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ORIGINAL ARTICLE

The Research Progress of T Lymphocytes in Myocardial Infarction

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Abstract

Myocardial infarction is a severe clinical manifestation of acute coronary syndrome. Despite advancements in early treatment, the long-term impact of ischemia-related heart damage remains a major cause of heart failure. The immune response plays a role in cardiac complications following myocardial infarction. T lymphocytes exhibit different phenotypes after myocardial infarction. $CD4^+$ T cells differentiate into multiple subsets, contributing to immune regulation, promoting angiogenesis, regulating scar formation, and influencing cardiac remodeling. $CD8^+$ T cells are primarily cytotoxic and may directly kill cardiomyocytes, promoting adverse ventricular remodeling in myocardial infarction. Understanding the role of T cells at each stage of myocardial infarction could identify potential targets for developing new treatments

Keywords:T lymphocytes, myocardial infarction, inflammation, immune regulation

Introduction

Myocardial infarction (MI) is the most severe clinical manifestation of acute coronary syndromes and is associated with high morbidity and mortality [1]. Although considerable progress has been made in the early treatment of acute coronary thrombotic occlusion—including rapid mechanical restoration of coronary blood flow, thrombolytic therapy, and antiplatelet therapy—the long-term effects of ischemia-related cardiac injury remain a clinical and societal burden due to increased risks of arrhythmias, heart failure, and recurrent hospitalizations [2]. Therefore, further efforts are needed to clarify its pathophysiological pathways to improve the treatment of late post-ischemic cardiac complications. Extensive experimental evidence in both humans and animals suggests that immune responses play a role in cardiac complications after MI. In both human and experimental myocardial infarction, disruption of blood supply causes rapid cardiomyocyte death in the ischemic heart, followed by the recruitment of circulating T lymphocytes by inflammatory signals involved in the pathophysiological process of MI [3]. This article reviews the role of T lymphocytes following MI.

1. T lymphocyte phenotypes following myocardial infarction

T lymphocytes are a crucial component of acquired immunity, playing key roles in cancer, autoimmunity, intracellular pathogen clearance, and tissue regeneration. T cells are the primary mediators of the acquired immune response and are mainly divided into subpopulations, including CD8+ T cells and CD4+ Th1/Th2/Th17/Treg cells [4]. CD4+ and CD8+ T cells are vital in the immune response. After myocardial injury, the innate immune response activates, leading to the recruitment of adaptive immune cells, particularly CD4+ T cells [5]. CD4+ T cells can differentiate into subpopulations, including Th1, Th2, Th17, and FoxP3+ regulatory (Treg) cells, primarily depending on the cytokines and surface markers they express [6]. CD4+ T cells contribute to cardiac healing [7], repair ischemia-reperfusion

injury [8] and regulate the local innate immune response, especially monocyte infiltration and polarization. After myocardial infarction, $CD8^+$ T cells can be classified into cytotoxic and regulatory subtypes. Cytotoxic $CD8^+$ T cells primarily exert cytotoxicity and antigen recognition. They can recognize and directly attack specific antigens on damaged cells, such as cardiomyocytes and vascular endothelial cells, and aid in the removal of necrotic tissue by inducing apoptosis through the release of substances like perforin and granzyme [9]. Regulatory $CD8^+$ T cells differ from conventional cytotoxic $CD8^+$ T cells in their immunosuppressive function, which inhibits excessive inflammatory responses and prevents further damage to myocardial tissue [10].

2. The role of T lymphocytes in myocardial infarction

2.1 CD4+ T lymphocytes in myocardial infarction

2.1.1 Immunomodulation

Various subtypes of $CD4^+$ T cells secrete distinct cytokines that regulate the activity of other immune cells, influencing the extent and duration of the inflammatory response. For instance, interferon-γ (IFN-γ) secreted by Th1 cells activates macrophages and enhances their proinflammatory function, while IL-10 and transforming growth factor-β (TGF-β) secreted by Treg cells inhibit macrophage activity and reduce the inflammatory response [11]. $CD4^+$ T cells can also regulate the immune response through direct contact with other immune cells, such as interacting with dendritic cells [12]. For example, Treg cells promote cardiac repair after myocardial infarction by inhibiting the antigen-presenting capacity of dendritic cells and reducing T-cell activation through direct contact [13].

2.1.2 Promotes neovascularisation

In a mouse model of myocardial infarction, intramyocardial injection of human umbilical cord-derived mesenchymal stem cells has been shown to promote CD4+ T cell migration to the infarcted myocardium via the chemokine ligand 5/chemokine receptor 5 pathway, enhancing neovascularization of the ischemic tissue [14]. Treg cells also secrete the cardiovascularly active peptide apelin to promote endothelial cell proliferation and vascular regeneration [15].

2.1.3 Regulation of scar formation

$CD4^+$ T cells influence scar formation by regulating collagen synthesis and degradation. Th2 cells are the primary producers of pro-fibrotic factors [16, 17]. $CD4^+$ T cells can differentiate into Th2 cells under the influence of IL-4, which subsequently secrete IL-4, IL-5, and IL-13. Numerous studies in various models of fibrosis and scarring have shown that Th2 cells drive tissue fibrotic development. IL-13 secreted by Th2 cells promotes fibroblast proliferation and collagen synthesis, contributing to scar formation [18]. In contrast, TGF-β secreted by Treg cells inhibits fibroblast activity and reduces collagen synthesis, preventing excessive scar formation [19].

2.1.4 Impact on cardiac remodeling

$CD4^+$ T cells influence cardiac remodeling by regulating cardiomyocyte hypertrophy and apoptosis. Excessive immune and inflammatory responses can cause cardiomyocyte hypertrophy and apoptosis, worsening cardiac remodeling. Conversely, appropriate immune modulation reduces cardiomyocyte hypertrophy and apoptosis, preventing the worsening of cardiac remodeling. For example, Inui et al. found that in a mouse myocardial infarction model, XCR1+ dendritic cells induced and activated CD4+ Th1 cells, exacerbating cardiac remodeling after ischemic myocardial injury [20]. In a mouse myocardial infarction model, CD4+Foxp3+ Tregs showed marked proliferation in the heart in stages after infarction, exhibiting pro-inflammatory T helper cell features, including reduced IFN-γ and TNF-α expression and immunomodulatory capacity. They also displayed increased proliferation, anti-angiogenic, and pro-fibrotic properties. Selective Treg ablation reversed ventricular remodeling and dysfunction, reduced myocardial hypertrophy and fibrosis, suppressed CD4+ T cells and systemic inflammation, and induced neovascularization in ischemic myocardium [21]. Studies have shown that Tregs can be reprogrammed by purinergic signaling in infarcted hearts, leading to significant upregulation of CD73 expression. CD73-deficient Tregs exhibit reduced protection against myocardial infarction-induced remodeling. CD73 from FoxP3+ Tregs binds to CD4+FoxP3- T cells,

inhibiting the production of various pro-inflammatory cytokines and promoting cardiac repair after myocardial infarction [22].

2.2 CD8+ T lymphocytes and myocardial infarction

CD8+ T cells play a key role in antiviral and antitumor immune responses [23, 24]. In mouse models of myocardial infarction, both permanent and transient coronary artery ligation recruit CD69- and CD107a-positive activated CD8+ T cells to the ischemic myocardium [9, 25]. Clinical findings suggest that myocardial infarction patients with high CD8+ T-cell counts have larger infarct sizes and poorer ventricular function [26, 27]. CD8+ T cells may exacerbate myocardial injury by directly killing cardiomyocytes and promoting adverse ventricular remodeling.

2.2.1 Direct Cytotoxicity of Cardiomyocytes

Studies have shown that CD8+ T cells directly kill cardiomyocytes during myocardial infarction. Granzyme B (GZMB) is a serine protease primarily found in cytotoxic T lymphocytes and natural killer cells. Experimental studies show that blood from patients analyzed 7 days after myocardial infarction onset has significantly elevated GZMB levels, suggesting its role in the condition [28]. Further research indicates that GZMB elevation in myocardial infarction patients may be associated with downregulated miR-874-3p expression, suggesting miR-874-3p as a potential biomarker [29]. Xu et al. confirmed that applying a GZMB inhibitor after myocardial infarction effectively improves cardiac function [30]. Studies have shown that at the onset of myocardial infarction, CD8+ T cells are activated and release GZMB, which enters cardiomyocytes and induces apoptosis via the caspase cascade [9]. These studies indicate that GZMB released by CD8+ T cells is closely associated with myocardial damage after myocardial infarction. Additionally, studies show that CD8+ T cells regulate the inflammatory response by releasing IFN-γ and TNF-α [31, 32]. Zaidi et al. demonstrated that CD8+ T cell activation promotes a macrophage-mediated inflammatory response, worsening myocardial injury after myocardial infarction [33]. In the autoimmune response post-myocardial infarction, CD8+ T lymphocytes mediate myocardial inflammation and upregulate the cardiomyocyte pro-inflammatory factor IL-6, exacerbating myocardial injury [34]. After myocardial infarction, damaged cardiomyocytes release self-antigens, which are processed by antigen-presenting cells and presented to $CD8^+$ T cells. These cells are then activated, proliferate, and differentiate into effector cells, releasing inflammatory cytokines like IFN-γ and TNF-α, leading to myocardial injury. Curato et al. found that CD8+ T cells expressing angiotensin AT2R secreted more IL-10 and regulated the inflammatory response in the ischemic myocardium 7 days after myocardial infarction in a mouse model. This T-cell population was also identified in human peripheral blood [35].

2.2.2 Promoting Adverse Ventricular Remodeling

Studies have shown that CD8+ T cells are crucial in fibrosis formation. In hepatic fibrosis studies, CD40 expression on activated hepatic stellate cells was linked to immune effector cells expressing CD40 ligands. The addition of CD8+ T cells enhanced hepatic stellate cell activation and increased hepatic glutamate aminotransferase, indicating that CD8+ T cells significantly contribute to hepatic fibrosis formation [36]. Similar mechanisms may be present in myocardial infarction. CD8+ T cells could exacerbate fibrosis by releasing inflammatory cytokines, activating myocardial fibroblasts, and promoting collagen synthesis and deposition. Santos et al. demonstrated that GZMB released by CD8+ T cells contributes to adverse ventricular remodeling and impairs cardiac function after myocardial infarction. However, ablation or knockdown of GZMB in CD8+ T cells inhibited adverse remodeling and improved cardiac function [9]. Adverse ventricular remodeling can significantly impact cardiac function recovery. Following myocardial infarction, the heart undergoes repair and remodeling to restore normal function. However, CD8+ T cell-driven adverse remodeling can hinder this recovery. A study in an experimental mouse model of myocardial infarction found that mice lacking functional CD8+ T cells had improved cardiac physiology and reduced mortality 7 days post-infarction. However, despite increased survival, these mice exhibited delayed clearance of myocardial necrotic tissue, resulting in poor scar formation and increased cardiac rupture risk. This suggests

that CD8+ T cells may play a dual role in cardiac remodeling [37]. Therefore, targeting CD8+ T cells may be a promising therapeutic strategy after myocardial infarction.

Conclusion

T cells play a crucial role in the onset, progression, and repair of myocardial infarction. In the acute phase of myocardial infarction, T cell-mediated inflammation and cytotoxicity exacerbate myocardial injury. In the subacute and chronic phases, T cells' immunomodulatory functions are key to cardiac remodeling and functional recovery. A deeper understanding of T cell mechanisms in myocardial infarction can identify potential targets for developing new therapies. Strategies such as immunomodulatory, vaccine, and gene therapies are potential future directions for treating myocardial infarction. However, these therapies are still in the research phase, and further clinical studies are required to confirm their safety and efficacy. As research progresses, the role of T cells in myocardial infarction treatment will be better utilized, offering new hope for improving patient prognosis.

References

1. Teo KK, Rafiq T. Cardiovascular Risk Factors and Prevention: a Perspective From Developing Countries. *Can J Cardiol*. (2021) 37:733-43. doi: 10.1016/j.cjca.2021.02.009
2. Lavoie L, Khoury H, Welner S, Briere JB. Burden and Prevention of Adverse Cardiac Events in Patients with Concomitant Chronic Heart Failure and Coronary Artery Disease: a Literature Review. *Cardiovasc Ther*. (2016) 34:152-60. doi: 10.1111/1755-5922.12180
3. Nahrendorf M. Myeloid cell contributions to cardiovascular health and disease. *Nat Med*. (2018) 24:711-20. doi: 10.1038/s41591-018-0064-0
4. Zhang L, Yu X, Zheng L, Zhang Y, Li Y, Fang Q, et al. Lineage tracking reveals dynamic relationships of T cells in colorectal cancer. *Nature*. (2018) 564:268-72. doi:10.1038/s41586-018-0694-x
5. Yan X, Anzai A, Katsumata Y, Matsuhashi T, Ito K, Endo J, et al. Temporal dynamics of cardiac immune cell accumulation following acute myocardial infarction. *J Mol Cell Cardiol*. (2013)62:24-35. doi:10.1016/j. yjmcc. 2013.04.023
6. Zhou L, Chong MM, Littman DR. Plasticity of CD4+ T cell lineage differentiation. *Immunity*. (2009)30:646-55. doi: 10.1016/j.immuni.2009. 05.001
7. Hofmann U, Frantz S. Role of lymphocytes in myocardial injury, healing, and remodeling after myocardial infarction. *Circ Res*. (2015) 116:354-67. doi: 10.1161/CIRCRESAHA.116.304072
8. Yang Z, Day YJ, Toufektsian MC, Xu Y, Ramos SI, Marshall MA, et al. Myocardial infarct-sparing effect of adenosine a2a receptor activation is due to its action on CD4+ T lymphocytes. *Circulation*. (2006) 114:2056-64. doi: 10.1161/CIRCULATIONAHA .106.649244
9. Santos-Zas I, Lemarie J, Zlatanova I, Cachanado M, Seghezzi JC, Benamer H, et al. Cytotoxic CD8(+) T cells promote granzyme B-dependent adverse post-ischemic cardiac remodeling. *Nat Commun*. (2021) 12:1483. doi: 10.1038/s41467-021-21737-9
10. Stephenson E, Savvatis K, Mohiddin SA, Marelli-Berg FM. T-cell immunity in myocardial inflammation: pathogenic role and therapeutic manipulation. *Br J Pharmacol*. (2017) 174:3914-25. doi: 10.1111/bph.13613
11. Gladow N, Hollmann C, Weirather J, Ding X, Burkard M, Uehlein S, et al. Role of CD4(+) T-cells for regulating splenic myelopoiesis and monocyte differentiation after experimental myocardial infarction. *Basic Res Cardiol*. (2024) 119:261-75. doi:10.1007/s00395-024-01035-3
12. Ngwenyama N, Kirabo A, Aronovitz M, Velazquez F, Carrillo-Salinas F, Salvador AM, et al. Isolevuglandin-Modified Cardiac Proteins Drive CD4+ T-Cell Activation in the Heart and Promote Cardiac Dysfunction. *Circulation*. (2021) 143:1242-55. doi:10.1161/CIRCULATIONAHA.120.051889
13. Wang W, Li X, Ding X, Xiong S, Hu Z, Lu X, et al. Lymphatic endothelial transcription factor Tbx1 promotes an immunosuppressive microenvironment to facilitate post-myocardial infarction repair. *Immunity*. (2023) 56:2342-57. doi: 10.1016/j.immuni. 2023.07.019
14. Liu J, Liang X, Li M, Lin F, Ma X, Xin Y, et al. Intramyocardial injected human umbilical

cord-derived mesenchymal stem cells (HucMSCs) contribute to the recovery of cardiac function and the migration of CD4(+) T cells into the infarcted heart via CCL5 /CCR5 signaling. *Stem Cell Res Ther*. (2022) 13:247. doi: 10.1186/s13287-022-02914-z
15. Leung OM, Li J, Li X, Chan VW, Yang KY, Ku M, et al. Regulatory T Cells Promote Apelin-Mediated Sprouting Angiogenesis in Type 2 Diabetes. *Cell Rep*. (2018) 24:1610-26. doi: 10.1016/j.celrep.2018.07.019
16. Borthwick LA, Barron L, Hart KM, Vannella KM, Thompson RW, Oland S, et al. Macrophages are critical to the maintenance of IL-13-dependent lung inflammation and fibrosis. *Mucosal Immunol*. (2016) 9:38-55. doi: 10.1038/mi.2015.34
17. Borthwick LA, Wynn TA, Fisher AJ. Cytokine mediated tissue fibrosis. *Biochim Biophys Acta*. (2013) 1832:1049-60. doi: 10.1016/j.bbadis.2012.09.014
18. Wilson MS, Wynn TA. Pulmonary fibrosis: pathogenesis, etiology and regulation. *Mucosal Immunol*. (2009) 2:103-21. doi: 10.1038/mi.2008.85
19. Miyara M, Sakaguchi S. Natural regulatory T cells: mechanisms of suppression. *Trends Mol Med*. (2007) 13:108-16. doi: 10.1016/j.molmed.2007.01.003
20. Inui H, Nishida M, Ichii M, Nakaoka H, Asaji M, Ide S, et al. XCR1(+) conventional dendritic cell-induced CD4(+) T helper 1 cell activation exacerbates cardiac remodeling after ischemic myocardial injury. *J Mol Cell Cardiol*. (2023) 176:68-83. doi: 10.1016/j.yjmcc.2023.01.011
21. Bansal SS, Ismahil MA, Goel M, Zhou G, Rokosh G, Hamid T, et al. Dysfunctional and Proinflammatory Regulatory T-Lymphocytes are Essential for Adverse Cardiac Remodeling in Ischemic Cardiomyopathy. *Circulation*. (2019) 139:206-21. doi: 10.1161/CIRCULATIONAHA.118.036065
22. Zhuang R, Meng Q, Ma X, Shi S, Gong S, Liu J, et al. CD4(+)FoxP3(+)CD73(+) regulatory T cell promotes cardiac healing post-myocardial infarction. *Theranostics*. (2022) 12:2707-21. doi: 10.7150/thno.68437
23. Tscharke DC, Croft NP, Doherty PC, La Gruta NL. Sizing up the key determinants of the CD8(+) T cell response. *Nat Rev Immunol*. (2015) 15:705-16. doi: 10.1038/nri3905
24. Yatim N, Cullen S, Albert ML. Dying cells actively regulate adaptive immune responses. *Nat Rev Immunol*. (2017) 17:262-75. doi: 10.1038/nri.2017.9
25. Rusinkevich V, Huang Y, Chen ZY, Qiang W, Wang YG, Shi YF, et al. Temporal dynamics of immune response following prolonged myocardial ischemia/reperfusion with and without cyclosporine a. *Acta Pharmacol Sin*. (2019) 40:1168-83. doi: 10.1038/s41401-018-0197-1
26. Padgett LE, Dinh HQ, Wu R, Gaddis DE, Araujo DJ, Winkels H, et al. Naive CD8(+) T Cells Expressing CD95 Increase Human Cardiovascular Disease Severity. *Arterioscler Thromb Vasc Biol*. (2020) 40:2845-59. doi: 10.1161/ATVBAHA.120.315106
27. Zhang L, Wang Z, Wang D, Zhu J, Wang Y. CD8(+)CD28(+) T cells might mediate injury of cardiomyocytes in acute myocardial infarction. *Mol Immunol*. (2018) 101:74-9. doi: 10.1016/j.molimm.2018.05.015
28. Kondo H, Hojo Y, Tsuru R, Nishimura Y, Shimizu H, Takahashi N, et al. Elevation of plasma granzyme B levels after acute myocardial infarction. *Circ J*. (2009) 73:503-7. doi: 10.1253/circj.cj-08-0668
29. Yan Y, Song X, Li Z, Zhang J, Ren J, Wu J, et al. Elevated levels of granzyme B correlated with miR-874-3p downregulation in patients with acute myocardial infarction. *Biomark Med*. (2017) 11:761-7. doi: 10.2217/bmm-2017-0144
30. Xu H, Wei Z, Chen B, Wang J, Weng H, Li J, et al. Granzyme B PET imaging inflammation and remodeling in myocardial infarction. *Eur J Nucl Med Mol Imaging*. (2024) 51:991-1001. doi: 10.1007/s00259-023-06521-9
31. Liao P, Wang W, Wang W, Kryczek I, Li X, Bian Y, et al. CD8(+) T cells and fatty acids orchestrate tumor ferroptosis and immunity via ACSL4. *Cancer Cell*. (2022) 40:365-78. doi: 10.1016/j.ccell.2022.02.003
32. Luu M, Riester Z, Baldrich A, Reichardt N, Yuille S, Busetti A, et al. Microbial short-chain fatty acids modulate CD8(+) T cell responses and improve adoptive immunotherapy for cancer. *Nat Commun*. (2021)12:4077. doi:10.1038/s41467-021-24331-1
33. Zaidi Y, Corker A, Vasileva VY, Oviedo K, Graham C, Wilson K, et al. Chronic Porphyromonas gingivalis lipopolysaccharide

induces adverse myocardial infarction wound healing through activation of CD8(+) T cells. *Am J Physiol Heart Circ Physiol*. (2021) 321:H948-62. doi: 10.1152/ajpheart.00082.2021

34. Neri SG, Prisco D, Martini F, Gori AM, Brunelli T, Poggesi L, et al. Acute T-cell activation is detectable in unstable angina. *Circulation*. (1997) 95:1806-12. doi: 10.1161/01.cir.95.7.1806
35. Curato C, Slavic S, Dong J, Skorska A, Altarche-Xifro W, Miteva K, et al. Identification of noncytotoxic and IL-10-producing CD8+at2R+ T cell population in response to ischemic heart injury. *J Immunol*. (2010) 185:6286-93. doi: 10.4049/jimmunol.0903681
36. Mehal W. Mechanisms of liver fibrosis in metabolic syndrome. *eGastroenterology*. (2023) 1. doi: 10.1136/egastro-2023-100015
37. Ilatovskaya DV, Pitts C, Clayton J, Domondon M, Troncoso M, Pippin S, et al. CD8(+) T-cells negatively regulate inflammation post-myocardial infarction. *Am J Physiol Heart Circ Physiol*. (2019) 317:H581-96. doi: 10.1152/ajpheart.00112.2019