INSIGHTS INTO THE PATHOPHYSIOLOGY OF HEART FAILURE BASED ON A NEW CONCEPT*

A kira M A T S U M O R I **


Abstract: We have reported the increased myocardial expression of cytokines in animal models of heart failure secondary to myocarditis, myocardial infarction, and hypertension and we have shown that the lesions in impaired hearts resemble inflammatory or proliferative changes in some respects. In addition, the occurrence of crosstalk between cytokines and the adrenal axis, as well as between cytokines and the renin-angiotensin or endothelin system, has been suggested. Crosstalk between the sympathetic nervous system, endocrine systems, and the immune system may be important in adaptation and failure of the myocardium caused by various factors, including mechanical overload, ischemia, and viral infection. Elucidation of the mechanisms of these processes may lead to the development of new therapy for heart failure.

Key words: Heart failure; Cardiomyopathy; Cytokines; Immunity

Introduction

Over the years, the concept of heart failure has undergone dramatic changes. At first, heart failure was thought as a disease associated with renal failure due to alteration of cardiac function. Consequently, diuretics were once the mainstay of treatment. Subsequently, cardiotonics and vasodilators were used for this condition, because it was considered to arise from abnormal cardiac metabolism and abnormal circulatory responses, including the peripheral vessels. Recently, beta-adrenergic blockers and ACE inhibitors have become central to treatment because heart failure has considered as a disorder of the neurohumoral system.

Considering heart failure to be based on immune abnormalities, we hope that immunomodulation and anti-cytokine therapy will bring about major progress in its treatment. This article describes our attempts to gain new insights into the pathophysiology of heart failure based on such a viewpoint.

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Cytokines and the Heart

Cytokines are important intercellular mediators, as well as being immunologically active substances. Recently, many cytokines have been shown to influence disorders of cardiac myocytes and cardiac function. This indicates that immunological factors such as cytokines, as well as neural and endocrine factors, may play an important role in the pathology of heart disease, and cytokines have come to attract particular attention.

When cardiac myocytes are injured by viruses, ischemia, and stress, there is an increase in the production of cytokines such as interleukin (IL)-1, IL-2, tumor necrosis factors (TNF-α), and interferon (IFN)-γ. Cytokines are deeply involved in the pathophysiology of heart disease. In addition, it has been shown that cytokines can act on the myocardium to decrease myocardial contractility and to promote myocardial hypertrophy and fibrosis (Fig. 1).1–3)

Cytokines and Heart Failure

The relationship between heart disease and cytokines has attracted attention since elevation of blood TNF-α levels in chronic heart failure and an association between TNF-α and cardiac cachexia were reported. We have demonstrated that the blood levels of IL-1α, IL-1β, and TNF-α are frequently elevated in myocarditis and the TNF-α level is also frequently elevated in dilated or hypertrophic cardiomyopathy. Such findings strongly suggest that these cytokines play an important role in the pathogenesis of cardiomyopathy.3) In addition, elevation of the blood levels of soluble TNF-α receptor, IL-2 receptor, and IL-1 receptor antagonists in heart failure and cardiomyopathy patients have been reported, and increased expression of myocardial IL-1β mRNA in patients with dilated cardiomyopathy has also been reported.

In patients with heart failure, the blood levels of chemokines or macrophage chemotactic factors (MCP-1, MIP-1α, and RANTES) were reported to be elevated and the blood levels of MCP-1 and MIP-1α were negatively correlated with the left ventricular ejection fraction. There was no evident relationship between the MCP-1 level and the cause of heart failure, but its blood level tended to rise in
patients with coronary disease. When we determined blood levels of MCP-1 in patients with heart failure secondary to dilated cardiomyopathy, however, it was not elevated.

Because the blood MCP-1 level was increased in acute myocardial infarction, however, the possibility that MCP-1 may be related to ischemic heart disease is high. It has been reported that cardiac function (as assessed by echocardiography) was decreased in rats administered TNF-α via an osmotic pump and recovered after administration of TNF-α was discontinued or when soluble TNF-α receptor was administered.

Recently, transgenic mice specifically expressing TNF-α in the myocardium were produced using an α-myosin heavy-chain promoter. These transgenic mice developed myocarditis in both ventricles and atria along with enlargement of the left and right ventricular cavities and a decrease of the ejection fraction. In transgenic mice produced with a similar promoter, myocardium expressing MCP-1 specifically showed infiltration by macrophages, while the heart showed hypertrophy and dilation with a decrease of cardiac function during the chronic phase. These mice are quite interesting models of myocarditis and cardiomyopathy.

To clarify the role of IL-1β, cardiac function was assessed in dogs receiving intracoronary injection of microspheres coated with recombinant human IL-1β. Dogs treated in this way with IL-1β developed persistent cardiac dysfunction. Aminoguanidine, an inducible NO synthase inhibitor, was able to prevent the development of cardiac dysfunction. Thus, dysfunction of the heart caused by IL-1β was demonstrated in vivo.

**Cytokines and Heart Failure Secondary to Myocardial Disease**

Using a mouse model that develops heart failure secondary to myocarditis caused by infection with EMC virus, we investigated the relationship between the expression of cytokine messenger RNAs (mRNAs) in the myocardium and the severity of heart failure. This study showed that the expression of IL-1β, IL-2, TNF-α, and IFN-γ mRNA was increased in the acute inflammatory phase, and that these cytokines were still expressed in the chronic phase after three months. These findings strongly suggested that such cytokines were relevant to pathogenesis of myocardial hypertrophy and fibrosis in the chronic phase.

There were positive correlations between the expression of IL-1β, the heart to body weight ratio, and the extent of fibrosis. In addition, survival was improved when the mice were treated with a high dose of anti-TNF-α antibodies in the early phase of heart failure, while disease progression was seen when cytokines such as recombinant TNF-α were administered. Consequently, IL-1β and TNF-α were considered to have potential injurious effects on cardiac myocytes that could lead to the aggravation of heart disease.

In recent years, hepatitis C virus (HCV) has been attracting attention as a cause of cardiomyopathy. In patients with HCV infection, it has been reported that CD4-positive cytotoxic T lymphocytes infected with HCV produce cytokines such as IL-8, TNF-α, IFN-γ, and GM-CSF, while CD4-positive T lymphocytes produce IL-2, IL-4, IL-5, TNF-α, TNF-β, and IFN-γ. In patients with hepatitis
caused by HCV, elevation of TNF-α and soluble TNF-α receptor in the blood has been reported.

**Cytokines and Heart Failure Secondary to Hypertension**

We studied the expression of cytokines in Dahl salt-sensitive rats, which develop heart failure secondary to cardiac hypertrophy caused by hypertension. Specimens of the myocardium were obtained from rats in the stages of hypertrophy and heart failure, and the expression of IL-1β and TNF-α mRNA was investigated. Although expression of TNF-α mRNA was not so remarkable, expression of IL-1β and MCP-1 mRNA was increased in both stages. Their expression in the stage of heart failure was stronger than in the stage of hypertrophy. The expression of IL-1β was positively correlated with the weight and diastolic diameter of the left ventricle, and was negatively correlated with left ventricular fractional shortening. Consequently, IL-1β appears to play a role in cardiac hypertrophy and heart failure. The infiltration of numerous macrophages in the left ventricular myocardium of Dahl rats suggested that IL-1β might have been produced by these macrophages and by endothelial cells.

The results of this study on Dahl rats led us to investigate whether mechanical stress could induce the production of cytokines. We studied cytokine production by human umbilical vein endothelial cells (HUVEC) that were subjected to stretching. This mechanical stretch induced a marked increase in the production of IL-8 and MCP-1 by these cells. This increase showed that vascular endothelial cells can produce MCP-1, a macrophage chemotactic factor, when stimulated mechanically by stretching. The enhanced ventricular expression of MCP-1 in Dahl rats suggested the possibility that infiltration of macrophages into the myocardium would be mediated by MCP-1 (Fig. 2).
Cytokines in Heart Failure after Myocardial Infarction

As described above, the cytokine production can be induced by stresses such as viral infection and hypertension. Whether cytokines can be induced by ischemia was also studied. In rats, marked expression of the mRNAs for TNF-α, IL-1β, and IL-6 was noted in the infarcted area at one week after the development of myocardial infarction, and then in the non-infarcted region at 20 weeks after its development. The expression of cytokine mRNAs in the non-infarcted region was correlated with the end-diastolic diameter of the left ventricle. Twenty weeks after infarction, the infarcted region was replaced with scar tissue, while vascular endothelial cells, smooth muscle cells, and macrophages were still IL-1β positive in the non-infarcted region. In addition, the myocardial collagen content was related to the expression of IL-1β in the non-infarcted region, suggesting an association between remodeling after myocardial infarction and cytokine expression.

Furthermore, it has been shown that expression of MCP-1 is increased during the acute phase of myocardial infarction, and that administration of anti-MCP-1 antibodies reduces the infarct size.

From these findings, it appears that the expression of cytokines may reflect the development and pathology of heart disease, so cytokines may be of value as diagnostic and therapeutic markers.

Treatment of Heart Failure and Cytokines

Recently, it has been demonstrated that phosphodiesterase inhibitors, which were developed to treat heart failure, can inhibit the production of cytokines. It has been recognized that different inhibitors produced different effects. It has been also recognized that digitalis can increase the production of cytokines. An antiarrhythmic agent amiodarone, which has been shown to improve the long-term prognosis of heart failure, was recently shown to inhibit the production of TNF-α and IL-6.

Because drugs that control the production of cytokines and signal transduction seem to be effective for the treatment of heart failure, it is expected that immunological response modifiers will be developed as a new form of therapy in the future.

Cytokines and Crosstalk between the Sympathetic Nervous System, Renin-angiotensin System, and Endothelin

The results of recent studies have highlighted the association between the immune system and the central and autonomic nervous systems. It has become clear that increased production of adrenocortical hormones secondary to activation of the hypothalamic-pituitary-adrenal axis reduces the production of cytokines. In heart failure, the sympathetic nervous system is activated, leading to increased secretion of catecholamines, which act on many immune cells such as macrophages and lymphocytes.

Many immune cells, including lymphocytes, macrophages, eosinophils, and neutrophils, possess β-receptors. It has become clear that when β-receptors are
stimulated, the intracellular cAMP level increases and various immune responses are suppressed. Psychological stress is known to increase norepinephrine, which suppresses cellular immunity through modification of helper T-cell functions and also increases humoral immunity.

The renin-angiotensin system and endothelin both play an important role in cardiovascular diseases and both show crosstalk with cytokines. For example, TNF-α increases the production of angiotensinogen by liver cells, while angiotensin II increases the production of IL-6, TNF-α, and MCP-1 by kidney cells. IL-1β and TNF-α increase the production of endothelin-1, which in turn increases the production of IL-6 by endothelial cells or IL-8 and G/M-CSF by bronchial cells. Thus, it is likely that cytokines form positive feedback circuits with the renin-angiotensin system and endothelin in cardiovascular disease.

**Conclusion**

In addition to the neural and endocrine factors that have been investigated extensively to date, immunological factors such as cytokines seem to play an important role in cardiovascular disease. If all these systems are taken into consideration, a new strategy for the treatment of heart failure may be designed.

**REFERENCES**