Chronic inflammation appears to underlie most, if not all, the chronic diseases of today, including cardiovascular disease, type 2 diabetes, chronic kidney disease, Alzheimer’s disease and cancer. We have demonstrated that obesity induces chronic local inflammation in adipose tissue. We also found that chronic inflammation is crucially involved in the development of heart failure and chronic kidney disease. In this article, I review recent findings reported by my group and others regarding the mechanisms underlying the chronic inflammatory processes commonly observed in adipose tissue, heart and kidney. I then discuss the key features of the chronic inflammation seen in chronic diseases. (Circ J 2011; 75: 2739–2748)

Key Words: Heart failure; Inflammation; Kidney; Metabolic syndrome

It is becoming increasingly clear that chronic inflammation plays a key role in the development and progression of various chronic diseases, including cancer, type 2 diabetes (T2D), Alzheimer’s disease, and cardiovascular and renal diseases. Clinically, elevated circulating levels of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β and IL-18, have been reported in patients with chronic heart failure, where they positively correlate with disease severity. Similarly, high levels of C-reactive protein (CRP) have been shown to be an independent risk factor for cardiovascular disease, and elevated levels of IL-1β, IL-6 and CRP are predictive of T2D. These findings all point to the pivotal involvement of inflammation in the progression of chronic disease. Mechanistically, however, much about how chronic inflammation is involved in the initiation and progression of chronic diseases remains unknown.

Acute inflammation is fundamentally a protective response to injury. Acute inflammatory processes deliver leukocytes and plasma proteins, such as antibodies, to sites of infection or tissue injury. Morphologically, acute inflammation is manifested by vascular changes, edema and predominantly neutrophilic infiltration, which cause the 4 cardinal signs of inflammation: rubor (redness), tumor (swelling), calor (heat) and dolor (pain). Acute inflammatory processes resolve when the offending agent is eliminated and the tissue returns to its normal homeostatic state. However, if injurious agents persist or the normal process of healing is perturbed, the acute inflammation may not resolve but instead progress to chronic inflammation.

Chronic inflammation is a prolonged condition in which inflammation, tissue injury and attempts at repair coexist. Although chronic inflammation may follow acute inflammation, in the most common chronic diseases of today, it likely begins insidiously as a low-grade, smoldering response with no manifestation of an acute reaction. Chronic inflammation also differs from the acute condition in that its underlying processes may be disease-specific and even temporally vary during disease progression. Nevertheless, chronic inflammatory diseases do share common features. Here, I will present an overview of recent progress in our understanding of chronic inflammation in adipose tissue, heart and kidney, after which I will discuss the key features of chronic inflammation in chronic diseases.

Adipose Tissue Inflammation and Metabolic Syndrome

The obesity epidemic has resulted in an increasing prevalence of a metabolic syndrome characterized by visceral obesity, hypertension, dyslipidemia and insulin resistance. Obesity, particularly visceral obesity, is thought to be centrally involved in increasing the clinical risk of metabolic and cardiovascular diseases.

In addition to its function as a reservoir of lipids, adipose tissue is now known to be an active endocrine organ that produces a variety of “adipokines” and controls energy homeostasis. Obese adipose tissue also secretes various proinflammatory cytokines, including IL-6 and TNF-α, and the release of free fatty acids (FFAs) may be increased as a result of activated lipolysis. It has been suggested that the dysregulated production of proinflammatory mediators relative to the production of antiinflammatory adipokines (eg, adiponectin) is an important contributor to adverse metabolic and cardiovascular consequences.

The increased secretion of inflammatory mediators seen in obese visceral fat reflects the ongoing chronic inflammation of the adipose tissue, itself. Proinflammatory cytokines are produced by cells in the adipose stroma, as well as by the adipocytes. Activation of inflammatory pathways in adipocytes impairs triglyceride storage and increases the release of FFAs.
an excess of which is known to induce insulin resistance in muscle and liver.\textsuperscript{11} Thus, chronic inflammation appears to be a clinically important change that occurs in adipose tissue when it becomes obese.\textsuperscript{12}

We have found that adipocytes, immune cells and vascular cells dynamically interact with one another within obese visceral fat.\textsuperscript{13} For instance, new adipocytes are generated via a coupled adipogenesis and angiogenesis mechanism within so-called “adipo-/angiogenic cell clusters”, and macrophages focally converge on dead adipocytes to form “crown-like structures (CLSs).” In addition, by directly observing adipose tissue in living mice, increased leukocyte–platelet–endothelial cell interactions in the microcirculation of obese visceral fat have been detected.\textsuperscript{15} This is indicative of activation of the leukocyte adhesion cascade, a hallmark of inflammation. My group also found fibrosis in chronically obese adipose tissue. Chronic inflammation is characterized by infiltration of the affected tissue by mononuclear cells, angiogenesis, destruction of the affected tissue, and subsequent healing by replacement of the damaged tissue through fibrosis. Our findings and those of others clearly indicate that obesity of visceral fat involves all of these features of chronic inflammation. Thus, obese visceral adipose tissue is clearly a site of chronic inflammation (Figure 1).

Recently, the different subclasses of macrophages have drawn substantial interest. In obese adipose tissue, for example, the polarity of macrophage subpopulations moves toward M1-type classically activated proinflammatory macrophages,\textsuperscript{16} while the M2-type alternatively activated macrophage fraction, which may suppress inflammatory responses, is reduced.\textsuperscript{17}

This suggests an alteration of the balance between M1 and M2 macrophages may contribute to the proinflammatory state of obese fat. Adipose tissue also contains large numbers of T cells, which account for up to 10% of stromal cells, even in lean animals.\textsuperscript{18} Among these T cells, the CD8\textsuperscript{+} fraction increases during the progression of obesity, while the CD4\textsuperscript{+} and regulatory T (T\textsubscript{reg}) cell fractions are diminished. Obese adipose tissue activates CD8\textsuperscript{+} T cells, which in turn initiate and propagate inflammatory cascades, leading to systemic insulin resistance and metabolic abnormalities. In lean mice, by contrast, T\textsubscript{reg} and T helper type 2 (T\textsubscript{H2}) cells restrict inflammatory responses in part via production of the antiinflammatory cytokine IL-10.\textsuperscript{19,20} In obese adipose tissue there is a shift to dominance of CD8\textsuperscript{+} and T\textsubscript{H1} T cells, which appear to propagate inflammation.\textsuperscript{21} In addition, B cells were recently shown to be involved in the progression of adipose inflammation, and eosinophils were shown to promote alternative activation of adipose tissue macrophages via production of IL-4.\textsuperscript{22} Natural killer (NK) and NKT cells and mast cells may also promote adipose inflammation.\textsuperscript{24-26} It is thus very clear that a variety of immune cells are crucially involved in maintaining homeostasis and activation of inflammatory processes in adipose tissue, and that the balance between antiinflammatory and proinflammatory cellular functions is a key determinant governing adipose tissue inflammation.

Interrupting the accumulation of macrophages and CD8\textsuperscript{+} T cells within obese adipose tissue suppresses adipose inflammation. Interestingly, it also ameliorates systemic insulin resistance and metabolic abnormalities, strongly suggesting adipose
inflammation has an important impact on systemic metabolism.\textsuperscript{13,27}

**Adipose Tissue Inflammation and Atherosclerosis**

Atherosclerosis is now widely considered to be a chronic inflammatory disease.\textsuperscript{28} Many of the cellular processes ongoing during atherosclerosis are similar to those involved in adipose tissue obesity. For instance, the leukocyte adhesion cascade is activated in both conditions. In addition, angiogenesis is indispensable to the progression of adipose tissue obesity;\textsuperscript{14} likewise, angiogenesis within the arterial wall is important for the progression of atherosclerosis.\textsuperscript{29} Finally, cellular interactions between resident cells and macrophages via inflammatory cytokines and other factors are actively ongoing within both atherosclerotic plaques and obese adipose tissue.\textsuperscript{30} These findings suggest that a number of common mechanisms underlie both atherosclerosis and adipose tissue obesity.

Morphologically, adipose tissue obesity involves dynamic structural changes, including adipocyte hypertrophy, angiogenesis, CLS formation, adipogenesis, stromal cell proliferation, adipocyte death and fibrosis.\textsuperscript{14,31,32} These dynamic changes in the organization of the adipose tissue architecture can be considered “adipose tissue remodeling”. Similarly, in atherosclerosis the arterial wall undergoes excessive remodeling as it forms the atheromatous plaque. Tissue remodeling is a hallmark of chronic inflammation, and is propelled by closely linked concomitant progression of both tissue destruction and healing.\textsuperscript{33} This too suggests common mechanisms that lead to tissue remodeling underlie both atherosclerosis and adipose tissue obesity.

**T2D and Inflammation**

The obesity epidemic has resulted in dramatic increases in the incidence of T2D. Numerous studies have shown that insulin resistance precedes the development of hyperglycemia in subjects who eventually develop T2D;\textsuperscript{34} however, T2D only develops in insulin-resistant subjects after the onset of pancreatic \(\beta\)-cell dysfunction.\textsuperscript{35} This makes both insulin resistance and \(\beta\)-cell dysfunction key pathological conditions in T2D. Proinflammatory signaling pathways can inhibit insulin signaling,\textsuperscript{12,36} providing a link between inflammation and insulin resistance. Recent reports have shown that expression of IL-1\(\beta\), which is involved in the autoimmune processes leading to T1D, is upregulated in the islets of patients and animal models with T2D,\textsuperscript{4} and an IL-1 receptor antagonist reportedly improves both blood glucose levels and \(\beta\)-cell function in T2D patients.\textsuperscript{37} Accumulation of macrophages within islets has also been observed in T2D subjects,\textsuperscript{38,39} suggesting activation of chronic inflammatory processes within T2D islets. Taken together, these results strongly suggest that chronic inflammation is crucially involved in the development of 2 major features of T2D.

**Crucial Involvement of Stromal Cells in Cardiac Hypertrophy and Heart Failure**

Cardiac hypertrophy is an essential adaptive process through which the heart responds to mechanophysical, metabolic and genetic stresses. On the other hand, the hypertrophy induced by sustained overload eventually leads to contractile dysfunction and heart failure. Although in cardiac hypertrophy each cardiomyocyte is hypertrophied, various non-myocytes, including fibroblasts, vascular endothelial cells, smooth muscle cells and immune cells, are also essential components of the myocardial hypertrophic response. My group recently showed that haploinsufficiency of the transcription factor gene, \(Klf5\), suppresses cardiac fibrosis and hypertrophy elicited by moderate-intensity pressure overload, indicating \(Klf5\) is an important regulator of myocardial responses to pressure overload.\textsuperscript{40} However, cardiomyocyte-specific deletion of \(Klf5\) did not alter the hypertrophic response. By contrast, cardiac fibroblast-specific deletion of \(Klf5\) ameliorated cardiac hypertrophy and fibrosis, indicating that it is \(Klf5\) expressed in fibroblasts that is important for the response to pressure overload, and that cardiac fibroblasts are required for cardiomyocyte hypertrophy. \(Klf5\) transactivates insulin growth factor 1 gene (\(Igf1\)) in cardiac fibroblasts, after which IGF-1 acts in a paracrine fashion to induce hypertrophic responses in cardiomyocytes. Notably in that regard, high-intensity pressure overload caused severe heart failure and early death in fibroblast-specific \(Klf5\) knockout mice.

Accomero et al recently reported that when subjected to pressure overload, mice lacking the placental growth factor gene (\(Pgf\)) died of heart failure within 1 week and showed suppressed angiogenesis and fibroblast activity; conversely, cardiomyocyte-specific overexpression of PGF enhanced the cardiac hypertrophic response to pressure overload.\textsuperscript{41} Because cardiomyocytes do not express the PGF receptor, it was proposed that PGF supports adaptive cardiac hypertrophy by facilitating growth factor release from non-myocytes in the heart. In addition, Del Re et al reported the Ras-associated domain family 1 isoform A (Rasfl1A), a tumor suppressor that activates mammalian sterile 20-like kinase 1 (Mst1), and inhibits fibroblast proliferation and the cardiomyocyte hypertrophy mediated in part by TNF-\(\alpha\) produced by fibroblasts.\textsuperscript{42} Collectively, these results demonstrate that cardiac fibroblasts play a pivotal role in the adaptive response of the myocardium.

It had been traditionally thought that resident fibroblasts were the sole source of cardiac fibroblasts, but more recently other cellular sources have been proposed.\textsuperscript{43} In particular, bone marrow-derived cells may acquire fibroblast-like phenotypes.\textsuperscript{44} Circulating myeloid cells of bone marrow origin that acquire a fibroblast-like phenotype and then contribute to wound healing and interstitial fibrosis in various tissues are often designated as circulating fibrocytes.\textsuperscript{45} Macrophages may also promote fibrosis by producing cytokines such as TGF-\(\beta\). It is therefore likely that bone marrow-derived cells play multiple roles in cardiac fibrosis.

Vascular endothelial cells are also crucially involved in the development of cardiac hypertrophy, remodeling and failure. Endothelial cells are capable of producing a wide variety of functional agonists and antagonists, including vasodilators and vasoconstrictors, procoagulants and anticoagulants, and inflammatory and antiinflammatory factors. Endothelial cells maintain homeostasis by controlling the balance among these mediators;\textsuperscript{46} consequently, endothelial dysfunction can disturb that balance, leading to the initiation of pathological inflammatory processes. For instance, activated endothelial cells express the adhesion molecules, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, which recruit and promote the infiltration of immune cells into the myocardium in response to various stimuli.

Accumulating evidence indicates that impaired angiogenesis contributes to the transition of cardiac hypertrophy to heart failure. Hypertrophic stimuli induce expression of the angiogenic growth factors vascular endothelial growth factor (VEGF) and angiopoietin 2,\textsuperscript{47} which promote angiogenesis and blood flow in response to reductions in coronary perfusion pressure or ischemia. Blockade of VEGF action using an
adenoviral vector encoding a decoy VEGF receptor or an anti-VEGF antibody promotes the transition from compensatory cardiac hypertrophy to failure in response to pressure overload in mice. Likewise, TNP-470, an inhibitor of angiogenesis, also induces cardiac dysfunction. Conversely, VEGF treatment during prolonged pressure overload preserves contractile function. Within myocardium subjected to pressure overload, hypoxia-inducible factor-1 (HIF-1)-mediated transactivation of VEGF in cardiomyocytes plays an important role in the induction of angiogenesis. It has also been proposed that in response to sustained pressure overload, p53 accumulates within cardiomyocytes and inhibits HIF-1 activity, thereby impairing cardiac angiogenesis and contractile function. However, there are conflicting data showing that ventricular deletion of HIF-1α prevents hypertrophy-induced activation of peroxisome proliferator-activated receptor-γ and contractile dysfunction.

A variety of immune cells, including macrophages, T cells and mast cells, reside in the myocardium under normal physiological conditions. They are also induced to infiltrate the myocardium under pathogenic conditions and to promote cardiac remodeling, in part by releasing cytokines, growth factors and matrix metalloproteinases (MMPs). For instance, angiotensin II-induced cardiac hypertrophy and fibrosis is diminished in macrophage-specific mineralocorticoid receptor-deficient mice. By contrast, macrophage depletion using liposomal clodronate induces abundant infiltration of inflammatory cells, predominantly CD4+ lymphocytes, and worsens cardiac dysfunction in hypertensive rats harboring the mouse renin gene (Ren2). This suggests macrophages exert a protective effect against cardiac dysfunction induced by hypertension. These results also indicate that macrophages have multiple functions during the development of cardiac hypertrophy and heart failure.

Although cardiac hypertrophy is not generally considered to be an inflammatory disease, it can be seen that it involves a number of non-myocytes, including vascular and immune cells, which play prominent roles in inflammation. Moreover, during cardiac hypertrophy and the progression to heart failure, the myocardium exhibits complex structural remodeling involving rearrangement of muscle fibers, fibrosis, accumulation of extracellular matrix (ECM), cellular death and angiogenesis. Many of the processes underlying these phenomena are also seen in chronic inflammatory diseases and are mediated by cellular interactions between cardiomyocytes and non-myocytes. Collectively then, it appears that chronic inflammatory processes play central roles in adaptive as well as maladaptive responses within the myocardium (Figure 2).

**Tubulointerstitial Damage in Chronic Kidney Disease (CKD)**

The incidence of end-stage renal disease is increasing worldwide and represents a growing clinical and economic burden.
Regardless of whether renal injury begins in the glomeruli or within the tubulointerstitium, tubulointerstitial damage is a common feature of all chronic progressive renal diseases and is considered to be the final common pathway leading CKD to end-stage renal disease.\textsuperscript{58–60} Inflammation is a critical mechanism that promotes closely interlinked fibrosis and cellular injury within the tubulointerstitium,\textsuperscript{61} and macrophages are the predominant infiltrating immune cells mediating that inflammatory process.\textsuperscript{60}

My group recently demonstrated that KLF5 is an important regulator of the macrophage activation and inflammatory processes ongoing after unilateral ureteral obstruction (UUO), a murine CKD model.\textsuperscript{62} We found that Klf5\textsuperscript{+/–} mice were protected from renal injury induced by UUO, but showed enhanced fibrosis. We also found that KLF5 induces S100a8 and S100a9 expression in response to UUO. The S100A8 and S100A9 proteins secreted from the collecting duct in turn recruit CD11b\textsuperscript{+}Ly-6C\textsuperscript{+} inflammatory monocytes to the kidneys, and then contribute to the cells’ differentiation into M1 macrophages, which promote renal injury and inflammation. Later, the renal microenvironment becomes permissive for M2 macrophage activation and proliferation. M2 macrophages promote fibrosis and may suppress inflammation.

Figure 3. A model for M1/M2 macrophage accumulation and tubulointerstitial inflammation. In response to unilateral ureteral obstruction, S100a8 and S100a9 expression is induced by KLF5 in collecting duct epithelial cells. S100A8 and S100A9 in turn recruit CD11b\textsuperscript{+}Ly-6C\textsuperscript{+} inflammatory monocytes to the kidneys, and then contribute to the cells’ differentiation into M1 macrophages, which promote renal injury and inflammation. Later, the renal microenvironment becomes permissive for M2 macrophage activation and proliferation. M2 macrophages promote fibrosis.

Key Features of the Chronic Inflammatory Processes in Chronic Diseases

Chronic inflammation clearly plays a key role in both the...
initiation and progression of the chronic diseases prevalent today, including cardiovascular, metabolic and renal diseases. Although the various chronic inflammatory processes may appear to be diverse, they involve similar cellular activities and utilize similar signaling pathways. In this section I will discuss some of the common features of chronic inflammation in chronic diseases.

**Chronic Inflammation Starts Insidiously Without Clear Manifestation of Acute Inflammation**

Inflammation in chronic diseases appears to be chronic from the outset; that is, the first cellular signs of inflammation often involve infiltration of the tissue by monocytes and macrophages, which is in contrast to the initial accumulation of polymorphonuclear leukocytes seen in acute inflammation. It is therefore likely that the factors that initiate and regulate chronic inflammatory processes differ from those involved in acute inflammation.

**Endogenous Insults May Initiate Chronic Inflammation**

It has been suggested that in some cases exogenous insults contribute to the activation of chronic inflammation. For instance, the development of atherosclerosis is reportedly associated with infection by various pathogens, though antibiotic treatments have proven ineffective for secondary prevention of cardiovascular events in large clinical trials. Furthermore, in many chronic diseases no pathogens have been identified, making it unlikely they play a primary role in the initiation of chronic inflammation. In atherosclerosis, mechanical force (shear stress) can alter gene expression in endothelial cells and induce atherogenic endothelial phenotypes, which exhibit increased low-density lipoprotein (LDL) permeability and promote monocyte infiltration. In addition, modified LDLs promote the formation of foam cells, which together with other mediators activate macrophages. All of these processes proceed in sterile settings, again suggesting it is highly unlikely that exogenous factors are required for initiation of chronic inflammation. It is similarly unlikely that activation of inflammation in obese adipose tissue depends on exogenous factors. That said, recent studies have shown that the gut microbiota affect systemic inflammation and metabolism. It was also reported that a high-fat diet not only increases plasma lipopolysaccharide (LPS) levels, it increases the proportion of LPS-containing bacteria in the gut. This makes it possible that commensal bacteria can modulate the progression of chronic inflammation, an issue that should be addressed.

**Innate Immunity Activated by Endogenous Factors Plays a Major Role**

Innate immunity represents the earliest barrier to invading pathogens and provides important cues for the adaptive immunity that follows. The innate immune system recognizes the repetitive molecular structures of pathogens, which are known as pathogen-associated molecular patterns (PAMPs), via pattern recognition receptors (PRRs). Cells of the innate immune system, such as macrophages, express a variety of PRRs, including the Toll-like receptors (TLRs). Upon recognition of a PAMP, TLRs activate several signaling molecules, among which the nuclear factor \( \kappa \) B (NF-\( \kappa \)B) pathway is the most distinctive. The resultant signaling causes innate immune cells to be activated to destroy the pathogen and/or pathogen-infected cells, and may also lead to activation of adaptive immunity. PRRs, including TLRs, are also expressed in non-immune cells, such as endothelial cells, and these too are likely important for regulation of inflammatory processes.

Damage to tissues and cells can also be caused by trauma induced by physical or chemical insults. The resultant damaged or dying cells release endogenous molecules called damage/danger-associated molecular patterns (DAMPs), which activate the immune system in a fashion analogous to PAMPs. A variety of different molecules have now been identified as DAMPs, including high-mobility group box 1 protein, genomic double-stranded DNA, and cleaved ECM proteins. It has also been proposed that modified endogenous molecules, such as oxidized lipoproteins, serve as DAMPs. In atherogenesis, for example, oxidized LDL may activate inflammatory signaling via PRRs, perhaps through activation of inflammatory cytokine secretion from macrophages via TLR signaling. In addition, it was recently shown that cholesterol crystals induce inflammation by stimulating the NLRP3 inflammasome. NLRP3 belongs to the nucleotide-binding domain and leucine-rich repeat-containing receptor (NLR) family of PRRs. The NLRP3 inflammasome is a cytosolic protein complex composed of a regulatory subunit, NLRP3; an adaptor protein, apoptosis-associated speck-like protein, and an effector subunit, caspase-1. Upon activation, the NLRP3 inflammasome cleaves pro-IL-1\( \beta \) and IL-18, activating them. In this way, modified self molecules, the production of which does not necessarily require cell death, may serve as danger signals that activate PRRs and innate immune responses.

Interestingly, TLR4 is also activated by FFAs, including palmitate. Within adipose tissue, proinflammatory cytokines produced by macrophages (e.g., TNF-\( \alpha \)) can activate lipolysis and increase release of FFAs from adipocytes. Saturated FFAs, in turn, activate macrophages via TLR4 signaling. It has therefore been proposed that adipocytes and macrophages form a vicious link that enhances inflammation in obese adipose tissue. These findings are remarkable because they suggest that nutrient molecules can directly activate the innate immune response. They also support the notion that chronic inflammatory processes are activated under sterile conditions by endogenous molecules, such as modified self molecules.

Finally, although innate immune responses are central to chronic inflammatory processes, the adaptive and innate immune systems appear to intrinsically interact to control inflammatory processes. For instance, T cells control inflammation in adipose tissue and are also involved in atherogenesis.

**Macrophages Are Versatile Effector Cells in Chronic Inflammatory Processes**

Macrophages are the major cell type in the innate immune system and are crucially involved in the various processes underlying chronic inflammation. In particular, recent studies have revealed that macrophages are quite heterogeneous. Whereas classical M1-type macrophages play a central role in host defense by secreting proinflammatory cytokines and reactive oxygen species, activated M2-type macrophages may promote wound healing and may also modulate immune responses. As described earlier in the sections on adipose tissue and kidney, these different macrophage subsets play different roles during disease development and progression and may also contribute to the maintenance of homeostasis.

**Chronic Inflammatory Processes May Be Essentially Protective**

It is clear that acute inflammation is initiated and employed as an adaptive and protective mechanism against insults. By contrast, the adaptive and homeostatic roles of chronic inflammation are not often apparent when looking at the consequences of inflammatory processes that have been ongoing for
an extended period of time. Nevertheless, they may also have essential homeostatic and protective functions. For instance, although DAMPs generated by tissue damage and cell death may initiate chronic inflammation, clearance of dead cells by macrophages is essential to prevent further release of intracellular materials and to restrain inflammation. Indeed, mice showing inadequate engulfment of apoptotic cells develop a systemic lupus erythematosus-like autoimmune disease.\(^{77}\)

In addition to TLRs, natural antibodies secreted by B-1 innate-type B cells may also recognize oxidized lipids and antigens expressed by apoptotic cells.\(^{78}\) These natural antibodies facilitate uptake of apoptotic cells by macrophages, which is essential for maintenance of tissue homeostasis,\(^{79}\) and may exert atheroprotective effects.\(^{80}\)

As also discussed, cardiac fibroblasts play an essential adaptive role in the response to pressure overload.\(^{81}\) It has been shown that angiogenesis is induced by pressure overload and is necessary if heart failure is to be prevented.\(^{82}\) These responses have certain commonalities with chronic inflammatory processes, which suggests inflammatory pathways are involved in protecting the myocardium from pressure overload, and may also be important for maintenance of myocardial homeostasis.

Within adipose tissue, inflammation can be activated under physiological conditions by both feeding and fasting. For example, fasting activates lipolysis and increases the release of FFAs from adipocytes, which recruit macrophages to the adipose tissue.\(^{83,84}\) The recruited macrophages then phagocytose the excess lipids. Importantly, these processes can be activated by a 24-h fast, as well as by weight loss induced by 30% caloric restriction, suggesting the macrophage accumulation is an embedded physiological program for the maintenance of homeostasis. Taken together, these findings suggest that in many cases of chronic disease, chronic inflammatory processes are initially activated to protect cells and tissue from stress. Clarifying how these processes, which are initially beneficial, become pathological will be important for understanding the mechanisms underlying chronic inflammatory diseases.

**Alteration of the Tissue Microenvironment May Prolong Inflammatory Processes**

In cases of acute inflammation, once the insult is removed, the inflammatory processes resolve and homeostasis is restored.\(^{83}\) With chronic inflammation, however, the inflammatory processes often do not subside when the insult is removed; instead, they may continue for a prolonged period, leading to irreversible tissue remodeling and dysfunction. It will therefore be important to identify the mechanisms that prevent resolution of chronic inflammatory processes.

Successful post-inflammatory tissue repair requires the coordinated restitution of not only the epithelial and mesenchymal cells, but also the ECM and vasculature.\(^{85}\) Ideally, complete tissue repair would recover the healthy tissue. However, failure of the tissue repair process may activate inflammatory processes in response to remaining stress and/or new stress generated by the incomplete repair. As mentioned, this response appears to be essentially protective: activation of macrophages is required for clearance of damaged cells and tissues, while angiogenesis and degradation of ECM are necessary for restoration of healthy tissue structure and function. Suboptimal inflammatory processes may result in failure to remove stress molecules, prolonging inflammation. It is therefore not surprising that genetic interventions affecting inflammatory processes may paradoxically worsen tissue damage in certain cases. For instance, deletion of the inflammasome genes, *Nlrp3* and *Casp1* (caspase 1), which are important for production of virus-induced IL-1β and IL-18 in macrophages, diminished neutrophil and monocyte recruitment and cytokine production in lungs infected with influenza A virus, which exacerbated early epithelial necrosis and collagen deposition, leading to later respiratory compromise.\(^{84}\)

Chronic inflammatory processes also often result in excess fibrosis and tissue remodeling (see later), which can interfere with the optimal function of the tissue. An example of this is fibrosis and remodeling of the left ventricle, which not only impedes contraction and relaxation because of the increased stiffness, it also impairs cardiomyocyte function by altering electrical coupling and metabolism.\(^{85}\) In that way, the structural remodeling imposes a new stress on the tissue, contributing to the perpetuation of the chronic inflammation.

In addition to modulating the physical properties of tissue, ECM proteins can activate various signaling pathways. ECM molecules can affect the adhesion, migration, proliferation and survival of the surrounding cells by acting through integrin molecules. What’s more, recent studies have shown that matrikines, fragments of ECM molecules with biological activities distinct from those of the parental protein, exert a variety of effects.\(^{86}\) Matrikines are generated by the proteolytic cleavage of ECM molecules by proteases, including serine proteases and MMPs. Matrikines are involved in wound healing, angiogenesis, inflammation and tumor progression. For instance, matrikines generated from collagen type IV (arrestin, canstatin, tumstatin and metastatin) are anti-angiogenic. Matrikines also affect such immune cell functions as migration and phagocytosis.\(^{86,87}\) As such, deposition of ECM proteins significantly modifies multiple aspects of the tissue microenvironment and may contribute to the perpetuation of inflammation. Future studies will need to identify the molecules that link alteration of the tissue microenvironment to the continuation of inflammatory processes.

**Altered Set-Point and Tissue Dysfunction**

Chronic inflammation may also induce cellular and tissue dysfunction without apparent tissue remodeling. For instance, inflammatory signaling interferes with insulin signaling, leading to insulin resistance,\(^{12}\) and studies have identified molecular links between inflammatory and insulin signaling pathways. Endothelial cell dysfunction is a crucial step in atherogenesis, as discussed earlier, but emerging evidence indicates that endothelial dysfunction can also significantly affect the function of other tissues. For instance, impaired insulin signaling in endothelial cells reduces glucose uptake by skeletal muscle.\(^{88}\) These examples demonstrate that activation of inflammatory signaling may modulate cell/tissue function such that the responsiveness to a given stimulus and/or the response per se is altered.

**Irreversible Tissue Remodeling**

Continuous chronic inflammatory processes eventually lead to tissue remodeling. Furthermore, the often extensive fibrosis and structural rearrangement of cells and interstitium may make the tissue remodeling irreversible.\(^{87}\) may severely damage normal tissue function and may contribute to the perpetuation of inflammatory processes.

**Conclusions and Future Perspectives**

Chronic inflammation appears to be a unifying pathological feature of the chronic diseases of today, and recent studies have been unraveling the common cellular and molecular con-
stituents and pathways involved in the diverse responses associated with different chronic diseases. On the other hand, there are likely mechanisms that distinguish each pathology from the others. For instance, the cells that sense insults and initiate inflammation may differ in each chronic disease. I anticipate that future studies of the molecular mechanisms that initiate and propagate inflammatory processes will reveal molecular and cellular targets that can be utilized for the development of therapeutic strategies that are selective and effective for each disease. These studies will also be important for identifying novel biomarkers useful for diagnosing the development stages of chronic diseases.

Therapeutics for the treatment of chronic inflammation in chronic diseases are already being tested. For instance, an IL-1 receptor antagonist (IL-1RA, anakinra) and an IL-1β-specific antibody were tested in T2D patients. Salsalate, a prodrug of salicylic acid with inhibitory effects on the NF-κB pathway, has also been tested in T2D. The positive results of these studies are consistent with the concept of targeting inflammation to treat T2D.

However, the features of chronic inflammation can impose obstacles that slow the development of novel therapeutic strategies. Of particular importance is temporal alteration of the cellular and molecular processes that operate during the progression of chronic inflammatory diseases. For instance, it is possible that the same therapeutic intervention could produce opposite effects when applied at different times to different subjects. Treatment of heart failure patients with a TNF-α antagonist exemplifies that concept. Large clinical trials of the TNF-α antagonist, etanercept, in patients with NYHA classes II–IV heart failure failed to show a beneficial effect on the incidences of death and hospitalization. Similarly, the monoclonal antibody, infliximab, failed to show a therapeutic benefit. There are several possibilities as to why these clinical trials failed: (1) the dose and timing of treatment were not sufficient to inhibit TNF-α; (2) the biological agents had unknown detrimental side effects and/or intrinsic toxicity; and (3) treatment interfered with other drug treatments. Although these explanations are all plausible, it is also known that TNF-α contributes to cardioprotection related to ischemic conditioning. This means that the choice of timing, dose and subjects very likely affected the therapeutic consequences. Clearly, a more detailed understanding of the mechanisms underlying chronic inflammation is needed, particularly in relation to the temporal progression of disease processes. It will also be important to determine how inflammatory processes become activated in multiple tissues if we are to understand the accumulation of tissue dysfunctions often seen in patients with chronic disease.

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