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Immune Cell and Other Non-Cardiomyocyte Regulation of Cardiac Hypertrophy and Remodeling

Ryan A. Frieler, PhD² and Richard M. Mortensen, MD, PhD^{1,2,3}

¹Dept of Internal Medicine, Metabolism, Endocrinology, and Diabetes Division, University of Michigan Medical School, Ann Arbor, MI

²Dept of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, MI

³Dept of Pharmacology, University of Michigan Medical School, Ann Arbor, MI

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Cardiac hypertrophy and remodeling is a pathological feature of many cardiac diseases with underlying causes including hypertension, cardiomyopathy, valvular dysfunction, and myocardial infarction. In these diseases, ventricular hypertrophy occurs in response to pathological stimuli such as pressure and volume overload, sarcomere gene mutations, and neurohumoral activation, and a major consequence of prolonged and uncontrolled hypertrophic remodeling is cardiac dysfunction, which can lead to heart failure or cardiac arrest due to arrhythmia.

Despite the various pathological stimuli, there are many common features in the hypertrophic response in different cardiac diseases. In addition to increased cardiomyocyte mass, sarcomere rearrangement and extracellular matrix deposition, other common features have recently been appreciated including inflammatory signaling and immune cell activation. Numerous cell types are involved in orchestrating this complex pathological response. The heart consists of a heterogeneous population of cells including cardiomyocytes and non-cardiomyocytes, and it is now clear that intercellular signaling and communication between these cell types is critical in the pathophysiology of ventricular hypertrophy and remodeling (Figure 1).

Non-cardiomyocytes display phenotypic changes during the development of cardiac hypertrophy and there is still much to be revealed about the specific roles of these cell types and their overall contribution to the hypertrophic response. Inflammatory cytokines like TNF- α , IL-1 β , IL-6, and TGF- β , and neurohumoral factors like angiotensin II and

Address for Correspondence: Richard M. Mortensen, Department of Molecular and Integrative Physiology, University of Michigan Medical School, 1301 E. Catherine St., 7708 Medical Science II, Ann Arbor, MI 48109, Tel: (734) 763-2021, Fax: (734) 936-8813, rmort@umich.edu.

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aldosterone are involved in the pathophysiology and correlate with disease progression, but the cell type-specific targets and their effects on the cardiomyocyte in vivo are not well understood. The influence of both resident and infiltrating immune cells during myocardial infarction and post-infarction remodeling is well recognized. Recently it has been shown that myeloid cell phenotypes play a critical role in ventricular hypertrophy and remodeling.^{1, 2} In addition, there is a small body of literature examining specific immune cell interactions in other models of ventricular hypertrophy like pressure overload. While the early phases of MI are dissimilar to the pathophysiology of progressive, chronic hypertrophy, studies focusing on the later phase of post-infarct hypertrophic remodeling may provide some insight for potential cellular mechanisms and therapeutic targets.

In this review, we summarize the current understanding of the role of non-cardiomyocytes during the pathogenesis of cardiac hypertrophy, placing particular emphasis on relevant immune cell interactions and inflammatory signaling mechanisms. We highlight seminal findings demonstrating the importance of specific cell types in regulating the cardiomyocyte hypertrophic response, and emphasize the relevant current and potential therapeutic targets. It is clear that this field is not fully developed and deserves increased attention.

RAAS and TGF- β signaling in the hypertrophic heart

Activation of the renin-angiotensin-aldosterone-system (RAAS) has direct hypertensive effects that contribute to cardiac hypertrophy and remodeling, and these effects can be blocked by RAAS inhibition with ACE inhibitors, ARBs and mineralocorticoid receptor (MR) antagonists. RAAS inhibitors are widely used in the treatment of heart failure and significantly reduce morbidity and mortality; however, it is now well established that these protective effects extend beyond simply reducing blood pressure. Angiotensin-II and aldosterone promote vascular and cardiac fibrosis and hypertrophy independent of blood pressure, and these signaling pathways have been shown to have pathogenic effects involving numerous cell types including cardiomyocytes and immune cells.

The role of angiotensin-II in both normal and pathological contexts is very complex. Cardiomyocytes express both AT1 and AT2 receptors, and both appear to have an important, but opposite role in maladaptive remodeling. In bone marrow derived cells, angiotensin-II type I receptors are involved in angiotensin-II-induced hypertensive responses,³ and AT1R has also been shown to regulate the mobilization of monocyte progenitor cells.⁴ AT1R responses may also be critical in regulating lymphocyte hypertensive responses.⁵ Our understanding of the many cell-specific effects is still undeveloped, but it is clear that localized, non-classical RAAS activation is an important target for RAAS inhibitors and a potential mechanism for their beneficial effects.

In the past decade there has been increasing interest in the direct role of MR activation during pathological remodeling. In severe heart failure, clinical trials have demonstrated that MR antagonism provides significant benefit independent of blood pressure lowering.⁶ MR is expressed in wide range of cells, and the use of cell-specific knockout technology has now delineated some of the cell-specific effects. Both cardiomyocyte and myeloid MR have now been shown to directly influence cardiac remodeling.^{2, 7, 8}

TGF- β is upregulated in the hypertrophied and fibrotic heart, and is regarded as one of the major pro-fibrotic cytokines and critical mediators of cardiac fibrosis. TGF- β has many pleiotropic effects in modulating cardiomyocyte and non-cardiomyocyte function, and induces cardiomyocyte hypertrophy and fibroblast proliferation and fibrosis. Inhibition of TGF- β signaling, as well as genetic ablation of TGF- β has been shown to reduce fibrosis and prevent cardiac dysfunction in several models of maladaptive cardiac remodeling,^{9, 10} where as TGF- β overexpression has been shown to induce cardiac hypertrophy.¹¹

In pressure overload-induced cardiac remodeling, Koitabashi et al. found that TGF- β neutralizing antibody reduced myocardial fibrosis without affecting hypertrophy or cardiac function.¹² They further revealed that cardiomyocyte-specific (Myh6-Cre) knockout of TGF- β receptor Type II, but not type I significantly reduced hypertrophy and fibrosis, and prevented cardiac dysfunction through a TAK1 signaling pathway. In fact, TAK1 activation is known to induce cardiac hypertrophy, therefore the TGF- β -TAK1 signaling pathway may be useful for therapeutic targeting.¹³ However, different TGF- β signaling pathways are context dependent, because both cardiomyocyte TGF- β R1 and TGF- β R2 knockout significantly ameliorated post-infarct cardiac remodeling.¹⁴ Global blockade of TGF- β with neutralizing antibody on the other hand resulted in complete mortality within five days suggesting that TGF- β has many diverse effects in specific cell types. In addition to highlighting the importance of specific TGF- β signaling mechanisms, this may also indicate that TGF- β is necessary in other target cells for proper regulation of adaptive remodeling.

Inflammatory signaling in hypertrophic remodeling

Inflammatory signaling molecules released during cardiac injury and hypertrophic remodeling can induce hypertrophic and fibrotic responses. Both cardiomyocyte and non-cardiomyocyte cells secrete and respond to numerous cytokines, but the responses are complex, depend on the cell type, and are mostly characterized in vitro (Figure 2).

In fibroblasts, major pro-inflammatory cytokines like IL-1 β , TNF- α and IL-6 inhibit proliferation, decrease matrix synthesis and increase MMP activity, where as in cardiomyocytes they induce hypertrophy and can cause apoptosis, and in immune cells they promote inflammation.^{15–18} However, the cell sources of the cytokines have usually not been identified, and even the target cells of the cytokines have not been fully defined in vivo. The complexity is further increased by the temporal changes that occur in the injury and immune responses leading to an incomplete understanding of these cytokines during disease.

In heart failure patients, the concentration of inflammatory cytokines TNF- α , IL-6, and IL-1 β correlates with disease severity.¹⁹ Experimental models have shown that infusion with TNF- α induces cardiac dysfunction,²⁰ and similarly cardiomyocyte-restricted overexpression of TNF- α induces cardiac hypertrophy and fibrosis, and leads to cardiac dysfunction and dilated cardiomyopathy.²¹ In contrast, global knockout of TNF- α ameliorates pressure overload-induced cardiac hypertrophy, fibrosis and cardiac dysfunction.²² Anti-TNF- α therapies are also beneficial in animal models, but to a lesser extent. Neutralization of TNF- α significantly blocked TNF- α -induced cardiac inflammation,

without affecting hypertrophy and producing minor decreases in cardiac dysfunction.²³ Although TNF- α causes cardiac dysfunction, and TNF- α inhibition ameliorates cardiac dysfunction in animal models, clinical studies have demonstrated that TNF- α inhibition with etanercept and infliximab had no benefit in chronic heart failure.^{24, 25}

IL-1 β deficient mice have reduced pressure overload-induced hypertrophy and cardiac dysfunction, suggesting that IL-1 β has an exacerbating role in hypertrophic remodeling.²⁶ In agreement with this, IL-1 β injections were shown to induce cardiac dysfunction in mice.²⁷ During heart failure, early clinical studies indicate that blocking IL-1 β signaling provides a significant health benefit. Patients that received IL-1 receptor antagonist anakinra had increased oxygen consumption and exercise performance.²⁷ These results are promising, although larger trials that assess cardiac function and remodeling are needed. In other pathologies, anakinra has been shown to reduce adverse cardiac remodeling. In patients with rheumatoid arthritis, treatment with anakinra reduced IL-6, CRP, and endothelin, and also significantly improved LV function.²⁸ Similarly, patients with acute myocardial infarction with ST elevation who received anakinra had a reduction in CRP, and treatment blocked the progression to heart failure.²⁹

IL-6 has many pleiotropic effects on cardiomyocytes and non-cardiomyocytes, and IL-6 infusion alone has been shown to induce cardiac hypertrophy, fibrosis, and diastolic dysfunction.³⁰ In support of having a detrimental role during cardiac hypertrophy, genetic deletion of IL-6 has been shown to ameliorate cardiac damage and suppress angiotensin-II induced cardiac hypertrophy, fibrosis and inflammation, as well as hypertrophic and fibrotic signaling.^{31, 32} IL-6 knockout has also been shown to prevent norepinephrine-induced hypertrophy and remodeling.³³ However, our understanding of the IL-6 signaling cascade remains incomplete. Knockout of IL-6 in other hypertrophic disease models such as pressure overload has no effect on hypertrophy or fibrosis, and deletion of GP130, part of the IL-6 receptor complex, actually increases mortality after pressure overload and impairs cardiac function leading to dilated cardiomyopathy.³⁴ It is clear that our understanding of the IL-6 signaling pathways is inadequate within the context of these different disease models and requires further exploration.

Anti-inflammatory signaling

Inactivation of pro-inflammatory responses has been shown to mitigate hypertrophic cardiac dysfunction and remodeling, therefore it is not surprising that many studies have targeted anti-inflammatory signaling pathways as a therapeutic strategy. IL-10 is a major anti-inflammatory cytokine, and IL-10 deficient mice have increased angiotensin-II-induced vascular inflammation and impaired vascular relaxation, indicating that IL-10 has a protective role in maintaining vascular function.³⁵ Another study demonstrated that IL-10 deficient mice had increased cardiac hypertrophy and fibrosis and increased cardiac dysfunction in response to isoproterenol.³⁶ During pressure overload, IL-10 deficient mice had increased perivascular fibrosis, but no differences in cardiac hypertrophy or cardiac function.³⁷ However, administration of IL-10 significantly reduced cardiac hypertrophy and fibrosis, and preserved cardiac function in both pressure-overload and isoproterenol models of cardiac hypertrophy.³⁶

Glucocorticoids have major anti-inflammatory and immunosuppressive effects and are among the most widely used and most effective anti-inflammatory therapeutic agents. Despite their highly potent anti-inflammatory effects, their utility in cardiovascular diseases is limited due to a lack of efficacy in the treatment of hypertrophic remodeling. However, it does appear that glucocorticoid receptors may have an important role in normal cardiac development and function since cardiomyocyte-specific (Myh6-Cre) glucocorticoid receptor knockout causes cardiac hypertrophy and impaired cardiac function, leading to heart failure and premature death.³⁸

Immune Cells

It is now evident that resident and recruited immune cells respond much earlier to cardiac injury than previously thought. These changes precede hypertrophy and remodeling, and persist throughout much of the major maladaptive hypertrophic response resulting in cardiac dysfunction and failure. Immune cells coordinate cardiomyocyte and non-cardiomyocyte responses during maladaptive remodeling, and the regulation of immune cell phenotypes represents an important pharmacological approach. These cells have critical roles in not only cardiomyocyte function, but also in injury responses involving scar formation and interstitial fibrosis, which affect cardiac function.

Cardiac Macrophages

The heart contains a heterogeneous population of macrophages that are present in both healthy and injured cardiac tissue in both humans and mice.³⁹ Similar to tissue macrophages in brain and liver, most macrophages in the heart are established embryonically from yolk sac and fetal liver progenitors, and resident macrophage subsets are maintained through local proliferation and to a lesser extent monocyte recruitment.^{40, 41} This is consistent with other recent findings demonstrating that in the absence of disease, most tissue macrophage populations are maintained locally through self-renewal.⁴² In the presence of tissue injury, monocyte-derived macrophages are much more prevalent.

During cardiac injury, the macrophage's phagocytic function is critical for clearance of necrotic debris and matrix remodeling. However, the function of cardiac macrophages is much more extensive than previously thought, and they have a much more substantial role in regulating cardiac hypertrophy and remodeling. During myocardial infarction or angiotensin-II infusion, expansion of macrophage populations occurs through both local proliferation and monocyte recruitment.⁴⁰ Consistent with a potential causal role, expansion of cardiac macrophage populations occurred as early as 2 days after Ang-II infusion, and before significant hypertrophy and fibrosis occur.⁴⁰ This suggests that during progressive cardiac hypertrophy and remodeling, inflammatory changes are occurring very early on and precede hypertrophic remodeling.

Epelman and colleagues recently identified four distinct macrophage subsets in the mouse heart that have unique functional roles.⁴⁰ All characterized subsets were capable of phagocytizing antigen and cardiomyocytes, and MHC-II^{hi} subsets were capable of antigen presentation and T-cell activation. During angiotensin-II infusion, the CCR2⁺, CD11c^{hi} subset was predominantly derived from circulating monocytes, and had robust

inflammasome activation and inflammatory gene expression. Angiotensin-II induced inflammasome activation and IL-1 β production were blocked by CCR2 deficiency, suggesting that the CCR2⁺ subset has a more predominant role in coordinating inflammation. In contrast, other cardiac tissue macrophage subsets probably function as sentinel immune cells, and have roles in tissue surveillance, phagocytosis of dying cardiomyocytes, response to cardiomyocyte signaling, and T-cell activation.

Macrophage depletion

Inhibition or depletion of specific immune cell types has provided some insight for their roles in hypertrophic remodeling (Table 1). Macrophage depletion studies using clodronate liposomes or CD11b-DTR transgenic mice have been performed in a wide range of pathologies to block inflammation. Depletion of macrophages in a hypertensive model with Ren-2 rats suggests that macrophages are necessary for cardiac repair. Although no differences in cardiac hypertrophy were observed, depletion with clodronate liposomes resulted in cardiac dysfunction with decreased ejection fraction and fractional shortening, and increased end-diastolic volume.⁴³ Greater cardiomyocyte loss and abundant increases in CD4⁺ T cells were present in macrophage-depleted rats, suggesting that macrophages are important in coordinating T cell responses.

During myocardial infarction, macrophage depletion also impairs post-infarction remodeling and repair.^{59–61} Macrophage depletion during the early inflammatory phase resulted in increased necrotic debris and neutrophil presence, where as depletion during the later remodeling phase prevented collagen deposition and granulation tissue formation. Since different subsets of cardiac macrophages have different functional roles, and depletion of macrophages with clodronate liposomes is non-selective and depletes all macrophage subsets and peripheral monocytes, it is understandable that macrophage depletion would prevent important reparative functions. In addition, timing of macrophage depletion and targeting of specific macrophage subsets may be critical in order to achieve effective amelioration of maladaptive remodeling.

Inhibition of monocyte trafficking

The CCR2⁺ macrophage subset is monocyte derived and is thought to be mainly involved in promoting and regulating inflammation. Therefore, targeting inflammatory monocytes might be an effective means to limit this macrophage subset. Recruitment of monocytes largely occurs through MCP1-CCR2 signaling, and CCR2 knockout in bone marrow cells markedly reduces angiotensin-II induced vascular inflammation and fibrosis without affecting hypertrophy.⁴⁵ Similarly, inhibition of MCP1 with neutralizing antibodies significantly reduces macrophage infiltration and prevents myocardial fibrosis in response to pressure overload.⁴⁷ Although there were no differences in cardiac hypertrophy, MCP1 neutralization restored diastolic function.

MCP1 knockout is also protective against angiotensin-II-induced hypertrophic remodeling. MCP1 knockout mice exhibited suppressed inflammatory cytokine production and reduced fibrosis during early time points, but by 6 weeks the inflammatory and profibrotic changes normalized and no differences in hypertrophy or cardiac function were present.⁴⁸ This

suggests that blocking monocytes by targeting the MCP1-CCR2 signaling pathway may be a useful strategy to reduce CCR2⁺ inflammatory macrophage subsets, while maintaining other resident populations carrying out sentinel, phagocytic, and remodeling functions. Blocking this chemotactic pathway appears to have a greater impact on fibrotic remodeling, and might have a more direct role in regulating fibroblast function. Since many of the targeting strategies are time-dependent, a more thorough characterization of the functional phenotypes at various pathophysiological stages will be necessary.

Different Macrophage Phenotypes and Polarization

Macrophages display a range of functionally heterogeneous phenotypes, and a major focus of research has been aimed at understanding the roles of different macrophage phenotypes during disease. Modulating specific immune cell phenotypes to ameliorate disease is an enticing strategy and could be an important therapeutic approach (Table 2).

In contrast to depleting or blocking macrophage responses, manipulation of the macrophage phenotypes may provide a novel way to prevent specific deleterious inflammatory effects, while still allowing for other critical phagocytic and reparative responses.

Macrophages are capable of integrating a wide array of environmental signals, and can respond through unique activation programs. Although initially designated M1 (classical) and M2 (alternative), based on activation by Th1 and Th2 mediated cytokines, macrophage activation falls within a spectrum of classically activated macrophage (CAM) and alternatively activated macrophage (AAM) phenotypes.

AAMs are thought to have beneficial, wound healing effects in many cardiovascular diseases and are one of the major macrophage subsets in the healthy heart.^{40,67} During myocardial infarction, the predominance of different macrophage phenotypes is phase dependent. During the initially inflammatory phase, there is an increase in CAMs where as during the later remodeling phase AAMs predominate.⁶⁸ Little is known about the functional macrophage phenotypes during the development of pressure overload and angiotensin-II induced hypertrophic remodeling.

Regulation of Hypertrophic Remodeling by Macrophage and Myeloid Phenotype

Although our understanding of the roles for AAM phenotypes in cardiovascular diseases is limited, several studies have demonstrated that these phenotypes correlate with cardiovascular protection. Through the use of cell type-specific targeting and knowledge of specific signaling effectors that regulate macrophage activation, it is now possible to delineate the roles of specific macrophage phenotypes during cardiac hypertrophy. Although comprehensive data is lacking, numerous regulators of macrophage activation have been identified, and several studies have shown that modulation of the myeloid phenotype can regulate the hypertrophic and fibrotic response.

MR is a regulator of macrophage polarization, and activation by mineralocorticoids enhances proinflammatory CAM phenotypes, whereas MR antagonists and MR knockout

suppress the inflammatory response and skew macrophages towards an AAM phenotype.² Importantly, myeloid-specific deletion of MR significantly reduced L-NAME/angiotensin-II-induced cardiac hypertrophy and fibrosis. Conditional myeloid MR knockout using LysM-Cre resulted in the suppression of inflammatory genes, and increased expression of AAM markers in cardiac tissue. This suggests that myeloid cell modulation may be an important mechanism for the beneficial effects of MR antagonists used clinically to treat heart failure and post-myocardial infarction patients. Myeloid MR has also been shown to be important in stroke and may also have important roles in other cardiovascular diseases.⁶⁹

Hypoxia inducible factor has important regulatory effects in myeloid cells, and HIF activation may be a critical regulator of myeloid phenotype during cardiac remodeling. A recent study demonstrated that myeloid-specific deletion (LysM-Cre) of prolyl hydroxylase domain protein 2 (PHD2), which hydroxylates and induces degradation of HIFs, attenuates L-NAME/angiotensin-II induced cardiac remodeling.⁶² Myeloid PHD2 knockout mice had reduced cardiac hypertrophy and fibrosis, decreased macrophage recruitment and inflammatory gene expression, and preserved cardiac function. PHD2 deficient macrophages were shown to have reduced expression of CAM markers, and increased expression of the AAM marker Arg1, suggesting that regulation of macrophage polarization could be a potential mechanism of cardioprotection.

PI3K is a downstream effector of many different signaling pathways including certain TLRs and cytokine receptors, and studies have implicated PI3K signaling in cardiac pathophysiology. IGF-1 has been shown to induce cardiac hypertrophy through PI3K dependent pathway.⁷⁰ A study using a kinase-dead PI3K (PI3K KD) found that PI3K inactivation ameliorated pressure overload-induced inflammation, fibrosis and cardiac dysfunction, without affecting cardiomyocyte hypertrophy.⁶³ Importantly, this protective phenotype was transferable to wild type mice with PI3K KD marrow, suggesting that PI3K regulates bone marrow-derived cell phenotype and this has a critical role in cardiac remodeling and dysfunction. PI3K KD-inactivation in bone marrow was necessary to reduce pressure overload-induced cardiac inflammation and fibrosis. PI3K KD mice with wild type marrow had similar inflammation and fibrosis as wild type mice, but had reduced cardiac dysfunction similar to mice with PI3K KD marrow. This implicates a role for PI3K in multiple cell types, likely through different mechanisms.

A wide array of non-coding miRNAs have been identified as modulators of cardiac hypertrophy and remodeling (Reviewed in Kumarswamy et al. ⁷¹), and many known miRNAs can be targeted to alter cellular function. Most targeting strategies have focused on understanding the role of miRNAs in regulating cardiomyocyte function, and cardiomyocyte-specific knockout or overexpression of many miRNAs can induce pathologic hypertrophy. A recent study has expanded the field and revealed that miRNAs can regulate myeloid cell phenotype to modulate cardiac hypertrophy and remodeling.¹ Knockout of miR155 reduced angiotensin-II and pressure overload-induced hypertrophy, inflammation and cardiac dysfunction. miR155 knockout also suppressed angiotensin-II induced pro-inflammatory genes and mitigated Arg1 and IL-10 suppression, and bone marrow transplant with miR155 deficient cells was sufficient to produce this phenotype.

IL-4 is potent inducer of AAMs and can be upregulated in cardiac tissue during injury. It also has direct effects on other cardiac cells and stimulates proliferation of fibroblasts. Inhibition of IL-4 with neutralizing antibodies attenuated cardiac fibrosis and hypertrophy during pressure overload, suggesting that IL-4 is pro-fibrotic and may exacerbate the hypertrophic response.⁷² The effect of blocking IL-4 signaling in macrophages, and its response in hypertrophic remodeling is unknown. The important effectors of this response are unclear since multiple cell types respond to IL-4, and further analysis using conditional targeting strategies will be necessary to understand how IL-4 signaling regulates specific cell types. It was suggested that mast cells might be important in initiating IL-4-induced hypertrophy and fibrosis since they secrete IL-4, although many other cells including Th2 cells and cardiomyocytes can also contribute to IL-4 production.

Manipulation of other regulators of macrophage polarization like IRF5 and class A scavenger receptor have been shown to be involved in cardiac remodeling after myocardial infarction,^{73, 74} although whether these myeloid modulators are also involved in hypertensive cardiac remodeling is unknown. While it is thought that AAMs are cardio protective, the present data are inconclusive since the mechanisms by which macrophage phenotypes regulate cardiac remodeling are unclear.

Lymphocytes

T cells have the ability to regulate inflammation through interactions with various immune cells, and can activate, modulate or suppress other leukocyte inflammatory responses. T cells are recruited to the heart during cardiac inflammation, and there is evidence that they are involved in the pathophysiology of cardiac diseases.

Depletion studies have demonstrated that T cells are involved in cardiac remodeling, and can significantly alter cardiac pathophysiology. In cardiac TNF- α overexpressing mice, which develop severe cardiomyopathy, neutralization of T cells with anti-CD3 antibody was shown to reduce inflammatory cell recruitment and block hypertrophy.⁵⁰ In pressure overload-induced hypertrophy, T cell depletion using Rag2 deficient mice have reduced myocardial fibrosis with decreased macrophage infiltration.⁵¹ This is associated with significantly attenuated cardiac dysfunction.⁵¹ MHCII knockout mice exhibited a similar phenotype, and this was suggested to be due to the lack of immature T cells, but could also be due to impaired responses from antigen presenting cells like dendritic cells or macrophages. However, another study has also reported that Rag1 deficient mice had no differences in hypertrophy, and actually had increased perivascular fibrosis.³⁷ Rag1 deficient mice also have been reported to have reduced angiotensin-II induced hypertension and vascular dysfunction,⁵² indicating that blood pressure regulation may be an important mechanism by which T cells alter cardiac hypertrophy and remodeling.

Regulatory T cells (Tregs) have a major role in suppressing inflammatory responses, and are increased in the heart after MI and HF. Patients with HF have decreased circulating Tregs with reduced functional capacity to suppress T cell activation, and that plasma Treg concentration correlated with cardiac function.⁷⁵ In animal models, several studies have shown that Fox3P+ regulatory T cells are beneficial and ameliorate cardiac damage.

Adoptive transfer of Tregs reduced angiotensin-II and pressure overload-induced cardiac hypertrophy and remodeling, and suppressed macrophage and T cell populations in the heart.^{64, 65} In cardiac TNF- α -overexpressing mice, Treg induction by Cocksackievirus B3 was also able to prevent cardiac hypertrophy and suppress inflammation through an IL-10 dependent manner.⁵⁰ A role for Tregs in regulating blood pressure responses is still unclear, since one report found that adoptive transfer of Tregs reduced angiotensin-II induced hypertension and vascular dysfunction,⁶⁶ where as another report found no difference in blood pressure.⁶⁴

Tregs have also been shown to attenuate hypertrophic remodeling and cardiac dysfunction after myocardial infarction. Adoptive transfer of Tregs, but not conventional T cells, reduced proinflammatory signaling while increasing anti-inflammatory IL-10 production, and this was associated with attenuated cardiac fibrosis and improved cardiac function.^{76, 77} While adoptive transfer of conventional T-cells does not reduce cardiac damage, it appears that these cells are necessary during myocardial infarction since CD4KO mice have impaired scar formation and increased mortality.⁷⁸ Depletion of Tregs using the FoxP3-DTR transgene also suggests a beneficial role for this T cell subset since Treg depletion resulted in increased infarct size, exacerbated inflammation and diminished clinical outcome.⁷⁹

Although the mechanisms by which Tregs ameliorate hypertension and hypertrophic remodeling are unknown, it likely involves suppressing or modulating other T cell or immune cell responses. Treg can suppress the Th17 T cell subset,^{80, 81} and a role for the Th17 subset has also been identified in the pathophysiology of hypertensive cardiac hypertrophy and remodeling. Th17 cells secrete IL-17, which induces a range of effects, and IL-17 concentrations are increased in hypertensive patients.⁸² In animal models, deletion of IL-17 significantly reduces angiotensin-II induced hypertension and attenuates vascular dysfunction.⁸² IL-17 blockade has also been shown to be beneficial in hypertensive cardiac hypertrophy and remodeling, dilated cardiomyopathy, and myocardial infarction disease models.^{83–85}

Th1 and Th2 cells can influence classical and alternative activation of macrophages and therefore could be potential targets for regulating macrophage phenotypes. Th1 responses are largely pro-inflammatory, while Th2 responses are in many situation profibrotic, therefore these cells may have critical roles and various stages during the pathogenesis of cardiac hypertrophy and remodeling. Macrophages and other antigen presenting cells might also induce or modulate T cell responses by presenting cardiomyocyte debris or through other signaling mechanisms. Collectively, these studies indicate that in addition to depleting T cells, enhancing or modulating specific T cell responses may also be an effective strategy to regulate cardiac remodeling and suppress unresolved inflammatory responses. In addition, how the modulation of T cells alters other immune cell phenotypes is still mostly unknown.

Mast cells

Mast cell numbers in the heart increase significantly in response to cardiac injury,⁵⁴ and numerous studies have shown that mast cells have a role in maladaptive cardiac remodeling. Mast cell deficient WBB6F1-W/W^v mice have a marked reduction in pressure overload-

induced cardiac hypertrophy and fibrosis with preserved cardiac function,⁵³ and they are protected from decompensated cardiac hypertrophy and failure during pressure overload. Similarly, mast cell deficiency also reduced cardiac hypertrophy, fibrosis and dysfunction in cardiac-TNF α overexpressing mice.⁵⁴

Mast cell function can also be inhibited pharmacologically using mast cell stabilizers. In spontaneously hypertensive rats, the mast cell stabilizer nedocromil significantly ameliorated cardiac fibrosis, although it had no effect on hypertrophy or cardiac function.⁵⁷ Nedocromil is also protective in a volume overload model, and significantly suppressed ventricular hypertrophy while preventing cardiac dysfunction and reducing mortality.⁵⁶

The mechanisms by which mast cells contribute to cardiac remodeling and dysfunction are not fully elucidated. Mast cells secrete molecules like histamine, growth factors, cytokines, and proteases, which may influence other cell types and adversely affect adaptive remodeling. Mast cells induce cardiomyocyte apoptosis, as well as fibroblast and myofibroblast proliferation and matrix deposition through the secretion chymase and tryptase. Mast cells secrete IL-4, which may have pro-fibrotic and immunomodulatory effects. Therefore, it will be important to fully delineate the role that mast cells have in regulating cardiomyocyte and non-cardiomyocyte function during cardiac remodeling.

Other immune cells

Inhibition of ICAM-1 with neutralizing antibodies was shown to reduce infiltrating macrophages and suppress cardiac fibrosis during pressure overload.⁵⁸ However, ICAM-1 inhibition prevents transmigration of many different leukocytes and therefore it is difficult to delineate the cell type-specific contributions. There are many other immune cell populations that likely contribute to pathologic cardiac remodeling that will not be thoroughly discussed due to a lack of data.

Neutrophils are the most abundant circulating leukocyte in humans, and they respond quickly to acute injury. Depletion of neutrophils is protective during models of myocardial infarction,⁸⁶ but until recently there has been limited data examining the role of neutrophils during the development of cardiac hypertrophy and remodeling. Neutrophils have now been recognized as having a more significant and direct role in promoting cardiac inflammation and regulating hypertrophic remodeling. A recent finding has shown that neutralization of the neutrophil secreted molecule S100A9 reduces angiotensin-II-induced cardiac hypertrophy and fibrosis, which implicates neutrophils in the pathophysiology of hypertrophic remodeling.⁸⁷ While the presence of neutrophils is commonly noted, few studies have focused on defining neutrophil function, and therefore the role of neutrophils during pathologic hypertrophy and remodeling requires further exploration.

Eosinophils are thought to have a major pathological role during eosinophilic myocarditis, but may also have a potential role during other more common cardiac diseases. Recent reports using eosinophil deficient (dbiGATA) and hypereosinophilic (IL-5TG) mice have shown that eosinophils are secretors of IL-4 and regulate AAM phenotypes in adipose tissue. Importantly, eosinophils were found to affect insulin sensitivity, thermogenesis, and beige fat formation.^{88, 89} It is currently unknown how the macrophage phenotype is

controlled during cardiac injury, and the possibility of eosinophils regulating macrophage phenotype in this context remains explored.

Experiments examining the roles of dendritic cells in cardiac hypertrophy and remodeling are also absent. Dendritic cells are present in injured cardiac tissue, and have been shown to be important in cardiac remodeling following myocardial infarction.^{90, 91} While this may suggest a possible role in other forms of chronic hypertensive remodeling, no studies have confirmed this.

Fibroblasts

Fibroblasts are one of the most prevalent cell types in the heart and have a major role in matrix deposition during cardiac remodeling. During cardiac development and injury, the origin of cardiac fibroblasts and myofibroblasts has remained somewhat controversial, and it has been speculated that proliferating cardiac fibroblasts are derived from a variety of sources such as resident fibroblasts, bone marrow-derived progenitors, fibrocytes, epithelial cells and endothelial cells. Recently, a lineage tracing study using multiple Cre lines and reporter systems to identify fibroblasts found that cardiac fibroblasts originate from epicardial-derived and endocardial-derived resident fibroblast populations during development.⁹² Interestingly, this was also found to be true during cardiac injury. During pressure overload, rapidly expanding populations of fibroblasts were also derived from these two populations and not from hematopoietic precursors.⁹²

The important fibroblast signaling mechanisms that influence cardiomyocyte function and hypertrophy in vivo are still poorly understood, partly due to a lack of fibroblast specific genes. Several Cre lines (Postn-Cre, Fsp1-Cre, Tcf21-Cre, Col1a1-Cre, Col1a2-Cre) have been created for fibroblast-specific gene deletion; however, some of these have been shown to be non-specific or the specificity is unknown under specific pathological conditions and therefore studies using these Cre lines need to be interpreted carefully. Krüppel-like factor 5 has been shown to be an important regulator of pressure overload-induced cardiac remodeling through regulation of fibroblast function.⁹³ Fibroblast-specific (Postn-Cre), but not cardiomyocyte-specific (Myh6-Cre) deletion of Klf5 significantly attenuated cardiac hypertrophy and fibrosis. After “high intensity” pressure overload with greater aortic constriction, mice displayed similar reductions in hypertrophy and fibrosis, but developed heart failure and had increased mortality. This suggests a role for Klf5 in adaptive remodeling during pressure overload, and also provides evidence that fibroblasts have direct roles in regulating cardiac hypertrophy and remodeling. Furthermore, this highlights the need to analyze cardiac function and mortality rates, since measurement and analysis of select pathological findings like hypertrophy and fibrosis does not always predict the functional consequences.

Co-culture studies have shown that fibroblast and cardiomyocyte interactions can influence hypertrophic and fibrotic responses, and modulate contractile function, but these influences are difficult to verify in vivo due to the multitude of different cell types with overlapping signaling mechanisms.^{94, 95} In a mouse model of hypertrophic cardiomyopathy, Kim et al. found a marked induction of profibrotic genes, that occurred very early on and before

cardiomyocyte hypertrophy and functional abnormalities had developed.⁹⁶ Transcriptional sequence analysis subsequently found a large number of pro-fibrotic genes upregulated in non-myocytes in both pre-hypertrophic and overtly hypertrophic mice.⁹⁷ Thus, fibrotic signaling is occurring much earlier than originally thought, and is not just a secondary manifestation due to hypertrophy. It also suggests that specific mutations in sarcomere proteins may induce early intercellular communication that initiates profibrotic signaling mechanisms and in turn influences hypertrophy and remodeling.

In these studies, TGF- β inhibition was able to reduce non-myocyte proliferation and attenuate cardiac hypertrophy and remodeling.⁹⁷ Similarly, treatment of mice with an AT1R blocker also significantly ameliorated hypertrophy and fibrosis, and this beneficial effect was dependent on early administration prior to established hypertrophic cardiomyopathy. This further suggests that inhibiting early pro-fibrotic signaling is essential for pharmacological inhibition of hypertrophic remodeling. Although these results are intriguing, TGF- β and angiotensin-II have effects in numerous non-cardiomyocyte populations and therefore these pharmacological interventions could reflect the functional roles of many cellular interactions.

Transcriptome profiling using microarrays and deep RNA sequencing has identified hundreds of noncoding RNAs with altered expression during pathological hypertrophic remodeling. Numerous studies have shown that overexpression, deletion, or silencing of these noncoding RNAs can regulate the pathophysiological response to cardiac injury, although most of these studies have focused on manipulating and understanding the role these noncoding RNAs in cardiomyocytes. A recent study found that fibroblasts can secrete miRNA-enriched exosomes to communicate with neighboring cardiomyocytes and directly promote hypertrophy. Bang and colleagues showed that fibroblast-derived, passenger strand microRNA 21, miR-21*, promotes hypertrophy in cardiomyocytes, and pharmacological inhibition of miR21* ameliorates the hypertrophic response to angiotensin-II.⁹⁸ These findings provide new evidence that fibroblasts can directly regulate cardiomyocyte hypertrophy, and demonstrate an important mechanism of fibroblast-cardiomyocyte crosstalk.

Summary

Although cardiac hypertrophy was once thought of as a simple response to increased workload, it is now clear that it is a complex process involving all cell types present in the heart and interactions with circulating cells. Identifying the cell types involved, particularly the many immune cells, is critical to our full understanding of the physiologic and pathologic responses. We rely largely on specific markers to identify different cell populations and phenotypes, while having little knowledge about functional importance. In addition to identifying specific immune cell populations, it will be necessary to understand how specific functional phenotypes contribute. This understanding may lead to potential clinical interventions.

In the future, we can bring a number of approaches and technologies to delineating the mechanisms of physiologic and pathologic hypertrophy. Novel technologies to test the cell

type-specific roles, such as conditional knockouts and cell type depletion, are available, but most of these studies have focused on myocardial infarction models. While many of these results might suggest a role in other hypertrophic responses in other cardiac pathologies, further studies will be necessary to determine a role. There are also limitations on which cell types can currently be addressed with these technologies. Furthermore, cardiac diseases are multi-phasic and most studies only focus on single time points. To fully understand the hypertrophic response, it will be necessary to identify critical, early time points and understand the functional role of specific immune cells during the early phases of hypertrophic remodeling. While this may prove to be difficult because of time and cost, the benefits of understanding the early immune responses could be critical to understanding the pathogenesis and for identifying specific therapeutic targets.

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Figure 1.

Overview of cardiomyocyte and non-cardiomyocyte interactions during cardiac hypertrophy and remodeling. Cardiomyocytes respond to pathogenic stimuli by secreting inflammatory cytokines, chemokines, and DAMPs, which are recognized by local non-cardiomyocyte cells. This induces activation and expansion of resident macrophages and fibroblasts, and also recruits bone marrow-derived immune cells from the circulation. Activated immune cells and fibroblasts secrete both pro-hypertrophic and pro-fibrotic cytokines, which induce cardiomyocyte hypertrophy and promote fibroblast differentiation, matrix deposition, and interstitial fibrosis.

Figure 2.

Detailed hypertrophic and fibrotic signaling mechanisms between cardiac cells. Interactions between cardiac cells involve complex signaling pathways that induce phenotypic changes in nearby cells. Hypertrophy and fibrosis can be augmented by pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and pro-fibrotic molecules (TGF- β , angiotensin-II). RAAS activation has direct pro-inflammatory, pro-hypertrophic, and pro-fibrotic effects in cardiac cells, and these responses are pharmacologically inhibited with ACE inhibitors, ARBs, and MR antagonists. Tregs and exogenous IL-10 treatment can also suppress inflammation and hypertrophic signaling.

Table 1

Depletion or inhibition of immune cells during cardiac hypertrophy and remodeling.

Cell Type	Treatment	Model	Function	Hypertrophy	Fibrosis	Inflammation	BP	Ref
<i>Monocyte/Macrophage/Phagocytic Cells</i>								
	Clodronate liposomes	Ren2 rats	↓	NE		↓Mp, ↓Mo, ↑TI	NE	43
	Clodronate liposomes	Ang-II			↓	↓Mp, ↓TNF-α, ↓TGF-β		44
	BM-CCR2 ^{-/-}	Ang-II	NE	NE	↓	↓Mp	NE	45, 46
	anti-MCP1	AAC	↑	NE	↓	↓Mp, ↓TGF-β		47
	MCP1 ^{-/-}	Ang-II	NE	NE	↓	↓Mp,	NE	44, 48
	LysM-iDTR	Ang-II	↑		↓ (PV)	↓Mp, ↑Np	↓	49
<i>T lymphocyte</i>								
	anti-CD3	CM-TNF-α Tg		↓		↓TI, ↑CD11b ⁺		50
	Rag2 ^{-/-}	TAC	↑		↓	↓Mp		51
	Rag1 ^{-/-}	TAC	NE	NE	↑ (PV)			37
	Rag1 ^{-/-}	Ang-II	↑				↓	52
	CD8 ^{-/-} , anti-CD8	Ang-II		NE	↓	↓TNF-α ↓TGF-β	NE	44
	CD8 ^{-/-}	TAC	NE		NE		-	51
<i>APCs</i>								
	MHCII ^{-/-}	TAC	↑		↓	↓Mp		51
<i>Mast Cells</i>								
	Deficient - cKit mutant	AAC	↑	↓	↓		NE	53
	Deficient - cKit mutant	CM-TNF-α Tg	↑	↓	↓	↓TGF-β		54
	Deficient - cKit mutant	TAC	NE, ↓AF	NE	↓			55
	Mast cell stabilizer	AV fistula	↑	↓			-	56
	Mast cell stabilizer	SHR rats	NE	NE	↓	↑IL-10, ↑IL-6	NE	57
<i>Leukocytes</i>								
	ICAM-1 ^{-/-}	AAC		NE	↓	↓Mp, ↓TGF-β	NE	58

Abbreviations: NE, No Effect; APCs, antigen presenting cells; Mp, macrophage; Mo, monocyte; Np, neutrophil; TI, T lymphocyte; PV, perivascular; AAC, abdominal aortic constriction; TAC, transverse aortic constriction; Ang-II, angiotensin-II.

Table 2

Modulation or enhancement of immune cells in cardiac hypertrophy and remodeling.

Cell Type	Treatment	Model	Function	Hypertrophy	Fibrosis	Inflammation	BP	Ref
BM/Myeloid Cells								
<i>Modulators</i>								
T lymphocyte	MR KO	L-NAME/Ang-II		↓	↓	↓Mp, ↓TNF-α,	NE	2
	PHD2 KO	L-NAME/Ang-II	↑	↓	↓	↓Mp, ↓TGF-β	NE	62
	BM-PI3K-KD (Inactive)	TAC	↑	NE	↓	↓CD18 ⁺ , ↓TGF-β		63
	BM-mi155 KO	Ang-II	↑	↓		↓CD45 ⁺ leukocytes	NE	1
<i>Enhancement</i>								
T lymphocyte	Treg adoptive transfer	Ang-II		↓	↓	↓Mp, ↓Tl, ↓TNF-α,	NE	64
	Treg adoptive transfer	TAC		↓	↓	↓Mp, ↓Tl, ↓TGF-β	NE	65
	Treg adoptive transfer	Ang-II				↓TNF-α ↓IFN-γ	↓	66
	Treg-CVB3-H310A1	CM-TNF-α Tg		↓		↓CD11b ⁺ , ↑IL-10,		50

Abbreviations: BM, bone marrow-derived; NE, No Effect; Mp, macrophage; Tl, T lymphocyte; Treg, regulatory T lymphocyte; TAC, transverse aortic constriction; Ang-II, angiotensin-II