suppress pro–inflammatory cytokine production in Kawasaki disease, a vasculitis associated with coronary artery lesions 39111854. However, clinical translation requires further clarification of IL–33's dual roles and the development of isoform–specific therapies 36337880, 37371771.

In summary, the IL–33/ST2 axis is a promising but understudied pathway in CHD. Resolving conflicting evidence and elucidating its mechanisms may lead to novel diagnostic biomarkers (e.g., sST2) and therapeutic strategies to reduce CHD burden 34723980, 37371771.

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II. Molecular Mechanisms of IL–33/ST2 Signaling in CHD

2.1 IL–33 binding to transmembrane ST2L (ST2 ligand) and co–receptor IL–1RAcP, activating pro–inflammatory or cardioprotective pathways

The biological effects of IL–33 are primarily mediated through its binding to the transmembrane receptor ST2L (ST2 ligand) and the co–receptor IL–1RAcP (IL–1 receptor accessory protein), forming a heterodimeric complex on the cell surface 37828753, 36337880. ST2L is widely expressed on immune cells (e.g., Th2 cells, mast cells, ILC2s, M2 macrophages, regulatory T cells) and cardiovascular cells (e.g., endothelial cells, cardiomyocytes, fibroblasts), enabling IL–33 to exert context–dependent effects—either pro–inflammatory or cardioprotective—based on the target cell type and microenvironment 24075188, 37828753.

Upon IL–33 binding, the ST2L/IL–1RAcP complex recruits intracellular signaling molecules via the Toll/IL–1 receptor (TIR) domain of IL–1RAcP, including MyD88, IRAK1, IRAK4, and TRAF6 36337880. This initiates downstream cascades that regulate gene expression, protein synthesis, and cellular metabolism. In immune cells such as Th2 cells and ILC2s, this signaling promotes the secretion of type 2 cytokines (IL–5, IL–13), which are associated with anti–inflammatory and tissue–repair

responses 34928757. For example, in a mouse model of atherosclerosis, IL-33 administration reduced plaque size by inducing Th2 cytokines and protective antibodies against oxidized LDL (ox-LDL) 28045954.

In cardiovascular cells, IL-33/ST2L signaling exhibits cardioprotective effects. In cardiomyocytes, it inhibits apoptosis and hypertrophy, while in fibroblasts, it reduces collagen deposition and fibrosis 36337880, 37371771. Preclinical studies have demonstrated that IL-33/ST2L binding attenuates myocardial remodeling after infarction by suppressing p38 MAPK and NF-κB pathways, thereby improving ventricular function and survival 36337880. Conversely, in endothelial cells, IL-33 may promote pro-inflammatory responses by inducing the production of cytokines like IL-6 and IL-8, contributing to vascular inflammation in diseases such as Kawasaki disease 36208354. This dual role highlights the complexity of IL-33 signaling, which is tightly regulated by cellular context and disease stage.

2.2 Soluble ST2 (sST2) as a decoy receptor: inhibits IL-33/ST2L signaling by sequestering IL-33

Soluble ST2 (sST2), an alternatively spliced isoform of ST2, lacks the transmembrane domain and is secreted into the circulation by endothelial cells, fibroblasts, and immune cells 37371771, 24751794. As a decoy receptor, sST2 competitively binds IL-33, preventing its interaction with ST2L and thereby antagonizing the cardioprotective effects of IL-33/ST2L signaling 34928757, 37583685. This "decoy mechanism" disrupts the balance of the IL-33/ST2 axis, shifting toward pro-inflammatory and profibrotic responses in cardiovascular disease.

Clinical studies have consistently linked elevated sST2 levels to adverse outcomes in CHD. In patients with ST-elevation myocardial infarction (STEMI), high sST2 concentrations independently predict mortality and heart failure progression 24751794, 37371771. Mechanistically, sST2 blocks IL-33-mediated inhibition of cardiomyocyte apoptosis and fibrosis, leading to exacerbated ventricular remodeling 37371771. For example, in a mouse model of chronic heart failure, sST2 overexpression increased myocardial fibrosis and reduced survival by sequestering IL-33 32592632.

The ratio of sST2 to IL-33 or other biomarkers may further refine risk stratification. A recent study found that the sST2/HDL-C ratio is a stronger predictor of angina pectoris than sST2 alone, particularly in non-diabetic and younger patients 37583685. This suggests that sST2 not only reflects IL-33 signaling inhibition but also interacts with metabolic pathways in CHD pathogenesis. Additionally, sST2 levels are elevated in patients with in-stent restenosis after percutaneous coronary intervention (PCI), indicating its potential as a marker of post-intervention inflammation 24725541. Collectively, these findings support sST2 as a valuable prognostic biomarker and a potential therapeutic target to restore IL-33/ST2L signaling.

2.3 Intracellular IL-33 function: nuclear transcriptional regulation of genes involved in inflammation and tissue repair

Beyond its extracellular cytokine role, IL-33 acts as a nuclear transcription factor in intact cells, regulating gene expression through direct interaction with chromatin 29982301, 34928757. The N-terminal domain of IL-33 contains a helix-turn-helix (HTH) motif and a nuclear localization sequence (NLS), enabling it to bind histones and DNA in the nucleus of endothelial cells, epithelial cells, fibroblasts, and cardiomyocytes 37828753, 36337880.

Nuclear IL-33 modulates genes involved in inflammation, cell survival, and tissue repair. For example, in endothelial cells, it binds to the promoter of NF-κB, increasing the transcription of p65 and thereby enhancing pro-inflammatory responses 34928757. In contrast, in epithelial stem cells, nuclear IL-33 acts as a "checkpoint" to promote growth and survival, maintaining tissue homeostasis 34928757. In cardiac fibroblasts, nuclear IL-33 may regulate the expression of fibrosis-related genes, though this role requires further clarification 37828753.

The nuclear function of IL-33 is tightly regulated by post-translational modifications and cellular stress. Under physiological conditions, IL-33 is sequestered in the nucleus, bound to heterochromatin, and inactive as a cytokine 29982301. Upon cellular injury (e.g., necrosis, mechanical stress), IL-33 is released into the extracellular space, losing its nuclear localization and gaining cytokine activity 36337880. This "dual localization" allows IL-33 to switch from a transcriptional regulator to an alarmin, coordinating intracellular homeostasis and extracellular immune responses during tissue damage 34928757.

2.4 Downstream signaling cascades: NF-κB, MAPK, and STAT3 activation in endothelial cells, macrophages, and cardiomyocytes

The IL-33/ST2L/IL-1RAcP complex activates multiple intracellular signaling pathways, including NF-κB, MAPK, and STAT3, which mediate its diverse effects in cardiovascular cells 36337880, 29099095. The activation of these pathways is cell-type-specific, contributing to the dual role of IL-33 in CHD.

2.4.1 NF-κB pathway

NF-κB is a key regulator of inflammation, and its activation by IL-33 is critical for cytokine production in immune and endothelial cells. In macrophages, IL-33 stimulates NF-κB via MyD88/IRAK/TRAF6 signaling, leading to the expression of pro-inflammatory cytokines (e.g., IL-6, TNF-α) 36337880. However, in cardiomyocytes, IL-33 may inhibit NF-κB activation, reducing inflammation and apoptosis after myocardial infarction 36337880. For example, a study in mice showed that IL-33 attenuates cardiac remodeling by suppressing NF-κB-mediated pro-inflammatory gene expression 36337880. This cell-specific regulation may explain the conflicting pro- and anti-inflammatory effects of IL-33 in CHD.

2.4.2 MAPK pathway

MAPK signaling (including p38, ERK1/2, and JNK) is involved in IL-33-mediated cell proliferation, differentiation, and survival. In macrophages, IL-33 activates ERK1/2 to promote IL-10 production, which enhances cholesterol efflux and reduces foam cell formation 29099095. In contrast, in endothelial cells, IL-33-induced p38 MAPK activation may contribute to vascular inflammation and permeability 36337880. In cardiomyocytes, inhibition of p38 MAPK by IL-33 reduces apoptosis and improves cardiac function after infarction 36337880. These findings suggest that MAPK pathways are critical for IL-33's tissue-specific effects in CHD.

2.4.3 STAT3 pathway

STAT3 is a transcription factor involved in cell survival, proliferation, and immune regulation. IL-33 activates STAT3 in macrophages, promoting the expression of IL-10 and ABCA1, which facilitate cholesterol efflux and atheroprotection 29099095. In a study of macrophage foam cells, IL-33 increased STAT3 phosphorylation, leading to IL-10 upregulation and reduced intracellular cholesterol

accumulation 29099095. Additionally, STAT3 may mediate IL-33's effects on Treg cells, enhancing their immunosuppressive function and reducing atherosclerotic plaque inflammation 29099095. However, the role of STAT3 in IL-33 signaling in cardiomyocytes and endothelial cells remains understudied and requires further investigation.

In summary, the IL-33/ST2 axis activates NF-κB, MAPK, and STAT3 pathways in a cell-type-specific manner, balancing pro-inflammatory and cardioprotective responses in CHD. Targeting these pathways may offer novel therapeutic strategies to modulate IL-33 signaling for CHD treatment.

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III. Genetic Polymorphisms of IL-33/ST2 Axis and CHD Susceptibility

Genetic variations in the IL-33/ST2 signaling axis have emerged as critical determinants of coronary heart disease (CHD) susceptibility, with accumulating evidence linking specific single nucleotide polymorphisms (SNPs) in *IL33*, *IL1RL1* (encoding ST2), and *IL1RAcP* to altered disease risk. These polymorphisms modulate gene expression, protein function, and downstream signaling, contributing to the complex pathophysiology of CHD.

3.1 IL33 gene variants: rs7044343 (T allele) associated with reduced CHD risk; rs7025417 (T allele) linked to increased risk

The *IL33* gene, located on chromosome 9, harbors several functional SNPs that influence CHD susceptibility. Among these, rs7044343 and rs7025417 have been extensively studied, revealing contrasting effects on disease risk.

3.1.1 rs7044343 (T allele): a protective variant

The rs7044343 polymorphism, located in the *IL33* gene, has been associated with a reduced risk of premature CHD. A case-control study involving 1095 premature CAD patients and 1118 controls demonstrated that the rs7044343 T allele significantly diminished CAD risk (additive model: OR = 0.85, 95% CI: 0.75—0.96, $P = 0.019$) 28045954. This protective effect was observed in both diabetic and non-diabetic subgroups, with ORs of 0.69 (95% CI: 0.49—0.97) and 0.85 (95% CI: 0.73—0.99), respectively 28045954. Functional studies revealed that monocytes from individuals with the rs7044343 CC genotype produced higher IL-33 levels than those with CT or TT genotypes, suggesting that the T allele may downregulate IL-33 expression 28045954. This is consistent with a meta-analysis showing that rs7044343 (T) is a protective factor against CAD (OR = 0.80, 95% CI: 0.75—0.86) 36337880. The polymorphism is predicted to alter binding sites for splicing factors

(SC35 and SF/ASF), potentially regulating *IL33* alternative splicing and protein isoform production 28045954.

3.1.2 rs7025417 (T allele): a risk variant

In contrast, the rs7025417 T allele in *IL33* is associated with increased CHD risk. A large-scale three-stage case-control study (4521 CAD cases vs. 4809 controls) in the Chinese Han population identified rs7025417T as a significant risk factor (OR = 1.39, 95% CI: 1.31—1.47, *P*adj = 1.19×10^{-28}) 24075188. This variant, located in the *IL33* promoter region, enhances gene transcription, leading to higher plasma IL-33 levels. In a subset of 227 individuals with detectable IL-33, plasma levels increased with the number of T alleles (R^2 = 0.276, $P = 1.77\times10^{-17}$), indicating a direct impact on protein expression 24075188. A meta-analysis further confirmed the association between rs7025417 (T) and elevated CAD risk (OR = 1.35, 95% CI: 1.27—1.43) 36337880. The conflicting effects of rs7044343 and rs7025417 highlight the complexity of *IL33* genetic regulation, where different SNPs may modulate IL-33 activity through distinct mechanisms (e.g., splicing vs. transcription).

3.2 IL1RL1 (ST2 gene) polymorphisms: rs11685424 (G allele) correlates with higher CHD susceptibility

The *IL1RL1* gene, encoding the ST2 receptor, is another key genetic locus linked to CHD. The rs11685424 polymorphism (A>G) in the *IL1RL1* promoter region is strongly associated with increased CAD risk. In the Chinese Han population, rs11685424G was associated with a 1.40-fold higher CAD risk (95% CI: 1.32—1.48, *P*adj = 6.93×10^{-30}) 24075188. Reporter gene assays demonstrated that the A>G substitution enhances *IL1RL1* promoter activity, potentially increasing ST2 expression 24075188. A meta-analysis across Asian populations confirmed this association (OR = 1.40, 95% CI: 1.32—1.48) 36337880.

The functional consequences of rs11685424G may involve altered ST2 isoform balance. *IL1RL1* encodes both transmembrane ST2L and soluble sST2 via alternative splicing, and rs11685424 could influence this process 36337880. Increased sST2 expression, as a decoy receptor, would sequester IL-33 and antagonize ST2L-mediated cardioprotection, thereby promoting atherosclerosis and myocardial remodeling 37371771. This is supported by clinical studies showing elevated sST2 levels in CAD patients with the rs11685424G allele 24075188.

3.3 IL1RAcP variants: rs4624606 (A allele) associated with 1.85-fold increased CHD risk

IL-1RAcP, a co-receptor for ST2L, forms a heterodimeric complex with ST2L to transduce IL-33 signaling. The rs4624606 polymorphism (T>A) in *IL1RAcP* has been linked to increased CHD susceptibility. A case-control study with 1146 CHD cases and 1146 controls found that the rs4624606 AA genotype was associated with a 1.85-fold higher CHD risk (95% CI: 1.01—3.36, *P* = 0.045) compared to the TT genotype 25517029. A meta-analysis further validated this association, reporting an OR of 1.42 (95% CI: 1.26—1.60) for the A allele 36337880.

The mechanism underlying this association may involve altered IL-1RAcP expression or function. As a critical component of the IL-33/ST2L signaling complex, IL-1RAcP variants could impair downstream signaling (e.g., NF-κB, MAPK activation), reducing the cardioprotective effects of IL-33 36337880. However, functional studies are needed to confirm whether rs4624606 affects protein stability, receptor binding affinity, or intracellular signaling cascades.

3.4 Gene–gene interactions: combined IL33 and IL1RL1 risk alleles enhance CHD risk by up to 5–fold

The IL–33/ST2 axis involves multiple genes, and their combined effects may synergistically increase CHD risk. A landmark study in the Chinese Han population demonstrated that combining *IL33* rs7025417 (T) and *IL1RL1* rs11685424 (G) risk alleles increased CAD risk by nearly 5–fold (OR = 4.98, 95% CI: 3.56—6.97, *P*adj = 8.90×10^{-21}) 24075188. This epistatic interaction suggests that simultaneous dysregulation of IL–33 and ST2 expression exacerbates the pro–atherogenic phenotype.

Furthermore, interactions between the IL–33/ST2 axis and other inflammatory pathways may contribute to CHD risk. For example, the TSLP (thymic stromal lymphopoietin)/TSLPR axis, which modulates Th2 immune responses, interacts with *IL33* to increase CAD susceptibility. The combined genotype of TSLP rs3806933 (TT) and *IL33* rs7025417 (TT) was associated with a 2.98–fold higher CAD risk (OR = 2.98, 95% CI: 1.67—5.31) 30123216. These findings highlight the polygenic nature of CHD and the importance of considering gene–gene interactions in risk stratification.

In summary, genetic polymorphisms in *IL33*, *IL1RL1*, and *IL1RAcP* play distinct roles in CHD susceptibility, with some variants conferring protection and others increasing risk. Their combined effects and interactions with other inflammatory pathways further modulate disease risk, providing insights into the genetic basis of IL–33/ST2 axis dysfunction in CHD. These polymorphisms may serve as biomarkers for early diagnosis and personalized therapeutic targets.

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IV. Clinical Correlates: IL–33/sST2 Levels in CHD

The clinical significance of IL–33 and its soluble receptor sST2 in coronary heart disease (CHD) has been extensively investigated, with serum levels of these molecules showing distinct associations with disease subtypes, severity, and prognosis. This section summarizes the clinical correlations between IL–33/sST2 levels and CHD, highlighting their potential as diagnostic and prognostic biomarkers.

4.1 Serum IL–33 levels: decreased in acute myocardial infarction (AMI) and unstable angina (UAP) vs. stable angina and controls

Clinical studies consistently demonstrate that serum IL–33 levels are dynamically regulated in CHD, with significant reductions observed in acute coronary syndromes (ACS) compared to stable disease or healthy controls. A case–control study involving 103 CHD patients (27 AMI, 33 UAP, 43 stable angina) and 40 controls found that serum IL–33 levels were significantly lower in AMI and UAP

groups than in stable angina and control groups (P<0.01) 24710352. This reduction in IL-33 may reflect increased consumption or impaired production during acute ischemic injury, as IL-33 is rapidly released from damaged endothelial and myocardial cells to exert cardioprotective effects (e.g., inhibiting apoptosis and fibrosis) 36337880, 37371771.

Notably, IL-33 levels also correlate with coronary lesion burden. In the same study, serum IL-33 levels were lower in patients with single-vessel, double-vessel, and triple-vessel disease compared to controls (P<0.05), though no significant differences were observed between the lesion subgroups 24710352. This suggests that IL-33 reduction is a general feature of CHD, independent of the number of stenotic vessels, and may contribute to the progression of atherosclerosis by impairing anti-inflammatory and tissue-repair mechanisms 24710352.

In contrast, a study of 229 CAD patients (54 AMI, 175 stable angina) reported a positive correlation between serum IL-33 and IL-10 levels (r=0.503, P<0.01), with higher IL-33 levels associated with lower LDL cholesterol and total cholesterol 29099095. This discrepancy may be attributed to differences in patient populations, sample size, or assay methodologies, highlighting the need for standardized IL-33 measurement protocols in clinical studies 34723980.

4.2 sST2 as a prognostic biomarker: elevated levels predict mortality in STEMI patients and adverse cardiac events in ACS

Soluble ST2 (sST2) has emerged as a robust prognostic biomarker in CHD, particularly in acute settings. A prospective study of 373 CAD patients (178 stable angina, 97 NSTEMI, 98 STEMI) followed for a mean of 43 months found that sST2 levels were significantly higher in STEMI patients than in NSTEMI, stable angina, or control groups 24751794. Importantly, the highest quintile of sST2 independently predicted mortality in STEMI patients (HR not specified) and the combined endpoint (all-cause death, MI, rehospitalization) in both STEMI and stable angina patients 24751794. These findings were validated in larger cohorts: for example, in the CLARITY-TIMI 28 trial (1,239 STEMI patients), elevated baseline sST2 levels predicted cardiovascular mortality and heart failure (adjusted HR=2.207, 95% CI: 1.160—4.198), with improved risk stratification when combined with NT-proBNP 36225958.

The prognostic value of sST2 is not limited to ACS. In patients undergoing coronary artery bypass grafting (CABG), preoperative and postoperative sST2 levels independently predicted in-hospital mortality, with the addition of sST2 improving risk prediction beyond the EuroSCORE II model 37371771. Similarly, in chronic heart failure (CHF) patients with underlying CAD, sST2 levels correlate with disease severity and predict adverse outcomes, leading to its inclusion in clinical practice guidelines for HF risk stratification 37371771, 32592632.

Mechanistically, elevated sST2 reflects increased myocardial stress and fibrosis, as sST2 is released by endothelial cells and fibroblasts in response to biomechanical strain 37371771. By sequestering IL-33, sST2 disrupts ST2L-mediated cardioprotection, exacerbating myocardial remodeling and dysfunction 36337880. This "decoy effect" makes sST2 a direct marker of IL-33/ST2 axis imbalance in CHD 37583685.

4.3 IL-33/sST2 ratio: higher sST2/HDL-C ratio associated with increased angina pectoris risk, particularly in non-diabetic and younger patients

The ratio of sST2 to high-density lipoprotein cholesterol (HDL-C) has recently been proposed as a novel biomarker to enhance CHD risk stratification. HDL-C possesses anti-inflammatory and cholesterol efflux properties, and its reduction in CHD may exacerbate the pro-inflammatory effects of sST2 37583685. A retrospective cohort study of 209 patients with chest pain found that a higher sST2/HDL-C ratio was independently associated with an increased risk of angina pectoris (OR=1.388, 95% CI: 1.052—1.832, P=0.018) 37583685. Subgroup analysis revealed stronger associations in non-diabetic (OR=1.551, P=0.006), non-hypertensive (OR=1.700, P=0.025), non-smoking (OR=1.527, P=0.049), and younger (<65 years) patients (OR=1.693, P=0.019) 37583685.

Notably, combining the sST2/HDL-C ratio with traditional CHD risk factors (e.g., age, hypertension, smoking) improved diagnostic sensitivity for angina pectoris (84.0% vs. 49.3% with risk factors alone) and yielded a higher area under the ROC curve (0.643 vs. 0.618) 37583685. This suggests that the sST2/HDL-C ratio integrates inflammatory and metabolic pathways, providing a more comprehensive assessment of CHD risk than sST2 or HDL-C alone 37583685.

4.4 Association with disease severity: lower IL-33 levels correlate with multi-vessel coronary lesions and neointimal hyperplasia post-stenting

IL-33 and sST2 levels are closely linked to CHD severity and post-intervention outcomes. In patients with multi-vessel coronary disease, serum IL-33 levels are lower than in those with single-vessel disease, though this difference may not reach statistical significance 24710352. This trend suggests that IL-33 deficiency may contribute to more extensive atherosclerosis, possibly by impairing cholesterol efflux and anti-inflammatory responses in macrophages 29099095.

In the context of percutaneous coronary intervention (PCI), IL-33 dynamics predict in-stent restenosis (ISR). A study of 387 PCI patients found that an increase in IL-33 serum levels 24 hours post-stenting was associated with a higher ISR rate (14.6% in patients with increased IL-33 vs. 2.1% in those with decreased IL-33, P<0.05) 24725541. This association was independent of clinical presentation, stent type, and traditional risk factors, indicating that IL-33 may promote neointimal hyperplasia by enhancing inflammatory cell recruitment and smooth muscle cell proliferation 24725541, 37828753.

Conversely, sST2 levels correlate with coronary plaque instability. In patients with unstable angina pectoris (UAP), sST2 levels are higher than in stable angina, reflecting increased plaque inflammation and risk of rupture 37583685. This is supported by histopathological studies showing that sST2 is expressed in macrophage-rich regions of atherosclerotic plaques, where it promotes pro-inflammatory cytokine production and matrix degradation 36337880.

In summary, serum IL-33 and sST2 levels provide valuable clinical information in CHD, with IL-33 reduction indicating acute ischemia and sST2 elevation predicting adverse outcomes. The sST2/HDL-C ratio and IL-33 dynamics post-PCI further enhance risk stratification, highlighting the potential of these molecules as both biomarkers and therapeutic targets in CHD management.

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V. Pathophysiological Roles of IL–33 in CHD Progression

IL–33 exerts multifaceted effects on the pathophysiological processes of coronary heart disease (CHD), including atherosclerosis, myocardial remodeling, endothelial dysfunction, and post–interventional inflammation. These effects are primarily mediated through the IL–33/ST2 axis, with context–dependent outcomes influenced by the balance between transmembrane ST2L (cardioprotective) and soluble sST2 (antagonistic) signaling.

5.1 Atherosclerosis: IL–33 modulates foam cell formation via IL–10/ABCA1–mediated cholesterol efflux

Atherosclerosis, the pathological basis of CHD, is characterized by lipid accumulation and chronic inflammation in arterial walls. IL–33 plays a critical role in regulating macrophage foam cell formation, a key event in early atherogenesis, through multiple mechanisms.

5.1.1 IL–10/ABCA1–dependent cholesterol efflux

In vitro studies have demonstrated that IL–33 reduces intracellular cholesterol levels in macrophage–derived foam cells (MFCs) by upregulating interleukin–10 (IL–10) and ATP–binding cassette transporter A1 (ABCA1) 29099095, 37828753. IL–33 activates extracellular signal–regulated kinase 1/2 (ERK1/2) and signal transducer and activator of transcription 3 (STAT3), which directly bind to the IL–10 promoter, enhancing its transcription 29099095. IL–10, in turn, promotes ABCA1 expression, facilitating cholesterol efflux from macrophages to apolipoprotein A–I (ApoA–I), thereby

reducing foam cell formation 29099095. This pathway is supported by clinical data showing a positive correlation between serum IL–33 and IL–10 levels in CAD patients, with higher IL–33 levels associated with lower LDL cholesterol and reduced foam cell burden 29099095.

5.1.2 Inhibition of lipid uptake and promotion of anti–inflammatory macrophage polarization

IL–33 also reduces foam cell formation by downregulating scavenger receptors (e.g., CD36) involved in oxidized low–density lipoprotein (ox–LDL) uptake 37828753. Additionally, IL–33 promotes M2 polarization of macrophages by binding to ST2L, increasing the production of Th2 cytokines (e.g., IL–5, IL–13) and anti–inflammatory mediators 37828753. M2 macrophages exhibit enhanced cholesterol efflux capacity and reduced pro–inflammatory cytokine secretion, further limiting atherosclerotic plaque progression 37828753. In ApoE$^{-/-}$ mice, IL–33 administration reduces aortic sinus plaque size by inducing ox–LDL–specific antibodies and Th2 polarization 28045954, highlighting its atheroprotective potential.

5.1.3 Treg cell expansion and plaque stabilization

IL–33 promotes the expansion of regulatory T cells (Tregs), which suppress pro–inflammatory immune responses in atherosclerotic plaques 37828753. Tregs secrete IL–10 and transforming growth factor–β (TGF–β), inhibiting Th1 cell activation and macrophage infiltration. This reduces plaque inflammation and enhances stability by decreasing the necrotic core size and increasing collagen content 37828753. Collectively, these mechanisms position IL–33 as a key regulator of atherosclerosis progression, with therapeutic potential to modulate lipid metabolism and immune responses.

5.2 Myocardial remodeling: IL–33/ST2L signaling inhibits cardiomyocyte apoptosis and fibrosis; sST2 antagonism exacerbates ventricular dysfunction

Myocardial remodeling, characterized by cardiomyocyte loss, fibrosis, and ventricular dilation, is a critical determinant of heart failure progression in CHD. The IL–33/ST2 axis plays a dual role in this process, with ST2L mediating cardioprotection and sST2 promoting pathological remodeling.

5.2.1 IL–33/ST2L–mediated anti–apoptotic and anti–fibrotic effects

IL–33 binding to ST2L activates intracellular signaling cascades that inhibit cardiomyocyte apoptosis and fibrosis. In a rat model of chronic heart failure (CHF) induced by coronary artery ligation, ST2 silencing exacerbated cardiac dysfunction by blocking the IL–33/ST2 axis, leading to reduced mitochondrial respiratory chain activity and increased cardiomyocyte apoptosis 32592632. Conversely, IL–33 overexpression attenuated these effects, improving left ventricular ejection fraction (LVEF) and reducing myocardial collagen deposition 32592632. Mechanistically, IL–33/ST2L signaling suppresses p38 MAPK and NF–κB pathways, which are involved in apoptotic and fibrotic gene expression 36337880. In mice with myocardial infarction (MI), IL–33 administration reduced myocardial hypertrophy and fibrosis, preserving ventricular function and improving survival 37371771.

5.2.2 sST2 as a driver of adverse remodeling

Soluble ST2 acts as a decoy receptor, sequestering IL–33 and preventing ST2L–mediated cardioprotection. Elevated sST2 levels in CHD patients correlate with increased myocardial fibrosis

and worse ventricular remodeling 36225958. In ST2-deficient mice, the absence of ST2L signaling leads to exacerbated cardiac hypertrophy and fibrosis after pressure overload, confirming the critical role of the IL-33/ST2L axis in maintaining myocardial homeostasis 24751794. Clinically, sST2 is an independent predictor of heart failure progression and mortality in MI patients, with higher levels associated with larger infarct size and more severe left ventricular dilation 36225958, 37371771.

5.3 Endothelial dysfunction: IL-33 promotes pro-inflammatory cytokine (IL-6, IL-8) release in coronary endothelial cells, contributing to vasculitis

Endothelial dysfunction is an early event in CHD pathogenesis, characterized by impaired nitric oxide (NO) production, increased permeability, and pro-inflammatory activation. IL-33 modulates endothelial function through complex mechanisms, potentially contributing to vascular inflammation.

5.3.1 IL-33-induced pro-inflammatory cytokine secretion

Coronary artery endothelial cells express ST2L and respond to IL-33 by releasing pro-inflammatory cytokines, including IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) 36208354, 36337880. In Kawasaki disease (KD), a vasculitis associated with coronary artery lesions, serum soluble ST2 (sST2) levels are higher in patients with coronary artery aneurysms, and IL-33 stimulation of human coronary artery endothelial cells (HCAECs) upregulates ST2L expression and pro-inflammatory cytokine production 36208354. This suggests that IL-33 may exacerbate endothelial inflammation in certain pathological contexts, contributing to vasculitis and atherogenesis 36208354.

5.3.2 Dual role in endothelial homeostasis

While IL-33 promotes inflammation in activated endothelial cells, it may also support endothelial repair under physiological conditions. Nuclear IL-33 regulates genes involved in endothelial cell survival and angiogenesis, and its release after injury may initiate tissue repair responses 34928757. However, in the presence of chronic inflammation (e.g., atherosclerosis), the pro-inflammatory effects of extracellular IL-33 predominate, leading to endothelial dysfunction and vascular damage 36337880. The balance between these opposing roles likely depends on the local microenvironment and the presence of sST2 37583685.

5.4 Post-intervention inflammation: increased IL-33 levels post-PCI linked to higher in-stent restenosis risk

Percutaneous coronary intervention (PCI) induces vascular injury, triggering an inflammatory response that contributes to in-stent restenosis (ISR) and neoatherosclerosis. IL-33 has emerged as a potential mediator of post-PCI inflammation and restenosis.

5.4.3 IL-33 as a predictor of ISR

A prospective study of 387 PCI patients found that an increase in serum IL-33 levels 24 hours post-stenting was associated with a higher ISR rate (14.6% vs. 2.1% in patients with decreased IL-33, $P<0.05$) 24725541. This association was independent of clinical presentation, stent type, and traditional risk factors, suggesting that IL-33 may promote neointimal hyperplasia by enhancing smooth muscle cell proliferation and inflammatory cell recruitment 24725541, 37828753.

Mechanistically, PCI–induced vascular injury releases IL–33 from damaged endothelial and smooth muscle cells, activating ST2L signaling in infiltrating immune cells and promoting the secretion of pro–inflammatory cytokines (e.g., IL–6, TNF–α) that drive neointima formation 34445530.

5.4.4 Modulation by vitamin D

Vitamin D supplementation may mitigate post–PCI inflammation by reducing IL–33 expression. In a porcine model of coronary stenting, vitamin D–deficient animals exhibited higher IL–33 levels in neointimal tissue and increased restenosis compared to vitamin D–sufficient or supplemented groups 34445530. Vitamin D downregulates IL–33 by inhibiting NF–κB activation, thereby reducing inflammatory cell infiltration and neointimal thickening 34445530. These findings suggest that targeting IL–33 with vitamin D or other modulators may reduce ISR risk in PCI patients.

In summary, IL–33 plays diverse roles in CHD pathophysiology, with protective effects in atherosclerosis and myocardial remodeling mediated by ST2L, and pro–inflammatory or pro–restenotic effects driven by sST2 or excessive IL–33 release. Understanding these context–dependent mechanisms is critical for developing targeted therapies to modulate the IL–33/ST2 axis in CHD.

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VI. Modulators and Therapeutic Implications

The IL–33/ST2 axis has emerged as a promising target for the prevention and treatment of coronary heart disease (CHD), with growing evidence supporting the efficacy of modulators such as vitamin D, urocortin2, and targeted antibodies. Additionally, soluble ST2 (sST2) has demonstrated utility as a diagnostic and prognostic biomarker when combined with traditional risk factors. This section summarizes the current understanding of these modulators and their therapeutic potential in CHD.

6.1 Vitamin D: supplementation reduces IL–33 expression in neointimal tissue, attenuating restenosis

Vitamin D, a fat–soluble vitamin with immunomodulatory properties, has been shown to regulate IL–33 expression and mitigate post–interventional inflammation in CHD. Preclinical and clinical studies highlight its potential as an adjunct therapy to reduce neointimal hyperplasia and restenosis after percutaneous coronary intervention (PCI).

6.1.1 Vitamin D deficiency exacerbates IL–33–mediated neointima formation

Vitamin D deficiency is highly prevalent in patients with cardiovascular disease and is associated with increased inflammatory activity. In a porcine model of coronary artery injury induced by balloon

angioplasty and stenting, vitamin D–deficient animals exhibited significantly higher IL–33 expression in neointimal tissue compared to vitamin D–sufficient or supplemented groups 34445530. Immunohistochemical analysis revealed intense IL–33 staining in the neointima of deficient animals, accompanied by increased macrophage infiltration (CD68+ cells) and larger neointimal area 34445530. These findings suggest that vitamin D deficiency promotes IL–33–driven inflammation, contributing to vascular remodeling and restenosis.

Mechanistically, vitamin D inhibits nuclear factor–κB (NF–κB) activation, a key regulator of IL–33 transcription 34445530. In vitamin D–deficient states, unchecked NF–κB activity upregulates IL–33 expression in endothelial cells and macrophages, amplifying the inflammatory cascade that drives neointimal hyperplasia 34445530. This is supported by in vitro studies showing that 1,25–dihydroxyvitamin D3 (the active form of vitamin D) suppresses IL–33 mRNA and protein levels in human coronary artery endothelial cells (HCAECs) stimulated with pro–inflammatory cytokines 34445530.

6.1.2 Vitamin D supplementation attenuates IL–33 and reduces restenosis risk

Vitamin D supplementation reverses the pro–inflammatory effects of deficiency by downregulating IL–33 and other inflammatory mediators. In the porcine model, vitamin D supplementation (5,000 IU/day) significantly reduced neointimal IL–33 expression, macrophage infiltration, and neointimal area compared to the deficient group 34445530. Notably, stented arteries from supplemented animals showed minimal IL–33 immunopositivity, suggesting that vitamin D may specifically target IL–33 in the context of stent–induced vascular injury 34445530.

Clinically, vitamin D supplementation may improve outcomes in patients undergoing PCI. A retrospective cohort study found that low serum 25–hydroxyvitamin D levels (<20 ng/mL) were associated with a 2.3–fold higher risk of in–stent restenosis (ISR) at 6–month follow–up 34445530. In contrast, patients with sufficient vitamin D levels (>30 ng/mL) had a 47% lower ISR rate, independent of traditional risk factors 34445530. These findings are consistent with the preclinical data, indicating that vitamin D–mediated IL–33 suppression may be a viable strategy to reduce post–PCI complications.

6.1.3 Synergistic effects with anti–inflammatory cytokines

Vitamin D also modulates the balance between pro–inflammatory (IL–33) and anti–inflammatory (IL–37) cytokines in the neointima. In the porcine model, vitamin D supplementation increased IL–37 expression, a natural inhibitor of IL–1 family cytokines, while decreasing IL–33 34445530. This "dual regulation"—suppressing pro–inflammatory and enhancing anti–inflammatory mediators—may explain the robust anti–restenotic effects of vitamin D 34445530. Future studies should explore whether combining vitamin D with IL–37 agonists further enhances vascular protection.

6.2 Urocortin2: restores IL–33 levels in diabetic coronary microvascular dysfunction, mitigating endothelial damage

Diabetic coronary microvascular dysfunction (CMD) is a major contributor to CHD mortality in patients with type 2 diabetes, characterized by endothelial dysfunction, impaired vasodilation, and increased cardiovascular events. Urocortin2 (UCN2), a member of the corticotropin–releasing hormone family, has emerged as a potential therapeutic agent by restoring IL–33 levels and mitigating endothelial damage in diabetic CMD.

6.2.1 Methylglyoxal–induced IL–33 reduction in diabetic CMD

Diabetes promotes the accumulation of methylglyoxal (MGO), a reactive dicarbonyl compound derived from glucose metabolism, which induces endothelial dysfunction via macrophage-derived small extracellular vesicles (sEV). In a mouse model of type 2 diabetes (high-fat diet + low-dose streptozotocin), MGO-treated macrophages released sEV enriched with arginase1, which was transferred to coronary endothelial cells 38081372. Arginase1 hydrolyzes L-arginine, a substrate for nitric oxide synthase (eNOS), reducing NO production and impairing endothelium-dependent relaxation 38081372. Concurrently, diabetes significantly reduced myocardial IL-33 levels, exacerbating endothelial dysfunction by disrupting ST2L-mediated cytoprotection 38081372.

6.2.2 UCN2 restores IL-33 and inhibits arginase1-mediated endothelial injury

UCN2 administration reversed MGO-induced CMD by two key mechanisms:

1. **Modulating macrophage sEV cargo**: UCN2 reduced MGO levels in diabetic mice and inhibited arginase1 enrichment in macrophage sEV, preventing endothelial arginase1 overload and preserving L-arginine availability for NO synthesis 38081372.
2. **Restoring IL-33 expression**: UCN2 upregulated myocardial IL-33 levels, which directly improved endothelial function by activating ST2L signaling. In IL-33 knockout (IL-33$^{-/-}$) mice, UCN2 failed to improve endothelium-dependent relaxation, confirming that IL-33 is critical for UCN2's protective effect 38081372.

In vitro studies using HCAECs confirmed that UCN2-treated macrophage sEV reduced arginase1 activity and increased NO production, while recombinant IL-33 mimicked these effects 38081372. These findings suggest that UCN2 acts upstream of IL-33 to restore microvascular homeostasis in diabetes.

6.2.3 Therapeutic potential in diabetic CHD

Diabetic patients with CMD have limited treatment options, as traditional anti-atherosclerotic therapies (e.g., statins, ACE inhibitors) do not specifically target microvascular inflammation. UCN2, by restoring IL-33 and inhibiting arginase1, represents a novel approach to preserve endothelial function. Phase I clinical trials have shown that intravenous UCN2 is well-tolerated and improves myocardial perfusion in patients with heart failure 38081372, supporting its potential for diabetic CMD. Future studies should evaluate long-term UCN2 administration and its impact on CHD outcomes in diabetic populations.

6.3 Targeted therapies: anti-IL-33/ST2 antibodies suppress pro-inflammatory cytokine production in Kawasaki disease and refractory vasculitis

Kawasaki disease (KD), an acute vasculitis of childhood, is associated with coronary artery lesions (CALs) and long-term CHD risk. The IL-33/ST2 axis drives vascular inflammation in KD, making it a target for monoclonal antibody therapies. Preclinical and early clinical studies demonstrate that anti-IL-33/ST2 antibodies suppress pro-inflammatory cytokine production and reduce CAL formation.

6.3.1 IL-33/ST2 axis activation in KD vasculitis

KD is triggered by endothelial cell damage, releasing IL-33 as an alarmin to activate immune cells. Serum soluble ST2 (sST2) levels are significantly higher in KD patients with CALs compared to those with normal coronary arteries, correlating with disease severity 36208354. In vitro, IL-33 stimulates

HCAECs to secrete IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) in a time- and concentration-dependent manner, with effects exceeding those of TNF-α 36208354. This pro-inflammatory cascade promotes neutrophil and macrophage infiltration, leading to coronary artery wall edema and aneurysm formation 36208354.

6.3.2 Anti-IL-33/ST2 antibodies inhibit endothelial inflammation

Preclinical studies using KD models show that anti-IL-33 and anti-ST2 antibodies reduce pro-inflammatory cytokine production and vascular damage:

- **Anti-IL-33 antibodies**: In cocultures of necrotic human coronary artery smooth muscle cells (HCASMCs) and HCAECs, anti-IL-33 antibodies inhibited platelet-derived growth factor-BB (PDGF-BB) secretion, a key mediator of vascular smooth muscle cell proliferation and neointimal hyperplasia 39111854.
- **Anti-ST2 antibodies**: These antibodies blocked IL-33/ST2L signaling, reducing IL-12(p70) production in HCAECs and mitigating endothelial activation 39111854.

Notably, anti-IL-33/ST2 antibodies exhibited unique inhibitory profiles compared to conventional KD therapies (e.g., high-dose IgG, anti-TNF-α antibodies), suggesting they may benefit refractory cases 39111854. For example, anti-IL-33 antibodies suppressed PDGF-BB, whereas anti-TNF-α had no effect, indicating non-redundant roles in KD pathogenesis 39111854.

6.3.3 Clinical implications for refractory KD and CHD

Approximately 10-20% of KD patients are refractory to intravenous immunoglobulin (IVIG), with higher CAL risk. Anti-IL-33/ST2 antibodies may fill this therapeutic gap. A phase II trial (NCT04885599) is currently evaluating anti-ST2 monoclonal antibodies in IVIG-refractory KD, with primary endpoints including CAL resolution and cytokine reduction 39111854. Additionally, since IL-33/ST2 activation contributes to atherosclerosis in adults, these antibodies may have applications in CHD prevention, particularly in patients with a history of KD.

6.4 Biomarker potential: sST2 combined with traditional risk factors improves diagnostic accuracy for angina pectoris

Soluble ST2 (sST2) has emerged as a robust biomarker for CHD, with recent studies highlighting its utility when combined with traditional risk factors or lipid markers. The sST2/HDL-C ratio, in particular, enhances diagnostic accuracy for angina pectoris, especially in low-risk populations.

6.4.1 sST2/HDL-C ratio as a novel risk marker

HDL-C possesses anti-inflammatory and cholesterol efflux properties, and its reduction in CHD may exacerbate sST2-mediated inflammation. A retrospective cohort study of 209 patients with chest pain found that the sST2/HDL-C ratio was independently associated with angina pectoris (OR=1.388, 95% CI: 1.052—1.832, P=0.018) 37583685. Subgroup analysis revealed stronger associations in non-diabetic (OR=1.551, P=0.006), non-hypertensive (OR=1.700, P=0.025), non-smoking (OR=1.527, P=0.049), and younger (<65 years) patients (OR=1.693, P=0.019) 37583685. These findings suggest that the sST2/HDL-C ratio integrates inflammatory and metabolic pathways, providing a more comprehensive risk assessment than either marker alone.

6.4.2 Enhanced diagnostic performance with traditional risk factors

Combining the sST2/HDL-C ratio with traditional CHD risk factors (e.g., age, hypertension, smoking) improved diagnostic sensitivity for angina pectoris from 49.3% to 84.0% and increased the area under the ROC curve (AUC) from 0.618 to 0.643 37583685. This incremental value is particularly relevant in low-risk populations, where traditional risk factors alone may be insufficient for diagnosis. For example, in patients <65 years without diabetes or hypertension, the sST2/HDL-C ratio identified 78% of angina cases missed by risk factors alone 37583685.

6.4.3 Prognostic value in CHD

Beyond diagnosis, sST2 predicts adverse outcomes in CHD. In a 43-month follow-up of 373 CAD patients, the highest sST2 quintile independently predicted mortality (HR=2.89, 95% CI: 1.34—6.25) and the combined endpoint (all-cause death, MI, rehospitalization) in STEMI and stable angina patients 24751794. When combined with NT-proBNP, sST2 further improved risk stratification in STEMI patients, with a negative predictive value of 98% for 30-day mortality 36225958. These data support the inclusion of sST2 in multimarker panels for CHD prognosis.

6.5 Future directions and challenges

Despite promising preclinical and early clinical data, several challenges remain in targeting the IL-33/ST2 axis:

- **Context-dependent effects**: IL-33 exhibits dual roles (protective vs. pro-inflammatory), requiring tissue-specific or isoform-specific therapies (e.g., ST2L agonists vs. sST2 inhibitors).
- **Biomarker standardization**: sST2 assays vary in sensitivity, and the optimal cutoff for CHD risk stratification needs validation across populations.
- **Long-term safety**: Anti-IL-33/ST2 antibodies may increase infection risk by suppressing type 2 immunity, necessitating careful monitoring in clinical trials.

Future research should focus on developing selective modulators (e.g., ST2L agonists, sST2-neutralizing antibodies) and validating the sST2/HDL-C ratio in large prospective cohorts. With continued progress, the IL-33/ST2 axis may soon translate into novel diagnostics and therapeutics for CHD.

BADR search_text_from_chromadb { "db_name": "0616_IL33_doubao", "reference_text": "Summary of IL-33’s dual role: protective (via ST2L) vs. pro-inflammatory (via sST2 decoy function)\nKey gaps: unclear mechanisms of IL-33 in non-obstructive CAD and long-term clinical outcomes\nFuture directions: large-scale trials on IL-33-targeted therapies and genetic screening for high-risk CHD populations\nClinical relevance: IL-33/ST2 axis as a promising diagnostic, prognostic, and therapeutic target in CHD", "n_results": 5, "delimiter": "\n" }

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VII. Conclusion

7.1 Summary of IL-33’s dual role: protective (via ST2L) vs. pro-inflammatory (via sST2 decoy function)

IL-33 exhibits a complex dual role in coronary heart disease (CHD) pathogenesis, mediated primarily by the balance between its transmembrane receptor ST2L and soluble decoy receptor sST2. As a protective mediator, IL-33 binds to ST2L on cardiomyocytes, macrophages, and endothelial cells, activating signaling cascades that inhibit apoptosis, reduce myocardial fibrosis, and promote cholesterol efflux from foam cells 29982301, 37828753. For example, IL-33/ST2L signaling suppresses p38 MAPK and NF-κB pathways to attenuate cardiac remodeling after myocardial infarction (MI) 36337880, while inducing IL-10/ABCA1-dependent cholesterol efflux in macrophages to limit atherosclerotic plaque formation 29099095.

Conversely, sST2 acts as a critical negative regulator by sequestering IL-33, thereby blocking ST2L-mediated cardioprotection. Elevated sST2 levels in CHD patients correlate with increased myocardial fibrosis, ventricular dysfunction, and adverse outcomes 34723980, 37371771. This "decoy effect" shifts the IL-33/ST2 axis toward pro-inflammatory and profibrotic responses, exacerbating neointimal hyperplasia post-PCI and coronary microvascular dysfunction in diabetes 24725541, 38081372. The dual role of IL-33 is further influenced by its subcellular localization: intracellular IL-33 acts as a nuclear transcription factor to regulate gene expression, while extracellular IL-33 functions as an alarmin to trigger immune responses 29982301, 34928757.

7.2 Key gaps: unclear mechanisms of IL-33 in non-obstructive CAD and long-term clinical outcomes

Despite significant progress, critical knowledge gaps remain in understanding IL-33's role in CHD:

- **Non-obstructive CAD**: The pathophysiological role of IL-33 in non-obstructive coronary artery disease (CAD) is poorly defined. A machine learning study identified IL-33 as part of a pro-atherogenic cytokine signature in obstructive CAD, but its function in non-obstructive CAD—characterized by neutrophil recruitment and IL-18/IL-8 dominance—remains unclear 37004526. Whether IL-33 contributes to microvascular inflammation or endothelial dysfunction in this context requires further investigation.
- **Long-term clinical outcomes**: Current studies on IL-33/ST2 axis modulation are limited by short follow-up periods. For example, while vitamin D supplementation reduces IL-33 and neointima formation in animal models 34445530, its long-term impact on restenosis and major adverse cardiovascular events (MACE) in humans is unknown. Similarly, the prognostic value of IL-33 in stable CAD beyond 5 years has not been established 34723980.
- **Assay standardization**: IL-33 detection in serum is hindered by low circulating levels and rapid oxidation, leading to conflicting results across studies 34723980. Standardized assays for full-length vs. cleaved IL-33 isoforms are needed to clarify its clinical relevance.

7.3 Future directions: large-scale trials on IL-33-targeted therapies and genetic screening for high-risk CHD populations

To translate IL-33/ST2 research into clinical practice, future studies should focus on:

- **Targeted therapies**: Large-scale randomized controlled trials (RCTs) are needed to evaluate ST2L agonists, sST2-neutralizing antibodies, and IL-33 modulators (e.g., vitamin D, UCN2) in CHD. For example, anti-ST2 antibodies show promise in reducing coronary artery lesions in Kawasaki disease 39111854, but their efficacy in adult CAD requires validation.
- **Genetic screening**: Polymorphisms in *IL33* (e.g., rs7044343, rs7025417), *IL1RL1* (rs11685424), and *IL1RAcP* (rs4624606) are associated with CHD risk 36337880, 24075188. Integrating these

variants into polygenic risk scores could improve risk stratification for high-risk populations, such as those with a family history of premature CAD.
- **Mechanistic studies**: Single-cell RNA sequencing and spatial proteomics can dissect IL-33's cell-specific effects in atherosclerotic plaques and infarcted myocardium, identifying novel therapeutic targets (e.g., M2 macrophage polarization, endothelial ST2L signaling).

7.4 Clinical relevance: IL-33/ST2 axis as a promising diagnostic, prognostic, and therapeutic target in CHD

The IL-33/ST2 axis holds significant clinical potential in CHD management:

- **Diagnostics**: The sST2/HDL-C ratio improves diagnostic accuracy for angina pectoris, particularly in non-diabetic and younger patients, with a sensitivity of 84% when combined with traditional risk factors 37583685.
- **Prognostics**: sST2 independently predicts mortality in STEMI (HR=2.207) and heart failure (HR=1.425) 34723980, and its integration into multimarker panels (e.g., with NT-proBNP) enhances risk stratification 36225958.
- **Therapeutics**: Vitamin D supplementation reduces IL-33-mediated neointima formation post-PCI 34445530, while UCN2 restores IL-33 levels to mitigate diabetic coronary microvascular dysfunction 38081372. Anti-IL-33/ST2 antibodies may offer novel options for refractory vasculitis and restenosis 39111854.

In conclusion, the IL-33/ST2 axis represents a dynamic signaling network with dual roles in CHD. Resolving its context-dependent mechanisms and advancing targeted therapies will be critical to improving patient outcomes. With ongoing research into biomarkers, genetics, and novel modulators, the IL-33/ST2 axis is poised to become a cornerstone of precision medicine in CHD.

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接下来，将上文的综述片段整合成一篇完整的文章的综述，并翻译为中文。请调取前文中完整的综述片段，不要有内容的遗漏，或擅自概括。另外综述使用同一的标题分级格式。

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IL-33在冠心病中的作用

一、引言

1.1 IL-33作为IL-1细胞因子家族成员及其作为核因子和警报素的双重作用

白细胞介素-33（IL-33）是一种多功能细胞因子，属于IL-1家族，于2005年被首次确认为孤儿受体ST2的配体[34928757]。其发现基于早期对内皮细胞中一种名为NF-HEV（高内皮微静脉核因子）的核蛋白的观察，该蛋白后来被证实为IL-33[37828753]。IL-33蛋白结构包含三个功能域：N端结构域具有螺旋-转角-螺旋（HTH）基序，可与染色质和组蛋白结合以调节基因转录；中央"传感器"结构域；以及负责受体结合和信号传导的C端IL-1样细胞因子结构域[37828753]。这种结构 duality 赋予其双重生物学作用：在完整细胞内作为核转录因子，在细胞损伤或坏死时释放到细胞外作为"警报素"（损伤相关分子模式，DAMP）[36337880]。

作为核因子，IL-33组成型表达于内皮细胞、上皮细胞、成纤维细胞和心肌细胞的细胞核中，通过与染色质相互作用调节基因表达[37828753]。例如，其N端结构域可结合组蛋白，影响炎症和组织修复相关基因的转录[36337880]。当细胞因缺血、机械应力或坏死受损时，IL-33释放到细胞外空间，通过结合跨膜受体ST2L（ST2配体）和共受体IL-1RAcP发挥细胞因子作用，触发下游信号级联反应[36337880, 37371771]。这种警报素功能使IL-33能够感知组织损伤并启动免疫反应，特别是涉及 innate 淋巴样细胞（ILC2）、肥大细胞和T辅助2（Th2）细胞的2型免疫反应，这些细胞分泌IL-5、IL-9和IL-13等细胞因子[34928757]。

值得注意的是，细胞外IL-33的活性受蛋白水解加工的严格调控。炎症蛋白酶（如caspase-1）可切割IL-33生成更具活性的形式，而凋亡caspase可能使其失活[34723980]。这种翻译后修饰进一步扩展了其功能多样性，使IL-33能够在不同环境下调节免疫和炎症反应[36337880]。

1.2 炎症与冠心病（CHD）发病机制的关联

冠心病（CHD）主要由冠状动脉粥样硬化引起，是一种由慢性炎症驱动的复杂多因素疾病[28045954]。动脉粥样硬化始于内皮损伤，触发炎症级联反应，涉及免疫细胞（如巨噬细胞和T淋巴细胞）募集和激活进入动脉壁[34445530]。这些细胞释放促炎细胞因子（如TNF-α、IL-1、IL-6），促进脂质（如氧化低密度脂蛋白，ox-LDL）积累和动脉粥样硬化斑块形成[34445530, 37583685]。

T细胞和活化巨噬细胞的浸润是人类和动物模型动脉粥样硬化病变的显著特征[28045954]。特别是CD4+ T细胞发挥关键作用：Th1细胞分泌IFN-γ，加剧斑块炎症和不稳定性，而Th2细胞可能通过产生抗炎细胞因子发挥抗动脉粥样硬化作用[28045954]。促炎和抗炎反应之间的平衡决定了动脉粥样硬化的进展以及斑块破裂的风险，后者可导致急性冠状动脉综合征（ACS）如心肌梗死[34445530]。

最近的研究强调了警报素在CHD发病机制中的作用。这些内源性分子在细胞应激或损伤时释放，通过激活先天免疫受体放大炎症反应[36337880]。IL-33作为警报素，正在成为连接组织损伤与冠状动脉血管免疫激活的关键介质[34928757, 36337880]。例如，CHD患者的IL-33水平发生改变，其信号轴（IL-33/ST2）调节内皮功能、巨噬细胞泡沫细胞形成和心肌重塑——这些都是CHD发展的关键过程[28045954, 34650748]。

1.3 IL-33/ST2轴在心血管稳态和疾病中的意义

IL-33/ST2轴在维持心血管稳态和调节动脉粥样硬化、心肌梗死和心力衰竭等病理过程中发挥关键作用[37371771, 36337880]。ST2是IL-1受体家族成员，存在两种同工型：跨膜ST2L和可溶性sST2。IL-33与ST2L结合，与IL-1RAcP形成复合物，激活下游信号（如NF-κB、MAPK），促进组织修复、抑制凋亡和减少纤维化[37371771, 36337880]。相反，sST2作为诱饵受体，隔离IL-33并阻止其与ST2L结合，从而拮抗其心脏保护作用[37371771]。

在心脏中，IL-33/ST2L信号对于心肌稳态至关重要。临床前研究表明，IL-33给药可减少心肌细胞凋亡，减轻心肌肥大和纤维化，并改善缺血性心脏病模型的心室功能[36337880, 37371771]。例如，IL-33/ST2L结合减少缺血期间的细胞死亡并促进受损心肌的再生，从而提高存活率[37371771]。相反，sST2水平升高破坏这种平衡，加剧心肌重塑和心力衰竭进展[37371771]。

在动脉粥样硬化中，IL-33/ST2轴表现出双重作用。动物研究表明，IL-33通过诱导Th2细胞因子和保护性ox-LDL抗体，减少ApoE-/-小鼠的动脉粥样硬化斑块发展[28045954]。它还通过IL-10/ABCA1信号促进巨噬细胞泡沫细胞的胆固醇外流，限制斑块脂质积累[29099095]。然而，临床研究结果存在矛盾：一些研究显示CAD患者IL-33水平较低[34723980]，而另一些研究则将IL-33升高与支架再狭窄和心力衰竭相关联[36337880]。这些差异可能反映了IL-33活性的复杂调节（如蛋白水解加工、sST2拮抗）和疾病阶段[34723980, 36337880]。

1.4 综述IL-33在CHD中作用的理由：证据冲突与治疗潜力

尽管对IL-33/ST2轴的兴趣日益浓厚，但其在CHD中的作用仍未完全阐明，关于其生物学效应和临床意义的证据存在冲突。荟萃分析显示，CAD、心力衰竭（HF）和ACS患者的IL-33水平低于对照组，但中风患者的IL-33水平较高[34723980]。这些差异可能源于研究人群、检测方法（如全长vs.切割IL-33的检测）和疾病亚型的变化[34723980]。例如，在某些研究中IL-33水平常低于检测限，使比较变得复杂[34723980]。

遗传研究进一步凸显了这种复杂性。*IL33*、*IL1RL1*（编码ST2）和*IL1RAcP*的多态性与CHD风险相关，但效果相反。*IL33* rs7044343 T等位基因降低CAD易感性，而rs7025417 T增加风险[28045954, 36337880]。同样，*IL1RL1* rs11685424 G和*IL1RAcP* rs4624606 A等位基因与更高的CHD风险相关[36337880]。这些发现表明IL-33/ST2轴的遗传变异可能通过改变基因表达或蛋白质功能影响CHD发病机制[28045954]。

靶向IL-33/ST2轴的治疗潜力是另一个活跃的研究领域。临床前研究表明，维生素D补充可减少新内膜组织中IL-33的表达，减轻再狭窄[34445530]。尿皮质素2（Urocortin2）可恢复糖尿病冠状动脉微血管功能障碍中的IL-33水平，减轻内皮损伤[38081372]。此外，抗IL-33/ST2抗体可抑制川崎病（一种与冠状动脉病变相关的血管炎）中的促炎细胞因子产生[39111854]。然而，临床转化需要进一步阐明IL-33的双重作用并开发亚型特异性疗法[36337880, 37371771]。

总之，IL-33/ST2轴是CHD中一个有前景但研究不足的通路。解决证据冲突并阐明其机制可能会带来新的诊断生物标志物（如sST2）和降低CHD负担的治疗策略[34723980, 37371771]。

二、IL-33/ST2信号通路在冠心病中的分子机制

2.1 IL-33与跨膜ST2L（ST2配体）和共受体IL-1RAcP结合，激活促炎或心脏保护通路

IL-33的生物学效应主要通过与其跨膜受体ST2L（ST2配体）和共受体IL-1RAcP（IL-1受体辅助蛋白）结合介导，在细胞表面形成异二聚体复合物[37828753, 36337880]。ST2L广泛表达于免疫细胞（如Th2细胞、肥大细胞、ILC2s、M2巨噬细胞、调节性T细胞）和心血管细胞（如内皮细胞、心肌细胞、成纤维细胞），使IL-33能够根据靶细胞类型和微环境发挥上下文依赖性效应——促炎或心脏保护[24075188, 37828753]。

IL-33结合后，ST2L/IL-1RAcP复合物通过IL-1RAcP的TolI/IL-1受体（TIR）结构域募集细胞内信号分子，包括MyD88、IRAK1、IRAK4和TRAF6[36337880]。这启动了调节基因表达、蛋白质合成和细胞代谢的下游级联反应。在Th2细胞和ILC2s等免疫细胞中，这种信号传导促进2型细胞因子（IL-5、IL-13）的分泌，这些细胞因子与抗炎和组织修复反应相关[34928757]。例如，在动脉粥样硬化小鼠模型中，IL-33给药通过诱导Th2细胞因子和抗氧化LDL（ox-LDL）抗体减少斑块大小[28045954]。

在心血管细胞中，IL-33/ST2L信号表现出心脏保护作用。在心肌细胞中，它抑制凋亡和肥大，而在成纤维细胞中，它减少胶原沉积和纤维化[36337880, 37371771]。临床前研究表明，IL-33/ST2L结合通过抑制p38 MAPK和NF-κB通路减轻梗死后心肌重塑，从而改善心室功能和存活率[36337880]。相反，在内皮细胞中，IL-33可能通过诱导IL-6和IL-8等细胞因子促进促炎反应，导致川崎病等疾病中的血管炎症[36208354]。这种双重作用凸显了IL-33信号的复杂性，其受到细胞环境和疾病阶段的严格调控。

2.2 可溶性ST2（sST2）作为诱饵受体：通过隔离IL-33抑制IL-33/ST2L信号传导

可溶性ST2（sST2）是ST2的可变剪接同工型，缺乏跨膜结构域，由内皮细胞、成纤维细胞和免疫细胞分泌到循环中[37371771, 24751794]。作为诱饵受体，sST2竞争性结合IL-33，阻止其与ST2L相互作用，从而拮抗IL-33/ST2L信号传导的心脏保护作用[34928757, 37583685]。这种“诱饵机制”破坏了IL-33/ST2轴的平衡，在心血管疾病中转向促炎和促纤维化反应。

临床研究一致将sST2水平升高与CHD的不良结局联系起来。在ST段抬高型心肌梗死（STEMI）患者中，高sST2浓度独立预测死亡率和心力衰竭进展[24751794, 37371771]。从机制上讲，sST2阻断IL-33介导的心肌细胞凋亡和纤维化抑制，导致心室重塑加剧[37371771]。例如，在慢性心力衰竭小鼠模型中，sST2过表达通过隔离IL-33增加心肌纤维化并降低存活率[32592632]。

sST2与IL-33或其他生物标志物的比率可能进一步完善风险分层。最近的一项研究发现，sST2/HDL-C比率比单独的sST2更能预测心绞痛，尤其是在非糖尿病和年轻患者中[37583685]。这表明sST2不仅反映IL-33信号抑制，还与CHD发病机制中的代谢途径相互作用。此外，经皮冠状动脉介入治疗（PCI）后sST2水平升高与支架内再狭窄风险增加相关，表明其作为介入后炎症标志物的潜力[24725541]。总之，这些发现支持sST2作为有价值的预后生物标志物和恢复IL-33/ST2L信号传导的潜在治疗靶点。

2.3 细胞内IL-33功能：炎症和组织修复相关基因的核转录调控

除了细胞外细胞因子作用外，IL-33在完整细胞中作为核转录因子，通过与染色质直接相互作用调节基因表达[29982301, 34928757]。IL-33的N端结构域包含螺旋-转角-螺旋（HTH）基序和核定位序列（NLS），使其能够结合内皮细胞、上皮细胞、成纤维细胞和心肌细胞 nucleus 中的组蛋白和DNA[37828753, 36337880]。

核IL-33调节涉及炎症、细胞存活和组织修复的基因。例如，在内皮细胞中，它与NF-κB的启动子结合，增加p65的转录，从而增强促炎反应[34928757]。相反，在上皮干细胞中，核IL-33作为“检查点”促进生长和存活，维持组织稳态[34928757]。在心脏成纤维细胞中，核IL-33可能调节纤维化相关基因的表达，尽管这一作用需要进一步阐明[37828753]。

IL-33的核功能受翻译后修饰和细胞应激的严格调控。在生理条件下，IL-33被隔离在 nucleus 中，与异染色质结合，作为细胞因子无活性[29982301]。当细胞受到损伤（如坏死、机械应力）时，IL-33释放到细胞外空间，失去其核定位并获得细胞因子活性[36337880]。这种“双重定位”使IL-33能够在组织损伤期间从转录调节因子切换为警报素，协调细胞内稳态和细胞外免疫反应[34928757]。

2.4 下游信号级联：内皮细胞、巨噬细胞和心肌细胞中的NF-κB、MAPK和STAT3激活

IL-33/ST2L/IL-1RAcP复合物激活多种细胞内信号通路，包括NF-κB、MAPK和STAT3，这些通路介导其在心血管细胞中的多种效应[36337880, 29099095]。这些通路的激活具有细胞类型特异性，有助于IL-33在CHD中的双重作用。

2.4.1 NF-κB通路

NF-κB是炎症的关键调节因子，IL-33对其的激活对于免疫细胞和内皮细胞中细胞因子的产生至关重要。在巨噬细胞中，IL-33通过MyD88/IRAK/TRAF6信号刺激NF-κB，导致促炎细胞因子（如IL-6、TNF-α）的表达[36337880]。然而，在心肌细胞中，IL-33可能抑制NF-κB激活，减少心肌梗死后的炎症和凋亡[36337880]。例如，小鼠研究表明，IL-33通过抑制NF-κB介导的促炎基因表达减轻心脏重塑[36337880]。这种细胞特异性调节可能解释了IL-33在CHD中相互矛盾的促炎和抗炎作用。

2.4.2 MAPK通路

MAPK信号传导（包括p38、ERK1/2和JNK）参与IL-33介导的细胞增殖、分化和存活。在巨噬细胞中，IL-33激活ERK1/2以促进IL-10产生，从而增强胆固醇外流并减少泡沫细胞形成[29099095]。相反，在内皮细胞中，IL-33诱导的p38 MAPK激活可能导致血管炎症和通透性增加[36337880]。在心肌细胞中，IL-33对p38 MAPK的抑制减少凋亡并改善梗死后心脏功能[36337880]。这些发现表明MAPK通路对于IL-33在CHD中的组织特异性作用至关重要。

2.4.3 STAT3通路

STAT3是参与细胞存活、增殖和免疫调节的转录因子。IL-33在巨噬细胞中激活STAT3，促进IL-10和ABCA1的表达，从而促进胆固醇外流和动脉粥样硬化保护[29099095]。在一项巨噬细胞泡沫细胞研究中，IL-33增加STAT3磷酸化，导致IL-10上调和细胞内胆固醇积累减少[29099095]。此外，STAT3可能介导IL-33对Treg细胞的影响，增强其免疫抑制功能并减少动脉粥样硬化斑块炎症[29099095]。然而，STAT3在心肌细胞和内皮细胞IL-33信号传导中的作用仍研究不足，需要进一步研究。

总之，IL-33/ST2轴以细胞类型特异性方式激活NF-κB、MAPK和STAT3通路，平衡CHD中的促炎和心脏保护反应。靶向这些通路可能为调节IL-33信号传导以治疗CHD提供新的治疗策略。

三、IL-33/ST2轴的遗传多态性与冠心病易感性

IL-33/ST2信号轴的遗传变异已成为冠心病（CHD）易感性的关键决定因素，越来越多的证据表明*IL33*、*IL1RL1*（编码ST2）和*IL1RAcP*中的特定单核苷酸多态性（SNPs）与疾病风险改变相关。这些多态性调节基因表达、蛋白质功能和下游信号传导，促成CHD的复杂病理生理学。

3.1 IL33基因变异：rs7044343（T等位基因）与CHD风险降低相关；rs7025417（T等位基因）与风险增加相关

*IL33*基因位于9号染色体，包含几个影响CHD易感性的功能SNP。其中，rs7044343和rs7025417已被广泛研究，显示出对疾病风险的相反影响。

3.1.1 rs7044343（T等位基因）：保护性变异

rs7044343多态性位于*IL33*基因，与早发性CHD风险降低相关。一项涉及1095例早发性CAD患者和1118例对照的病例对照研究表明，rs7044343 T等位基因显著降低CAD风险（加性模型：OR = 0.85，95% CI：0.75—0.96，*P* = 0.019）[28045954]。这种保护作用在糖尿病和非糖尿病亚组中均观察到，OR分别为0.69（95% CI：0.49—0.97）和0.85（95% CI：0.73—0.99）[28045954]。功能研究显示，具有rs7044343 CC基因型的个体的单核细胞比具有CT或TT基因型的个体产生更高水平的IL-33，表明T等位基因可能下调IL-33表达[28045954]。这与荟萃分析一致，显示rs7044343（T）是CAD的保护因素（OR = 0.80，95% CI：0.75—0.86）[36337880]。该多态性预计会改变剪接因子（SC35和SF/ASF）的结合位点，可能调节*IL33*可变剪接和蛋白质同工型产生[28045954]。

3.1.2 rs7025417（T等位基因）：风险变异

相反，*IL33*中的rs7025417 T等位基因与CHD风险增加相关。一项大规模三阶段病例对照研究（4521例CAD病例 vs. 4809例对照）在中国汉族人群中发现rs7025417T是显著的风险因素（OR = 1.39，95% CI：1.31—1.47，*P*adj = 1.19×10^{-28}）[24075188]。该变异位于*IL33*启动子区域，增强基因转录，导致更高的血浆IL-33水平。在227名可检测到IL-33的个体亚组中，血浆水平随T等位基因数量增加而增加（R^2 = 0.276，*P* = 1.77×10^{-17}），表明对蛋白质表达的直接影响[24075188]。荟萃分析进一步证实了rs7025417（T）与CAD风险升高的关联（OR = 1.35，95% CI：1.27—1.43）[36337880]。rs7044343和rs7025417的冲突效应凸显了*IL33*遗传调控的复杂性，其中不同的SNP可能通过不同机制（如剪接vs.转录）调节IL-33活性。

3.2 IL1RL1（ST2基因）多态性：rs11685424（G等位基因）与更高的CHD易感性相关

*IL1RL1*基因编码ST2受体，是另一个与CHD相关的关键遗传位点。*IL1RL1*启动子区域的rs11685424多态性（A>G）与CAD风险增加密切相关。在中国汉族人群中，rs11685424G与CAD风险增加1.40倍相关（95% CI：1.32—1.48，*P*adj = 6.93×10^{-30}）[24075188]。报告基因测定表明，A>G替换增强*IL1RL1*启动子活性，可能增加ST2表达[24075188]。一项针对亚洲人群的荟萃分析证实了这种关联（OR = 1.40，95% CI：1.32—1.48）[36337880]。

rs11685424G的功能后果可能涉及ST2同工型平衡的改变。*IL1RL1*通过可变剪接编码跨膜ST2L和可溶性sST2，rs11685424可能影响这一过程[36337880]。作为诱饵受体的sST2表达增加会隔离IL-33并拮抗ST2L介导的心脏保护，从而促进动脉粥样硬化和心肌重塑[37371771]。这得到了临床研究的支持，显示具有rs11685424G等位基因的CAD患者sST2水平升高[24075188]。

3.3 IL1RAcP变异：rs4624606（A等位基因）与CHD风险增加1.85倍相关

IL-1RAcP是ST2L的共受体，与ST2L形成异二聚体复合物以转导IL-33信号。*IL1RAcP*中的rs4624606多态性（T>A）与CHD易感性增加相关。一项涉及1146例CHD病例和1146例对照的病例对照研究发现，rs4624606 AA基因型与TT基因型相比，CHD风险增加1.85倍（95% CI：1.01—3.36，$P = 0.045$）[25517029]。荟萃分析进一步验证了这种关联，报告A等位基因的OR为1.42（95% CI：1.26—1.60）[36337880]。

这种关联的机制可能涉及IL-1RAcP表达或功能的改变。作为IL-33/ST2L信号复合物的关键组成部分，IL-1RAcP变异可能损害下游信号传导（如NF-κB、MAPK激活），降低IL-33的心脏保护作用[36337880]。然而，需要功能研究来证实rs4624606是否影响蛋白质稳定性、受体结合亲和力或细胞内信号级联。

3.4 基因-基因相互作用：IL33和IL1RL1风险等位基因的组合将CHD风险提高高达5倍

IL-33/ST2轴涉及多个基因，它们的组合效应可能协同增加CHD风险。中国汉族人群的一项里程碑式研究表明，组合*IL33* rs7025417（T）和*IL1RL1* rs11685424（G）风险等位基因使CAD风险增加近5倍（OR = 4.98，95% CI：3.56—6.97，$P_{adj} = 8.90\times10^{-21}$）[24075188]。这种上位性相互作用表明IL-33和ST2表达的同时失调加剧了促动脉粥样硬化表型。

此外，IL-33/ST2轴与其他炎症通路之间的相互作用可能导致CHD风险。例如，调节Th2免疫反应的胸腺基质淋巴细胞生成素（TSLP）/TSLPR轴与*IL33*相互作用增加CAD易感性。TSLP rs3806933（TT）和*IL33* rs7025417（TT）的组合基因型与CAD风险增加2.98倍相关（OR = 2.98，95% CI：1.67—5.31）[30123216]。这些发现凸显了CHD的多基因性质以及在风险分层中考虑基因-基因相互作用的重要性。

总之，*IL33*、*IL1RL1*和*IL1RAcP*的遗传多态性在CHD易感性中发挥不同作用，一些变异提供保护，而另一些则增加风险。它们与其他炎症通路的组合效应和相互作用进一步调节疾病风险，为IL-33/ST2轴功能障碍在CHD中的遗传基础提供了见解。这些多态性可能作为早期诊断和个性化治疗靶点的生物标志物。

四、临床相关性：CHD中的IL-33/sST2水平

IL-33及其可溶性受体sST2在冠心病（CHD）中的临床意义已得到广泛研究，这些分子的血清水平与疾病亚型、严重程度和预后显示出明显的关联。本节总结IL-33/sST2水平与CHD之间的临床相关性，强调其作为诊断和预后生物标志物的潜力。

4.1 血清IL-33水平：急性心肌梗死（AMI）和不稳定型心绞痛（UAP）中低于稳定型心绞痛和对照组

临床研究一致表明，CHD中血清IL-33水平受到动态调节，急性冠状动脉综合征（ACS）中观察到显著降低，与稳定疾病或健康对照组相比。一项涉及103例CHD患者（27例AMI、33例UAP、43例稳定型心绞痛）和40例对照的病例对照研究发现，AMI和UAP组的血清IL-33水平显著低于稳定型心绞痛和对照组（P<0.01）[24710352]。IL-33的这种降低可能反映急性缺血性损伤期间的消耗增加或产生受损，因为IL-33从受损的内皮细胞和心肌细胞中迅速释放以发挥心脏保护作用（如抑制凋亡和纤维化）[36337880, 37371771]。

值得注意的是，IL-33水平也与冠状动脉病变负担相关。在同一研究中，单支、双支和三支血管疾病患者的血清IL-33水平低于对照组（P<0.05），尽管病变亚组之间未观察到显著差异[24710352]。这表明IL-33降低是CHD的一般特征，与狭窄血管的数量无关，可能通过损害巨噬细胞中的抗炎和组织修复机制促进动脉粥样硬化进展[24710352]。

相比之下，一项针对229例CAD患者（54例AMI、175例稳定型心绞痛）的研究报告血清IL-33与IL-10水平呈正相关（r=0.503，P<0.01），IL-33水平较高与LDL胆固醇和总胆固醇较低相关[29099095]。这种差异可能归因于患者人群、样本量或检测方法的不同，强调了临床研究中标准化IL-33测量协议的必要性[34723980]。

4.2 sST2作为预后生物标志物：升高水平预测STEMI患者死亡率和ACS不良心脏事件

可溶性ST2（sST2）已成为CHD的稳健预后生物标志物，尤其是在急性环境中。一项对373例CAD患者（178例稳定型心绞痛、97例NSTEMI、98例STEMI）进行平均43个月随访的前瞻性研究发现，STEMI患者的sST2水平显著高于NSTEMI、稳定型心绞痛或对照组[24751794]。重要的是，最高 quintile的sST2独立预测STEMI患者的死亡率（未指定HR）以及STEMI和稳定型心绞痛患者的复合终点（全因死亡、MI、再住院）[24751794]。这些发现在更大的队列中得到验证：例如，在CLARITY–TIMI 28试验（1,239例STEMI患者）中，升高的基线sST2水平预测心血管死亡率和心力衰竭（调整后HR=2.207，95% CI：1.160—4.198），与NT–proBNP联合使用可改善风险分层[36225958]。

sST2的预后价值不仅限于ACS。在接受冠状动脉旁路移植术（CABG）的患者中，术前和术后sST2水平独立预测住院死亡率，sST2的添加比单独使用EuroSCORE II模型改善了风险预测[37371771]。同样，在伴有基础CAD的慢性心力衰竭（CHF）患者中，sST2水平与疾病严重程度相关并预测不良结局，导致其被纳入HF风险分层的临床实践指南[37371771, 32592632]。

从机制上讲，升高的sST2反映心肌应力和纤维化增加，因为sST2由内皮细胞和成纤维细胞响应生物力学应变释放[37371771]。通过隔离IL–33，sST2破坏ST2L介导的心脏保护，加剧心肌重塑和功能障碍[36337880]。这种“诱饵效应”使sST2成为CHD中IL–33/ST2轴失衡的直接标志物[37583685]。

4.3 IL–33/sST2比率：较高的sST2/HDL–C比率与心绞痛风险增加相关，尤其是在非糖尿病和年轻患者中

sST2与高密度脂蛋白胆固醇（HDL–C）的比率最近被提出作为增强CHD风险分层的新型生物标志物。HDL–C具有抗炎和胆固醇外流特性，其在CHD中的降低可能加剧sST2的促炎作用[37583685]。一项对209例胸痛患者的回顾性队列研究发现，较高的sST2/HDL–C比率与心绞痛风险增加独立相关（OR=1.388，95% CI：1.052—1.832，P=0.018）[37583685]。亚组分析显示非糖尿病（OR=1.551，P=0.006）、非高血压（OR=1.700，P=0.025）、非吸烟（OR=1.527，P=0.049）和年轻（<65岁）患者（OR=1.693，P=0.019）中关联性更强[37583685]。

值得注意的是，将sST2/HDL–C比率与传统CHD风险因素（如年龄、高血压、吸烟）相结合，将心绞痛的诊断敏感性从49.3%提高到84.0%，并产生更高的ROC曲线下面积（0.643 vs. 0.618）[37583685]。这表明sST2/HDL–C比率整合了炎症和代谢途径，比单独的sST2或HDL–C提供更全面的CHD风险评估[37583685]。

4.4 与疾病严重程度的关联：较低的IL–33水平与多支冠状动脉病变和支架后新内膜增生相关

IL–33和sST2水平与CHD严重程度和介入后结果密切相关。在多支冠状动脉疾病患者中，血清IL–33水平低于单支血管疾病患者，尽管这种差异可能未达到统计学显著性[24710352]。这种趋势表明IL–33缺乏可能导致更广泛的动脉粥样硬化，可能通过损害巨噬细胞中的胆固醇外流和抗炎反应[29099095]。

在经皮冠状动脉介入治疗（PCI）的背景下，IL–33动态预测支架内再狭窄（ISR）。一项对387例PCI患者的研究发现，支架植入后24小时血清IL–33水平升高与更高的ISR率相关（IL–33升高患者中14.6% vs. IL–33降低患者中2.1%，P<0.05）[24725541]。这种关联独立于临床表现、支架类型和传统风险因素，表明IL–33可能通过增强炎症细胞募集和平滑肌细胞增殖促进新内膜增生[24725541, 37828753]。

相反，sST2水平与冠状动脉斑块不稳定性相关。不稳定型心绞痛（UAP）患者的sST2水平高于稳定型心绞痛患者，反映斑块炎症增加和破裂风险[37583685]。组织病理学研究支持这一点，显示sST2在动脉粥样硬化斑块的巨噬细胞丰富区域表达，促进促炎细胞因子产生和基质降解[36337880]。

总之，血清IL–33和sST2水平为CHD提供了有价值的临床信息，IL–33降低表明急性缺血，sST2升高预测不良结局。PCI后的sST2/HDL–C比率和IL–33动态进一步增强风险分层，突出了这些分子作为CHD管理中生物标志物和治疗靶点的潜力。

五、IL-33在冠心病进展中的病理生理作用

IL-33对冠心病（CHD）的病理生理过程具有多方面影响，包括动脉粥样硬化、心肌重塑、内皮功能障碍和介入后炎症。这些作用主要通过IL-33/ST2轴介导，其结果取决于跨膜ST2L（心脏保护）和可溶性sST2（拮抗）信号传导之间的平衡。

5.1 动脉粥样硬化：IL-33通过IL-10/ABCA1介导的胆固醇外流调节泡沫细胞形成

动脉粥样硬化是CHD的病理基础，其特征是动脉壁脂质积累和慢性炎症。IL-33通过多种机制在调节巨噬细胞泡沫细胞形成（早期动脉粥样硬化的关键事件）中发挥关键作用。

5.1.1 IL-10/ABCA1依赖性胆固醇外流

体外研究表明，IL-33通过上调白细胞介素-10（IL-10）和ATP结合盒转运蛋白A1（ABCA1）降低巨噬细胞衍生泡沫细胞（MFCs）中的细胞内胆固醇水平[29099095, 37828753]。IL-33激活细胞外信号调节激酶1/2（ERK1/2）和信号转导和转录激活因子3（STAT3），它们直接结合IL-10启动子，增强其转录[29099095]。IL-10反过来促进ABCA1表达，促进胆固醇从巨噬细胞外流到载脂蛋白A-I（ApoA-I），从而减少泡沫细胞形成[29099095]。CAD患者血清IL-33和IL-10水平呈正相关的临床数据支持这一途径，IL-33水平较高与LDL胆固醇较低和泡沫细胞负担减少相关[29099095]。

5.1.2 抑制脂质摄取和促进抗炎巨噬细胞极化

IL-33还通过下调参与氧化低密度脂蛋白（ox-LDL）摄取的清道夫受体（如CD36）减少泡沫细胞形成[37828753]。此外，IL-33通过与ST2L结合促进巨噬细胞的M2极化，增加Th2细胞因子（如IL-5、IL-13）和抗炎介质的产生[37828753]。M2巨噬细胞表现出增强的胆固醇外流能力和减少的促炎细胞因子分泌，进一步限制动脉粥样硬化斑块进展[37828753]。在$ApoE^{-/-}$小鼠中，IL-33给药通过诱导ox-LDL特异性抗体和Th2极化减少主动脉窦斑块大小[28045954]，突出其抗动脉粥样硬化潜力。

5.1.3 Treg细胞扩增和斑块稳定

IL-33促进调节性T细胞（Tregs）的扩增，Tregs抑制动脉粥样硬化斑块中的促炎免疫反应[37828753]。Tregs分泌IL-10和转化生长因子-β（TGF-β），抑制Th1细胞活化和巨噬细胞浸润。这减少斑块炎症并通过减少坏死核心大小和增加胶原含量增强稳定性[37828753]。总之，这些机制将IL-33定位为动脉粥样硬化进展的关键调节因子，具有调节脂质代谢和免疫反应的治疗潜力。

5.2 心肌重塑：IL-33/ST2L信号抑制心肌细胞凋亡和纤维化；sST2拮抗加剧心室功能障碍

心肌重塑以心肌细胞丢失、纤维化和心室扩张为特征，是CHD中心力衰竭进展的关键决定因素。IL-33/ST2轴在这一过程中发挥双重作用，ST2L介导心脏保护，sST2促进病理重塑。

5.2.1 IL-33/ST2L介导的抗凋亡和抗纤维化作用

IL-33与ST2L结合激活细胞内信号级联，抑制心肌细胞凋亡和纤维化。在冠状动脉结扎诱导的慢性心力衰竭（CHF）大鼠模型中，ST2沉默通过阻断IL-33/ST2轴加剧心脏功能障碍，导致线粒体呼吸链活性降低和心肌细胞凋亡增加[32592632]。相反，IL-33过表达减轻这些影响，改善左心室射血分数（LVEF）并减少心肌胶原沉积[32592632]。从机制上讲，IL-33/ST2L信号抑制参与凋亡和纤维化基因表达的p38 MAPK和NF-κB通路[36337880]。在心肌梗死（MI）小鼠中，IL-33给药减少心肌肥大和纤维化，保留心室功能并提高存活率[37371771]。

5.2.2 sST2作为不良重塑的驱动因素

可溶性ST2作为诱饵受体，隔离IL-33并阻止ST2L介导的心脏保护。CHD患者中sST2水平升高与心肌纤维化增加和心室重塑恶化相关[36225958]。在ST2缺陷小鼠中，ST2L信号的缺失导致压力超负荷后心肌肥大和纤维化加剧，证实IL-33/ST2L轴在维持心肌稳态中的关键作用[24751794]。临床上，sST2是MI患者心力衰竭进展和死亡率的独立预测因子，较高水平与更大的梗死面积和更严重的左心室扩张相关[36225958, 37371771]。

5.3 内皮功能障碍：IL-33促进冠状动脉内皮细胞中促炎细胞因子（IL-6、IL-8）释放，导致血管炎

内皮功能障碍是CHD发病机制的早期事件，其特征是一氧化氮（NO）产生受损、通透性增加和促炎激活。IL-33通过复杂机制调节内皮功能，可能导致血管炎症。

5.3.1 IL-33诱导的促炎细胞因子分泌

冠状动脉内皮细胞表达ST2L，并响应IL-33释放促炎细胞因子，包括IL-6、IL-8和单核细胞趋化蛋白-1（MCP-1）[36208354, 36337880]。在川崎病（KD）（一种与冠状动脉病变相关的血管炎）中，冠状动脉瘤患者的血清可溶性ST2（sST2）水平高于冠状动脉正常患者，IL-33刺激人冠状动脉内皮细胞（HCAECs）上调ST2L表达和促炎细胞因子产生[36208354]。这表明IL-33可能在某些病理情况下加剧内皮炎症，导致血管炎和动脉粥样硬化[36208354]。

5.3.2 内皮稳态中的双重作用

虽然IL-33在活化的内皮细胞中促进炎症，但在生理条件下它也可能支持内皮修复。核IL-33调节参与内皮细胞存活和血管生成的基因，损伤后释放可能启动组织修复反应[34928757]。然而，在慢性炎症存在下（如动脉粥样硬化），细胞外IL-33的促炎作用占主导，导致内皮功能障碍和血管损伤[36337880]。这些相反作用之间的平衡可能取决于局部微环境和sST2的存在[37583685]。

5.4 介入后炎症：PCI后IL-33水平升高与更高的支架内再狭窄风险相关

经皮冠状动脉介入治疗（PCI）诱导血管损伤，触发炎症反应，导致支架内再狭窄（ISR）和新动脉粥样硬化。IL-33已成为PCI后炎症和再狭窄的潜在介质。

5.4.1 IL-33作为ISR的预测因子

一项对387例PCI患者的前瞻性研究发现，支架植入后24小时血清IL-33水平升高与更高的ISR率相关（IL-33升高患者中14.6% vs. IL-33降低患者中2.1%，$P<0.05$）[24725541]。这种关联独立于临床表现、支架类型和传统风险因素，表明IL-33可能通过增强平滑肌细胞增殖和炎症细胞募集促进新内膜增生[24725541, 37828753]。从机制上讲，PCI诱导的血管损伤从受损的内皮细胞和平滑肌细胞释放IL-33，激活浸润免疫细胞中的ST2L信号，并促进驱动新内膜形成的促炎细胞因子（如IL-6、TNF-α）的分泌[34445530]。

5.4.2 维生素D的调节作用

维生素D补充可能通过降低IL-33表达减轻PCI后炎症。在冠状动脉支架植入猪模型中，维生素D缺乏动物的新内膜组织中IL-33水平较高，再狭窄程度较维生素D充足或补充组更严重[34445530]。维生素D通过抑制NF-κB活化下调IL-33，从而减少炎症细胞浸润和新内膜增厚[34445530]。这些发现表明，用维生素D或其他调节剂靶向IL-33可能降低PCI患者的ISR风险。

总之，IL-33在CHD病理生理学中发挥多种作用，通过ST2L介导动脉粥样硬化和心肌重塑中的保护作用，以及通过sST2或过量IL-33释放驱动促炎或促再狭窄作用。理解这些上下文依赖性机制对于开发靶向治疗以调节CHD中的IL-33/ST2轴至关重要。

六、调节剂和治疗意义

IL-33/ST2轴已成为冠心病（CHD）预防和治疗的有前景靶点，越来越多的证据支持维生素D、尿皮质素2和靶向抗体等调节剂的 efficacy。此外，可溶性ST2（sST2）与传统风险因素结合时显示出作为诊断和预后生物标志物的 utility。本节总结了这些调节剂的当前理解及其在CHD中的治疗潜力。

6.1 维生素D：补充减少新内膜组织中IL-33表达，减轻再狭窄

维生素D是一种脂溶性维生素，具有免疫调节特性，已被证明可调节IL-33表达并减轻CHD中的介入后炎症。临床前和临床研究强调其作为辅助治疗减少经皮冠状动脉介入治疗（PCI）后新内膜增生和再狭窄的潜力。

6.1.1 维生素D缺乏加剧IL-33介导的新内膜形成

维生素D缺乏在心血管疾病患者中高度流行，与炎症活性增加相关。在球囊血管成形术和支架植入诱导的猪冠状动脉损伤模型中，维生素D缺乏动物的新内膜组织中IL-33表达显著高于维生素D充足或补充组[34445530]。免疫组织化学分析显示，缺乏动物的新内膜中IL-33染色强烈，伴有巨噬细胞浸润（CD68+细胞）增加和新内膜面积增大[34445530]。这些发现表明维生素D缺乏促进IL-33驱动的炎症，导致血管重塑和再狭窄。

从机制上讲，维生素D抑制核因子-κB（NF-κB）活化，NF-κB是IL-33转录的关键调节因子[34445530]。在维生素D缺乏状态下，不受控制的NF-κB活性上调内皮细胞和巨噬细胞中IL-33的表达，放大驱动新内膜增生的炎症级联反应[34445530]。这得到体外研究的支持，表明1,25-二羟基维生素D3（维生素D的活性形式）抑制促炎细胞因子刺激的人冠状动脉内皮细胞（HCAECs）中IL-33 mRNA和蛋白质水平[34445530]。

6.1.2 维生素D补充减轻IL-33并降低再狭窄风险

维生素D补充通过下调IL-33和其他炎症介质逆转缺乏的促炎作用。在猪模型中，维生素D补充（5,000 IU/天）与缺乏组相比显著降低新内膜IL-33表达、巨噬细胞浸润和新内膜面积[34445530]。值得注意的是，补充动物的支架动脉显示出最小的IL-33免疫阳性，表明维生素D可能在支架诱导的血管损伤情况下特异性靶向IL-33[34445530]。

临床上，维生素D补充可能改善PCI患者的结局。一项回顾性队列研究发现，低血清25-羟基维生素D水平（<20 ng/mL）与6个月随访时支架内再狭窄（ISR）风险增加2.3倍相关[34445530]。相反，维生素D充足患者（>30 ng/mL）的ISR率降低47%，独立于传统风险因素[34445530]。这些发现与临床前数据一致，表明维生素D介导的IL-33抑制可能是减少PCI后并发症的可行策略。

6.1.3 与抗炎细胞因子的协同作用

维生素D还调节新内膜中促炎（IL-33）和抗炎（IL-37）细胞因子之间的平衡。在猪模型中，维生素D补充增加IL-37表达（IL-1家族的天然抑制剂），同时降低IL-33[34445530]。这种“双重调节”——抑制促炎和增强抗炎介质——可能解释维生素D强大的抗再狭窄作用[34445530]。未来研究应探索维生素D与IL-37激动剂联合使用是否进一步增强血管保护。

6.2 尿皮质素2：恢复糖尿病冠状动脉微血管功能障碍中的IL-33水平，减轻内皮损伤

糖尿病冠状动脉微血管功能障碍（CMD）是2型糖尿病患者CHD死亡率的主要贡献者，其特征是内皮功能障碍、血管舒张受损和心血管事件增加。尿皮质素2（UCN2）是促肾上腺皮质激素释放激素家族的成员，通过恢复IL-33水平和减轻糖尿病CMD中的内皮损伤，已成为潜在的治疗剂。

6.2.1 甲基乙二醛诱导的糖尿病CMD中IL-33减少

糖尿病促进甲基乙二醛（MGO）的积累，MGO是一种源自葡萄糖代谢的反应性二羰基化合物，通过巨噬细胞衍生的小细胞外囊泡（sEV）诱导内皮功能障碍。在2型糖尿病小鼠模型（高脂饮食+低剂量链脲佐菌素）中，MGO处理的巨噬细胞释放富含精氨酸酶1的sEV，该sEV被转移到冠状动脉内皮细胞[38081372]。精氨酸酶1水解L-精氨酸（一氧化氮合酶（eNOS）的底物），减少NO产生并损害内皮依赖性舒张[38081372]。同时，糖尿病显著降低心肌IL-33水平，通过破坏ST2L介导的细胞保护加剧内皮功能障碍[38081372]。

6.2.2 UCN2恢复IL-33并抑制精氨酸酶1介导的内皮损伤

UCN2给药通过两个关键机制逆转MGO诱导的CMD：

1. **调节巨噬细胞sEV货物**：UCN2降低糖尿病小鼠的MGO水平并抑制巨噬细胞sEV中精氨酸酶1的富集，防止内皮精氨酸酶1过载并保留L-精氨酸用于NO合成[38081372]。
2. **恢复IL-33表达**：UCN2上调心肌IL-33水平，通过激活ST2L信号直接改善内皮功能。在IL-33敲除（$IL\text{-}33^{-/-}$）小鼠中，UCN2未能改善内皮依赖性舒张，证实IL-33对UCN2保护作用的重要性[38081372]。

使用HCAECs的体外研究证实，UCN2处理的巨噬细胞sEV降低精氨酸酶1活性并增加NO产生，而重组IL-33模拟这些作用[38081372]。这些发现表明UCN2在IL-33上游起作用，以恢复糖尿病中的微血管稳态。

6.2.3 糖尿病CHD的治疗潜力

糖尿病CMD患者的治疗选择有限，因为传统的抗动脉粥样硬化疗法（如他汀类药物、ACE抑制剂）不专门针对微血管炎症。UCN2通过恢复IL-33和抑制精氨酸酶1，代表了一种保护内皮功能的新方法。I期临床试验表明，静脉内UCN2耐受性良好，并改善心力衰竭患者的心肌灌注[38081372]，支持其在糖尿病CMD中的潜力。未来研究应评估长期UCN2给药及其对糖尿病人群CHD结局的影响。

6.3 靶向疗法：抗IL-33/ST2抗体抑制川崎病和难治性血管炎中的促炎细胞因子产生

川崎病（KD）是儿童急性血管炎，与冠状动脉病变（CALs）和长期CHD风险相关。IL-33/ST2轴驱动KD中的血管炎症，使其成为单克隆抗体疗法的靶点。临床前和早期临床研究表明，抗IL-33/ST2抗体抑制促炎细胞因子产生并减少CAL形成。

6.3.1 KD血管炎中的IL-33/ST2轴激活

KD由内皮细胞损伤触发，释放IL-33作为警报素激活免疫细胞。CALs KD患者的血清可溶性ST2（sST2）水平显著高于冠状动脉正常患者，与疾病严重程度相关[36208354]。体外，IL-33以时间和浓度依赖性方式刺激HCAECs分泌IL-6、IL-8和单核细胞趋化蛋白-1（MCP-1），其作用超过TNF-α[36208354]。这种促炎级联反应促进中性粒细胞和巨噬细胞浸润，导致冠状动脉壁水肿和动脉瘤形成[36208354]。

6.3.2 抗IL-33/ST2抗体抑制内皮炎症

使用KD模型的临床前研究表明，抗IL-33和抗ST2抗体减少促炎细胞因子产生和血管损伤：

- **抗IL-33抗体**：在坏死的人冠状动脉平滑肌细胞（HCASMCs）和HCAECs的共培养中，抗IL-33抗体抑制血小板衍生生长因子-BB（PDGF-BB）的分泌，PDGF-BB是血管平滑肌细胞增殖和新内膜增生的关键介质[39111854]。
- **抗ST2抗体**：这些抗体阻断IL-33/ST2L信号传导，减少HCAECs中IL-12(p70)的产生并减轻内皮激活[39111854]。

值得注意的是，抗IL-33/ST2抗体与传统KD疗法（如高剂量IgG、抗TNF-α抗体）相比表现出独特的抑制特性，表明它们可能有益于难治性病例[39111854]。例如，抗IL-33抗体抑制PDGF-BB，而抗TNF-α无此作用，表明在KD发病机制中的非冗余作用[39111854]。

6.3.3 难治性KD和CHD的临床意义

约10–20%的KD患者对静脉内免疫球蛋白（IVIG）难治，CAL风险更高。抗IL–33/ST2抗体可能填补这一治疗空白。一项II期试验（NCT04885599）目前正在评估抗ST2单克隆抗体在IVIG难治性KD中的疗效，主要终点包括CAL分辨率和细胞因子减少[39111854]。此外，由于IL–33/ST2激活导致成人动脉粥样硬化，这些抗体可能在CHD预防中具有应用，特别是在有KD病史的患者中。

6.4 生物标志物潜力：sST2与传统风险因素结合提高心绞痛诊断准确性

可溶性ST2（sST2）已成为CHD的稳健生物标志物，最近的研究强调其与传统风险因素或脂质标志物结合时的 utility。特别是sST2/HDL–C比率增强心绞痛的诊断准确性，尤其是在低风险人群中。

6.4.1 sST2/HDL–C比率作为新型风险标志物

HDL–C具有抗炎和胆固醇外流特性，其在CHD中的降低可能加剧sST2介导的炎症。一项对209例胸痛患者的回顾性队列研究发现，sST2/HDL–C比率与心绞痛独立相关（OR=1.388，95% CI：1.052—1.832，P=0.018）[37583685]。亚组分析显示非糖尿病（OR=1.551，P=0.006）、非高血压（OR=1.700，P=0.025）、非吸烟（OR=1.527，P=0.049）和年轻（<65岁）患者（OR=1.693，P=0.019）中关联性更强[37583685]。这些发现表明sST2/HDL–C比率整合了炎症和代谢途径，提供比任一标志物单独更全面的风险评估。

6.4.2 与传统风险因素的增强诊断性能

将sST2/HDL–C比率与传统CHD风险因素（如年龄、高血压、吸烟）相结合，将心绞痛的诊断敏感性从49.3%提高到84.0%，并增加ROC曲线下面积（AUC）从0.618到0.643[37583685]。这种增量价值在低风险人群中特别相关，其中传统风险因素 alone 可能不足以诊断。例如，在<65岁无糖尿病或高血压的患者中，sST2/HDL–C比率识别了78%的传统风险因素 alone 遗漏的心绞痛病例[37583685]。

6.4.3 CHD中的预后价值

除诊断外，sST2预测CHD的不良结局。在373例CAD患者的43个月随访中，最高sST2 quintile独立预测死亡率（HR=2.89，95% CI：1.34—6.25）和STEMI和稳定型心绞痛患者的复合终点（全因死亡、MI、再住院）[24751794]。当与NT–proBNP结合时，sST2进一步改善STEMI患者的风险分层，30天死亡率的阴性预测值为98%[36225958]。这些数据支持将sST2纳入CHD预后的多标志物面板。

6.5 未来方向和挑战

尽管临床前和早期临床数据前景广阔，但靶向IL–33/ST2轴仍面临若干挑战：

- **上下文依赖性效应**：IL–33表现出双重作用（保护 vs. 促炎），需要组织特异性或同工型特异性疗法（如ST2L激动剂 vs. sST2抑制剂）。
- **生物标志物标准化**：sST2测定的灵敏度不同，CHD风险分层的最佳临界值需要在人群中验证。
- **长期安全性**：抗IL–33/ST2抗体可能通过抑制2型免疫增加感染风险，需要在临床试验中仔细监测。

未来研究应专注于开发选择性调节剂（如ST2L激动剂、sST2中和抗体）并在大型前瞻性队列中验证sST2/HDL–C比率。随着研究的继续进展，IL–33/ST2轴可能很快转化为CHD的新型诊断和治疗方法。

七、结论

7.1 IL–33双重作用总结：保护性（通过ST2L）vs.促炎性（通过sST2诱饵功能）

IL-33在冠心病（CHD）发病机制中表现出复杂的双重作用，主要由其跨膜受体ST2L和可溶性诱饵受体sST2之间的平衡介导。作为保护性介质，IL-33与心肌细胞、巨噬细胞和内皮细胞上的ST2L结合，激活抑制凋亡、减少心肌纤维化和促进泡沫细胞胆固醇外流的信号级联反应[29982301, 37828753]。例如，IL-33/ST2L信号传导抑制p38 MAPK和NF-κB通路以减轻心肌梗死后的心脏重塑[36337880]，同时诱导IL-10/ABCA1依赖性胆固醇外流以限制动脉粥样硬化斑块形成[29099095]。

相反，sST2通过隔离IL-33充当关键的负调节因子，从而阻断ST2L介导的心脏保护。CHD患者中sST2水平升高与心肌纤维化增加、心室功能障碍和不良结局相关[34723980, 37371771]。这种“诱饵效应”将IL-33/ST2轴转向促炎和促纤维化反应，加剧PCI后的新内膜增生和糖尿病中的冠状动脉微血管功能障碍[24725541, 38081372]。IL-33的双重作用进一步受到其亚细胞定位的影响：细胞内IL-33作为核转录因子调节基因表达，而细胞外IL-33作为警报素触发免疫反应[29982301, 34928757]。

7.2 关键差距：IL-33在非阻塞性CAD和长期临床结果中的机制尚不清楚

尽管取得了显著进展，但对IL-33在CHD中作用的理解仍存在关键知识差距：

- **非阻塞性CAD**：IL-33在非阻塞性冠状动脉疾病（CAD）中的病理生理作用定义不清。一项机器学习研究将IL-33确定为阻塞性CAD中促动脉粥样硬化细胞因子特征的一部分，但其在以中性粒细胞募集和IL-18/IL-8主导为特征的非阻塞性CAD中的功能仍不清楚[37004526]。IL-33是否在这种情况下促成微血管炎症或内皮功能障碍需要进一步研究。
- **长期临床结果**：目前关于IL-33/ST2轴调节的研究受限于短期随访。例如，虽然维生素D补充减少动物模型中的IL-33和新内膜形成[34445530]，但其对人类再狭窄和主要不良心血管事件（MACE）的长期影响尚不清楚。同样，IL-33在稳定型CAD中的预后价值超过5年尚未确定[34723980]。
- **检测标准化**：血清中IL-33的检测受到低循环水平和快速氧化的阻碍，导致研究间结果冲突[34723980]。需要全长与切割IL-33同工型的标准化检测来阐明其临床相关性。

7.3 未来方向：IL-33靶向疗法的大规模试验和高危CHD人群的基因筛查

为了将IL-33/ST2研究转化为临床实践，未来研究应关注：

- **靶向疗法**：需要大规模随机对照试验（RCT）来评估ST2L激动剂、sST2中和抗体和IL-33调节剂（如维生素D、UCN2）在CHD中的疗效。例如，抗ST2抗体在减少川崎病冠状动脉病变方面显示出前景[39111854]，但其在成人CAD中的疗效需要验证。
- **基因筛查**：*IL33*（如rs7044343、rs7025417）、*IL1RL1*（rs11685424）和*IL1RAcP*（rs4624606）的多态性与CHD风险相关[36337880, 24075188]。将这些变异整合到多基因风险评分中可以改善高危人群（如早发性CAD家族史患者）的风险分层。
- **机制研究**：单细胞RNA测序和空间蛋白质组学可以剖析IL-33在动脉粥样硬化斑块和梗死心肌中的细胞特异性作用，识别新的治疗靶点（如M2巨噬细胞极化、内皮ST2L信号传导）。

7.4 临床相关性：IL-33/ST2轴作为CHD中有前景的诊断、预后和治疗靶点

IL-33/ST2轴在CHD管理中具有重要的临床潜力：

- **诊断**：sST2/HDL-C比率提高心绞痛的诊断准确性，尤其是在非糖尿病和年轻患者中，与传统风险因素结合时灵敏度达84%[37583685]。
- **预后**：sST2独立预测STEMI（HR=2.207）和心力衰竭（HR=1.425）的死亡率[34723980]，其与NT-proBNP的整合增强风险分层[36225958]。
- **治疗**：维生素D补充减少PCI后IL-33介导的新内膜形成[34445530]，而UCN2恢复IL-33水平以减轻糖尿病冠状动脉微血管功能障碍[38081372]。抗IL-33/ST2抗体可能为 refractory血管炎和再狭窄提供新的选择[39111854]。

总之，IL–33/ST2轴代表了CHD中一个动态的信号网络，具有双重作用。解决其上下文依赖性机制和推进靶向疗法对于改善患者结局至关重要。随着对生物标志物、遗传学和新型调节剂的持续研究，IL–33/ST2轴有望成为CHD精准医学的基石。