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Review article

Physiological and pathological cardiac hypertrophy

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ABSTRACT

The heart must continuously pump blood to supply the body with oxygen and nutrients. To maintain the high energy consumption required by this role, the heart is equipped with multiple complex biological systems that allow adaptation to changes of systemic demand. The processes of growth (hypertrophy), angiogenesis, and metabolic plasticity are critically involved in maintenance of cardiac homeostasis. Cardiac hypertrophy is classified as physiological when it is associated with normal cardiac function or as pathological when associated with cardiac dysfunction. Physiological hypertrophy of the heart occurs in response to normal growth of children or during pregnancy, as well as in athletes. In contrast, pathological hypertrophy is induced by factors such as prolonged and abnormal hemodynamic stress, due to hypertension, myocardial infarction etc. Pathological hypertrophy is associated with fibrosis, capillary rarefaction, increased production of pro-inflammatory cytokines, and cellular dysfunction (impairment of signaling, suppression of autophagy, and abnormal cardiomyocyte/non-cardiomyocyte interactions), as well as undesirable epigenetic changes, with these complex responses leading to maladaptive cardiac remodeling and heart failure. This review describes the key molecules and cellular responses involved in physiological/pathological cardiac hypertrophy.

Contents

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1. Introduction

Mammalian cardiomyocytes generally exit the cell cycle soon after birth, so most cardiomyocytes are terminally differentiated in adults and do not proliferate under physiological conditions. However, cardiac tissue exhibits plasticity that enables the heart to respond to environmental demands, and cells can grow, shrink, or die in reaction to various physiological or pathological stresses. Cardiac hypertrophy is classified as physiological when associated with normal cardiac function or as pathological when associated with cardiac dysfunction.

Normal physiological enlargement of the heart chiefly occurs through hypertrophy of cardiomyocytes in response to growth of the body or exercise, and the enlarged cardiomyocytes receive adequate nourishment due to corresponding expansion of the capillary network. Structural or functional cardiac abnormalities do not occur in this setting, and physiological hypertrophy is generally not considered to be a risk factor for heart failure. In contrast, pathological hypertrophy is associated with production of high levels of neurohumoral mediators, hemodynamic overload, injury and loss of cardiomyocytes. In the pathological setting, cardiomyocyte growth exceeds the capacity of the capillaries to adequately supply nutrients and oxygen, leading to cardiac hypoxia and remodeling in rodents [1,2]. Because cardiac hypertrophy plays a central role in cardiac remodeling and is an independent risk factor for cardiac events, understanding this process is critically important.

Cardiac dysfunction is associated with a complex spectrum of pathophysiological changes, including capillary rarefaction, metabolic derangement, sarcomere disorganization, altered calcium handling, inflammation, cellular senescence, cell death and fibrosis. Due to such complexity, no simple therapeutic approach is adequate for the management of this condition. There is some overlap between the mechanisms of physiological and pathological cardiac hypertrophy, since there is evidence for a central role of Akt signaling or mechanotransduction in physiological hypertrophy, while neurohormonal factors or continuously overloaded biomechanical stress induce multiple signaling pathways, including Akt, in pathological hypertrophy.

2. Classification of heart failure

There are two broad types of heart failure, heart failure with reduced (HFrEF) and heart failure with preserved (HFpEF) ejection fraction. HFrEF develops through the accumulation of myocardial damage and progressive loss of cardiomyocytes, and is commonly caused by myocardial infarction, hypertensive heart disease, or cardiomyopathy. Oxidative stress present within the cardiomyocytes induces cardiomyocytes death and replacement fibrosis [3]. Cardiomyocyte loss promotes alterations within the extracellular matrix and contributes to left ventricular (LV) dilatation and eccentric LV remodeling [4].

It is estimated that 50% of heart failure patients have preserved LV ejection fraction and described as HFpEF. In addition to preserved LV ejection fraction, concentric remodeling and diastolic LV dysfunction are characteristically observed in HFpEF patients. Overweight/obesity, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, anemia and chronic kidney disease induces a systemic inflammatory state and these systemic disorders are thought to increase the risk of developing HFpEF. Structural alterations of HFpEF are characterized with cardiomyocyte hypertrophy and interstitial fibrosis, and functional change is consisted of incomplete relaxation of myocardial strips and increased cardiomyocyte stiffness [5–8]. Replacement fibrosis is usually thought not to develop in HFpEF because cell death does not predominantly develop in HFpEF. Whether HFrEF and HFpEF are distinct pathological conditions or rather represent a syndrome that exists across a spectrum is yet to be defined [9]. Heart failure, defined on clinical terms, derives from numerous different disorders, however, understanding mechanisms of cardiac hypertrophy continues to be essential for describing pathologies in this critical condition.

3. Various types of cardiac hypertrophy

Heart responses to environmental conditions and able to grow or shrink. Heart increases in size and depending on the types, strength and duration of stimuli, it results in physiological or pathological cardiac hypertrophy. Physiological hypertrophy is characterized with normal or enhanced contractile function coupled with normal architecture and organization of cardiac structure [10]. Pathological hypertrophy associates with increased cardiomyocytes death and fibrotic remodeling, and it is characterized with reduced systolic and diastolic function that often progresses towards heart failure. Primary triggering events of cardiac hypertrophy are mechanical stress and neurohumoral stimulation, and these contribute for the modulation of various cellular responses including gene expression, protein synthesis, sarcomere assembly, cell metabolism, leading to the development and progression of cardiac hypertrophy [11–13]. Accumulating evidence indicates that pathological and physiological hypertrophy differs in the signaling pathways that drives these processes. Studies suggest that left ventricular hypertrophy provides short-term benefit and long-term harm, however, mechanism regulating this transition from adaptive to maladaptive hypertrophy is yet to be defined [14].

Cardiac hypertrophy can also be classified into various variants depending on the geometries of the heart, whether it develops eccentric or concentric growth (Fig. 1). Eccentric hypertrophy develops with volume overload and non-pathological eccentric hypertrophy shows increased ventricular volume with a coordinated growth in wall and septal thickness. In this condition, cardiomyocytes grow both in length and width. Pathological eccentric hypertrophy generally develops with cardiac diseases such as myocardial infarction and dilated cardiomyopathy, and lead to ventricular dilatation with preferential lengthening of cardiomyocytes. Concentric hypertrophy shows an increase in