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From the Laboratory to the Clinic: Molecular Treatment of Heart Failure

Laboratuvardan Kliniğe: Kalp Yetmezliğinin Moleküler Tedavisi

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ABSTRACT

Coronary and cardiovascular diseases are the leading cause of death today, with heart failure being among the primary culprits. Heart failure can occur as a result of many diseases, so research in this area is important in terms of clinical outcomes and treatment. Histopathology of heart failure includes cardiac hypertrophy, inflammation, angiogenesis, and apoptosis pathways. The issue of elucidating the pathology of heart failure is still an area of active research. In advanced heart failure, the typical management strategy is medical treatment, mechanical ventricular support devices, and heart transplantation. Heart failure, which occurs with modifiable and non-modifiable risk factors, can be controlled with both non-pharmacological and pharmacological treatment applications. It is especially important to focus on new treatment methods and introduce them to the clinic. Although they are all not yet used in clinics, many studies have yielded promising results with molecular treatment options for heart failure prevention. Studies in animals have shown that heart failure stops proceeding when angiogenesis is induced. Promising results have also been achieved with stem cell therapy, but these may not be implementable for years. It is expected that studies following phases 1 and 2, of the studies which had positive results in the treatment of heart failure, will be conducted and applied in the daily treatment practice.
Keywords: Heart failure; molecular treatment; stem cell therapy.

ÖZ

Koroner ve kalp-damar hastalıkları günümüzün önde gelen ölüm nedenidir; kalp yetmezliği ise primer etiyoloji arasında yer almaktadır. Kalp yetmezliği birçok hastalığın getirisi olarak ortaya çıkabildiğinden bu alanda yapılacak araştırmalar klinik sonuçlar ve tedavi açısından önemlidir. Kalp yetmezliğinin histopatolojisi, kalp hipertrofisi, inflamasyon, anjiyogenez ve apoptoz yolaklarını içerir. Kalp yetmezliği patolojisinin aydınlatılması konusu halen aktif bir araştırma alanıdır. İlerlemiş kalp yetmezliğinde tipik tedavi stratejisi tıbbi tedavi, mekanik ventriküler destek cihazları ve kalp naklidir. Değiştirilebilen ve değiştirilemeyen risk faktörleriyle ortaya çıkan kalp yetmezliği hem farmakolojik hem de non-farmakolojik tedavi uygulamalarıyla kontrol altına alınabilmektedir. Özellikle yeni tedavi yöntemlerine odaklanılması ve bunların kliniğe tanıtılması önemlidir. Henüz klinikte kullanılmamasına rağmen, birçok çalışma kalp yetmezliğinin önlenmesine yönelik moleküler tedavi seçenekleriyle umut verici sonuçlar vermiştir. In vivo yapılan çalışmalar, anjiyogenez uyarıldığında kalp yetmezliğinin ilerlemesinin durduğunu göstermiştir. Kök hücre tedavisinde de umut verici sonuçlar alınmakta iken aktif uygulama yapılamamaktadır. Kalp yetmezliği tedavisinde olumlu sonuç alınan çalışmalardan faz 1 ve 2. aşamayı takip eden çalışmaların yapılması ve günlük tedavi pratiğinde uygulanması beklenmektedir.
Anahtar kelimeler: Kalp yetmezliği; moleküler tedavi; kök hücre terapi.

INTRODUCTION

The most common cause of death in the United States (US) is heart disease. The life expectancy for females was 5.0 years higher than for males, and the life expectancy at birth was 78.6 years (1). Heart failure (HF) is a significant cause of morbidity and mortality. In 2016, there were 6.2 million HF patients in the US, and by 2030, this rate is expected to increase by 46% (2).

According to European Society of Cardiology (ESC) guidelines for acute and chronic HF, HF is defined as follows (3): "A clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress." The etiology of HF is varied and includes myocardial, pericardial, endocardial, heart valve disease, vascular disease, and metabolic disease (4).

Advanced HF, cardiogenic shock, and related deaths often occur despite optimal medical therapy (β-blockers, angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, and implantable cardioverter defibrillator (ICD) treatments). Symptoms should be noted, and congestion status should be assessed at each examination. Symptoms associated with fluid retention usually regress when treated with diuretics. Findings such as increased jugular venous pressure and displacement of the apex beat are more specific, but they may be difficult to detect, and their applicability is low (5,6). The most common symptoms of HF are dyspnea, orthopnea, paroxysmal nocturnal dyspnea, decreased exercise intolerance, fatigue, prolonged recovery time after exercise, and ankle edema. Typical findings of this are increased jugular venous pressure, hepatojugular reflux, 3rd heart sound (gallop rhythm), and lateral displacement of the apex beat.

It may be more difficult to identify symptoms and signs of HF in obese patients, elderly patients, and patients with chronic lung disease, so the symptom status should be monitored after treatment. HF is life-threatening, decreases the quality of life, is high in comorbidity, brings a significant economic burden to the health system, and is a progressive disease that often leads to long hospital stays, expensive mechanical devices, heart transplantation, and/or death. (7,8). Coronary artery disease is among the most common risk factors of HF, so controlling HF necessitates early diagnosis, control, and follow-up for coronary artery disease (9-11).

The aim of this review was to describe molecular treatment methods that depict myocyte loss in cases of HF in cardiovascular risk groups apart from routine treatment methods.

TREATMENT METHODS

Research areas are directed to both non-pharmacological and pharmacological management of HF, at the same time, close monitoring of the patient at home with various devices is also considered (12,13).

The most common cardiovascular disease is coronary artery disease. Many risk factors cause coronary artery disease, these are modifiable and non-modifiable factors. Correction of modifiable risk factors and lifestyle change are very important. Blood pressure control, lipid therapy, physical activity, diet, and stopping smoking are among modifiable reasons. (14-17).

Since both genetic and lifestyle features predispose to coronary artery disease, genomic sequencing, and analytical technologies provide patients the opportunity to lipid control strategy individually. Although it is not widely used in the clinic, it is an active research area to determine the genetic risk score by identifying the DNA variants causing cardiovascular disease. The individual risk can be identified, and susceptibility to disease can be understood and individualized strategies can be applied before the development of the disease to avoid or delay the disease (18-20).

β-blockers, angiotensin-converting enzyme inhibitor drugs, mineralocorticoid receptor antagonists, diuretics, and angiotensin receptor neprilysin inhibitors are recommended with strong indication to reduce the risk of hospitalization and death due to HF in symptomatic patients (21).

In patients with advanced HF, device therapy methods reduce the risk of sudden death of the patient, prolong life, and the use of ICD, cardiac resynchronization therapy-defibrillator (CRT-D) is recommended with definite indication despite the cause of HF being ischemic or non-ischemic the power which the heart required to spend is reduced, organ perfusion increases, and more oxygen is delivered to the tissues (22).

The gold standard treatment for advanced HF is heart transplantation. According to International Society for Heart and Lung Transplantation (ISLTH) records, from 1982 to 2012, more than 100,000 heart transplant operations were performed worldwide. The 1-year survival rate is 81%, the 5-year survival rate is 69%, and the median survival rate is 11 years (23).

Heart transplantation performed in end-stage HF provides long-term successful survival. Unfortunately, not all patients meet the criteria for heart transplantation and the problem of donor insufficiency continues. Besides, supportive therapy and rehabilitation are required. Cardiac rehabilitation is an evidence-based practice and patient education, and behavior modification are important for the secondary prevention of cardiovascular diseases (24).

MOLECULAR MECHANISMS IN HEART FAILURE

New insights into the pathophysiology and molecular mechanisms of HF are required to develop new therapeutic approaches. To overcome HF, some advances in understanding the molecular pathways associated with cardiac hypertrophy, inflammatory signaling (e.g. TNF-α, IL-6), and oxidant stress that may play an important role in modifying transcriptional regulatory networks which regulate adaptation or non-compliance should be identified. In addition to paracrine mechanisms (VEGF, CCN1) and intracellular signaling (IL-6-glycoprotein 130), the effects of current treatment options on these molecular pathways and the potential effects on cardiac failure progression should be clarified (25,26).

Molecular events occurring in pathological hypertrophy are characterized by activation of gene expression patterns. It is a fetal stage that generally includes the up-regulation of fetal isoforms of genes that regulate cardiac contractions

and calcium uptake which is mostly parallel with the down-regulation of adult isoforms (e.g. up-regulation b-MHC; down-regulation α-MHC). More recently, evidence has been presented that shows that pathophysiological stresses also affect normal cell transformation in the heart, leading to a negative rate of cardiac apoptosis and regeneration from circulating cardiac progenitor cells (27). In the last decade, great progress has been seen in understanding the molecular mechanisms of adaptive and maladaptive hypertrophy and HF in response to stress signals, and the involvement of several extracellular factors and signaling pathways (28).

Firstly, understanding the important role of neurohormonal activation in the pathophysiology of HF has led to the improvement of morbidity and mortality in the current medical treatment of patients with HF. Accordingly, recent experimental data support the concept that aldosterone blockade provides beneficial effects in addition to effective renin-angiotensin system blockade. Aldosterone is one of the stimulants for the production of cardiomyocyte reactive oxygen species (ROS) that play a role in the development of cardiac hypertrophy and dysfunction in response to both biomechanical and neurohormonal stimuli. Numerous studies have reported that ROS (superoxide, hydrogen peroxide, hydroxyl radical) increases myocardial production in experimental and clinical HF. After two weeks of treatment, angiotensin II-induced cardiac hypertrophy was related to NAD(P)H oxidase activation. Recent in vitro and in vivo studies have provided evidence that the antioxidant effects of statins have an important role in cardiac hypertrophy and vascular dysfunction in patients with HF (29,30).

It is well known that increased TNF-α levels occur in the circulation of patients with HF. In a study, a mouse with a transgene overexpressing TNF developed cardiac hypertrophy, and dilated cardiomyopathy indicated that this cytokine plays a deleterious role in the heart. Also, TNF-α exerts a strong direct effect on cardiomyocytes since it causes apoptosis in cardiomyocytes, depression of contractility, and in vitro downregulation of sarcomeric proteins (31).

Recently, IL-6-gp130-Janus kinase (JAK)-STAT signal cascade was investigated in patients with end-stage HF, and it was demonstrated that the pathway of this mechanism changes at all levels in people with HF (32). Although these studies did not identify the exact role of individual factors in the IL-6-gp130-JAK-STAT signaling system, it was identified with increasing experimental models that IL-6-associated cytokine signaling contributes to compensatory hypertrophy, ensures heart protection, and promotes neovascularization in the stressed heart (33).

In HF, the conversion of mechanical stress to biomechanical signals is thought to be largely mediated by a group of surface receptors called integrins. Furthermore, intracellular signaling pathways regulated by the melusin with integrin sensor have been shown to contain ERK1/2, PI3-K/Akt, and glycogen synthase kinase 3-beta (GSK-3). Gene mutations that cancel one of these pathways result in early HF in response to inadequate hypertrophic response and mechanical stress. Activation of these two signaling pathways is thought to be important for promoting adaptive hypertrophy and preventing failure during early dilatation and hemodynamic overload (34,35).

Failure to induce adequate neovascularization results in inadequate oxygen supply followed by loss and degeneration of cardiomyocytes, atrophy, and interstitial fibrosis, and may represent the main cause of myocardial dysfunction and HF. STAT3 plays a very important role among the signal molecules involved in the expression of proangiogenic factors in cardiomyocytes. Both STAT3 and JunD regulate the expression of proangiogenic secreted factor VEGF, pointing to the key role of this protein in postnatal myocardial angiogenesis, in which cardiomyocytes themselves play an important role as a source for VEGF. A second proangiogenic factor, CCN1 is induced in the heart in vivo and in cardiomyocytes in vitro by various extracellular stress-related stimuli such as neurohumoral activation, cytokines, mechanical stress, and ischemia (36).

GATA4, which is a cardiac-enriched zinc transcription factor, plays an important role in both cardiac hypertrophy and myocardial angiogenesis. GATA4 is abundantly expressed in cardiomyocytes at early embryonic stages, regulates cardio-specific gene expression, and is downregulated in adult hearts. HIf-1, on the other hand, is a transcription factor that is stabilized under hypoxic conditions, and transactivates angiogenesis-related proteins such as VEGF and erythropoietin in the hypoxic medium.

As is known, cardiac neovascularization is not dependent on a single gene or factor but is based on the regulation of multiple factors by various signaling pathways. In patients with HF, new treatment strategies that promote the endogenous secretion of angiogenic factors have been introduced by directly applying proangiogenic factors to increase neovascularization (37,38).

Apoptosis plays a role in cardiomyocyte cell loss during the development of HF. Apoptosis rates between 0.08% and 0.25% in patients with end-stage dilated cardiomyopathy are between 0.001 and 0.002% in control hearts. Activation of caspase-8 is a central step in apoptosis initiated by activation of cell surface death receptors (e.g. Fas/FasL). In the study conducted by Wencker et al. (39) in 2003, procaspase-8 treated with a broad-spectrum caspase inhibitor prevented before dilatation and impaired cardiac dysfunction that began before cardiac decompensation in transgenic mice. Caspase inhibition and inhibition of cardiomyocyte death were found to be significant; apoptosis was reduced, and treatment success was increased. Also, although drug therapies targeting signaling agents that induce apoptosis such as B-adrenergic receptor blockers and angiotensin II inhibitors are standard in HF therapy, apoptotic pathways seem to have direct effects on cardiomyocyte contractility and remodeling (40).

Recent research has shown that cardiac hepatocyte growth factor/insulin-like growth factor-1 signaling plays a crucial role in cardiac regeneration for the migration of cardiac stem cells into the heart and their proliferation and differentiation (41).

MOLECULAR TREATMENT OPTIONS

Further studies are needed to determine the optimal combination of angiogenic growth factors and improve the technology of myocardial administration methods to increase the efficacy and safety of therapeutic

interventions for myocardial angiogenesis. In a rat model of myocardial infarction, the combination of fibroblast growth factor-2 and hepatocyte growth factor prevented the progression of HF by synergistically inducing angiogenesis. Cardiomyocytes themselves produce angiogenic factors to maintain capillary density, oxygen supply, and function. Besides, in endothelial cells, short activation of Akt alleviates the damage caused by ischemia, while long-term activation of Akt leads to unorganized blood vessel formation similar to tumor vasculature (42).

In another study, copper supplementation reversed contraction dysfunction and prevented the transition to HF in pressure-overloaded mice, partly through the promotion of myocardial angiogenesis (43). In addition to cobalt and copper function, several approved drugs have been reported to affect myocardial angiogenesis. For example, pitavastatin has been reported to induce myocardial angiogenesis and prevent the progression of HF. Although the promotion of myocardial angiogenesis needs much more work before becoming a prescribed drug for HF patients, a certain amount of preclinical evidence has accumulated and the applying this concept in clinical practice will likely continue to progress steadily in the coming years (44).

In a study in which cardiomyocyte efficacy was tested, it was shown that transplanted fetal cardiomyocytes can survive in the scar tissue of the heart, limiting scar expansion and preventing HF (45).

Given these previous studies, what are the functional roles of p53 accumulated in HF? The two main roles of P53 are cell cycle arrest and prevention of blood vessel formation. In cases of severe cellular damage, p53 arrests proliferative cells in the G1 stage of the cell cycle to induce apoptosis or aging. Although cardiac myocytes do not proliferate after birth, the accumulation of p53 causes apoptotic cell death in cardiac myocytes. In vivo, chemical inhibition of p53 accumulation or transcriptional activity mitigated adriamycin-induced cardiomyopathy in heart and cardiac failure after myocardial infarction. Although it is certain that neurohumoral factors, mechanical and oxidative stresses, metabolic changes, and cardiac dysfunction accompanied by DNA damage have accompaniment, definite triggers and mechanisms for the disruption of coordinated angiogenesis remain unclear (46).

DISCUSSION

Increased ROS production is involved in key issues related to the development and progression of HF, such as cardiomyocyte hypertrophy, ventricular dysfunction, and endothelial dysfunction. Statin therapy is a treatment that can have beneficial effects on HF by reducing oxidative stress and increasing endothelial nitric oxide availability.

An in-depth understanding of the molecular mechanisms of HF will provide valuable insights for the design of new treatment strategies that support protective signaling pathways and prevent incompatible responses such as advanced hypertrophy, inadequate vascularization, and apoptosis. Some of these findings may have important effects on the development of new treatment strategies in HF (47).

Mesenchymal stem cells are non-hematopoietic cells that have the potential to differentiate into various cell types. They were initially diagnosed in the bone marrow, but are also found in umbilical cord blood, adipose tissue, and heart. The use of these cells in mouse myocardial infarction models has led to the development of remodeling and the reduction of infarct size after their differentiation into cardiomyocyte and endothelial phenotypes (48).

The application strategies of stem cells are transvascular approaches and direct injection into the LV wall. Intracoronary conduction, intravenous infusion, and mobilization of stem cells are among these strategies. It has been reported that stem cells initiate myocardial repair and improve heart function with direct and indirect mechanisms including differentiation into the heart and vascular cells, paracrine effects, and cell fusion. The paracrine effect is a concept used for the therapeutic effects of transplanted stem cells on injured tissues. Transplanted stem cells release cytokines, chemokines, growth factors, exosomes, or microparticles, repair damaged myocardium, and stimulate changes that initiate restoration processes in the extracellular matrix (49,50).

The most obvious question to be answered by preclinical studies is which type of stem cell or progenitor cell is the most suitable candidate for treatment. The potential for regeneration of bone marrow-derived progenitor cell therapy under prescribed conditions (acute myocardial infarction) has been controversial but proved to be safe and beneficial. Cardiac stem cells have the potential to be patient-specific, but isolation and culture procedures are at an early stage of development. Embryonic stem cells have the potential to differentiate but face ethical barriers and also have the greatest risk of teratoma formation. The survival and integration of transplanted cells can also be improved by placing them in matrices such as collagen or matrigel, placing cells in monolayered layers, or simultaneously transmitting growth factors (51).

Today, new gene transfer therapy protocols for cancer and some genetic diseases are also applied to strengthen angiogenesis and perform recovery faster, especially in ischemic heart diseases. Especially in recent years, SERC2A gene transfer made with adenoviruses, a commonly used viral vector, has helped to achieve important results by regulating calcium metabolism in HF patients (52).

Until now the number of drug groups, whose positive effects on both quality of life and prognosis in the treatment of HF are demonstrated, is still very small. Cardiac transplantation, dynamic cardiomyoplasty, Batista and Dor operations, left ventricular assist devices, total artificial heart, biventricular "pacing" and ultrafiltration are the other treatment methods used in the clinic (53).

CONCLUSION

In the treatment of HF, positive preliminary results were obtained and phase 1 and phase 2 studies began to be conducted in humans; methods such as cellular cardiomyoplasty (increasing endogenous and exogenous myocyte cells), gene therapy, regulation of cellular calcium metabolism, prevention of apoptosis, angiogenesis induction are expected to be applied in the daily treatment practice.

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