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Hypoxia-driven glycolytic and fructolytic metabolic programs: Pivotal to hypertrophic heart disease☆

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ABSTRACT

Pathologic cardiac growth is an adaptive response of the myocardium to various forms of systemic (e.g. pressure overload) or genetically-based (e. g. mutations in genes encoding sarcomeric proteins) stress. It represents a key aspect of different types of heart disease including aortic stenosis (AS) and hypertrophic cardiomyopathy (HCM). While many of the pathophysiological and hemodynamical aspects of pathologic cardiac hypertrophy have been uncovered during the last decades, its underlying metabolic determinants are only beginning to come into focus. Here, we review the epidemiological evidence and pathological features of hypertrophic heart disease in AS and HCM and consider in this context the development of microenvironmental tissue hypoxia as a key component of the heart's growth response to pathologic stress. We particularly reflect on recent evidence illustrating how activation of hypoxia-inducible factor (HIF) drives glycolytic and fructolytic metabolic programs to maintain ATP generation and support anabolic growth of the pathologically-stressed heart. Finally we discuss how this metabolic programs, when protracted, deprive the heart of energy leading ultimately to heart failure. This article is part of a Special Issue entitled: Cardiomyocyte Biology: Integration of Developmental and Environmental Cues in the Heart edited by Marcus Schaub and Hughes Abriel.

1. Introduction

Heart failure is a major cause of morbidity and mortality in cardiovascular diseases worldwide in both developed and developing countries and is a common endpoint of different forms of heart disease [1]. The underlying pathology includes diastolic and systolic dysfunctions in contexts of biomechanical stress [2,3] and alterations in cardiac blood supply leading to myocardial ischemia [4]. Inadequate tissue oxygenation is likely further heightened by the concurrent hypertrophic growth response of the heart to pathologic stress as it strains to maintain function. There is evidence for imbalances in the myo- and endocardial capillary microvasculature during hypertrophic growth of the myocardium that contributes to this mismatch between oxygen demand and supply [5,6]. Important consequences of decreased tissue oxygen availability (hypoxia) are that cells activate an angiogenic program to increase oxygen delivery in order to overcome the imbalance between tissue mass and vascularization, and that they adjust their cellular fuel metabolism from mitochondrial respiration to glycolysis [7]. This change in metabolic strategy is not simply a passive bystander response but rather serves key purposes that are the maintenance of ATP production under conditions of low oxygen and the supply of macromolecules such as lipids, proteins and nucleotides to support the anabolic requirements associated with hypertrophic growth of cardiomyocytes. Notably, cardiomyocytes of an unstressed heart produce enormous amounts of ATP. In fact, it is estimated that the heart generates ~6 kg ATP per day of which, under physiological conditions, over 90% are provided through mitochondrial oxidative phosphorylation [8]. Therefore, normal cardiomyocytes have adopted a catabolic metabolism to maximize ATP production by oxidizing primarily free fatty acids to sustain their normal contractile function. Cardiomyocytes of the pathologically-stressed heart, however, must reprogram their metabolism towards macromolecular synthesis in order to mount an appropriate hypertrophic growth response while upholding ATP production [9,10]. A strategy able to fulfill these demands is to increase glucose uptake and glycolytic flux and channel glycolytic intermediates into biosynthetic pathways to produce biomass [11]. This metabolic concept is central to cancer cell proliferation and survival [12] and is increasingly appreciated as a central aspect of chronic cardiac ischemia [10,13–17]. In acute ischemic events, e.g. myocardial infarction and acute coronary syndrome, increased glucose uptake and glycolysis are primarily relevant to ensure sufficient ATP production under low oxygen conditions to maintain cardiac function, at least in rest [18,19], a metabolic concept established already in the 1970s [20].

A central controller of such metabolic programs is hypoxia-inducible factor (HIF) [21]. HIF is a master regulator of oxygen homeostasis and a key mediator of the transcriptional response to low oxygen tension.

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Notably, HIF is also induced in settings of activated growth factor signaling and by hemodynamical changes that accompany pathologic stress-driven hypertrophic growth [22]. When activated, HIF enhances glucose uptake and glycolysis by directly inducing the transcription of the *glucose transporter 1* (*GLUT1*) and glycolytic genes. Additionally, HIF activates genes constraining mitochondrial metabolism of glucose carbon such as of *pyruvate dehydrogenase kinase 1* (*PDK1*) [23]. Thus, pathologic stress-instructed growth factor signaling pathways and microenvironmental changes provoking cell growth and myocardial ischemia, respectively, employ HIF to create a metabolic constellation permissive for further tissue expansion. This metabolic constellation, when protracted, leads ultimately to a state of energy deprivation, as well as reduced cardiac contractility and function, resulting in decreased perfusion and a vicious circle that contributes to heart failure [10,24,25].

In this review, we begin by describing hemodynamical and molecular aspects that lead to cardiac growth responses, the development of ischemia and the consequent metabolic effects in two common types of heart disease, aortic stenosis (AS) and hypertrophic cardiomyopathy (HCM). Pathophysiological, clinical and molecular features of ischemic cardiomyopathy due to coronary artery disease are extensively reviewed elsewhere (e.g. [26]) and will not be discussed in this review. Based on recent evidence suggesting a key role of HIF also in the promotion of fructose metabolism in the context of cardiac hypertrophy, we discuss the underlying mechanism and further develop the idea that functional interconnections between glycolysis and fructolysis are central for efficient macromolecular synthesis, hypertrophic growth and progression to heart failure.

2. Epidemiology and pathogenesis of AS and HCM

AS is the most common valvular heart disease in the Western world and defined as a constriction of the aortic valve opening resulting from the cumulative calcification of the aortic valve [27]. The calcific AS and congenital bicuspid AS account for the vast majority of AS cases. Less common forms are the rheumatic AS, radiation-induced AS and the unicuspid AS [28,29]. Whereas in healthy individuals with normal aortic valves the valve area is between 3.0 and 4.0 cm^2, patients with an established AS display an area of <1.0 cm^2 [30]. In addition, the pressure gradient between the left ventricle and the aorta is dramatically increased to more than 40 mm Hg in severe stenosis [30]. In around 2–9% of general population over 65 years an AS is present with an age-dependent increase in prevalence [31]. This points to the high relevance of the calcific form of AS in heart disease.

HCM is an idiopathic disease characterized by asymmetric septal hypertrophy of the (left) ventricular myocardium [32]. The myocardium exhibits considerable myofibrillar disarrays and the intraventricular cavity is frequently diminished [33]. HCM is the most common genetic cardiovascular disorder, caused by missense mutations in 11 or more genes, encoding proteins of the cardiac sarcomere [34]. Although >1400 single gene mutations are described, in most of the cases mutations in three genes predominate, namely, β-myosin heavy chain, cardiac troponin T and myosin-binding protein C [35]. Epidemiological studies suggest that HCM is phenotypically present in 1 of every 500 adults in the general population [35]. However, most of concerned persons, harboring a mutation of a relevant gene for HCM are clinically undetected. The overall mortality of HCM patients is lower than 1% per year [36]. Nevertheless, a subgroup of patients is at high risk for sudden cardiac death, resulting primarily from ventricular arrhythmias due to impaired impulse transmission resulting from hypertrophic growth [37].

A crucial component of the pathogenesis of calcific AS is pre-existing mechanical stress (e.g. due to hypertension) resulting in endothelial damage of the valve [38], deposition of cholesterol and activation of pro-inflammatory signaling cascades that may alter the blood flow, similar to atherosclerosis in the coronary vessels. These events negatively affect optimal nutrient and oxygen supply of the myocardium. As a result of the weakened myocardium, the left ventricular function and cardiac output decreases. In addition, the arterial hypertension and valvular stenosis result in an increased systolic left ventricular wall stress. On the cellular level, biomechanical stress is sensed at the cell membrane by stretch-sensitive ion channels and integrins that link extracellular matrix to the intracellular cytoskeleton [39]. Mechanical stress can also induce neurohumoral factors as further important triggers of cardiac hypertrophy [40,41]. Among those, insulin like growth factor and other growth hormones stimulate receptor tyrosine kinases, angiotensin II and endothelin-1 activate G-Protein coupled receptors and tumor necrosis factor α (TNFα) as well as other cytokines bind to cytokine receptors [2,42]. Receptor engagement results in the activation of several intracellular signaling cascades, including the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (PI3K–AKT–mTOR) pathway, mitogen-activated protein kinase (MAPK) signaling, janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway, and calcineurin-nuclear factor of activated T cell (NFAT) signaling, that activate pro-hypertrophic transcription factors such as myocyte enhancer factor 2c (MEF2c) and GATA-4 [42] (Fig. 2). Mechanical stress-based stimulation of the PI3K and MAPK pathways and the induction of nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NFκB) by increased cytokine receptor signaling have been shown to activate HIF1α through various mechanisms including induction of HIF1α transcription and translation or inhibition of prolyl hydroxylation of HIF1α by prolylhydroxylase domain proteins (PHD) through increased intramyocardial reactive oxygen species (ROS) levels [43]. Thus, extra- and intracellular cues and hemodynamic changes serve as instructional growth signals for the myocardium in response to pathologic stress.

According to the law of Laplace a growth response serves to normalize systolic wall stress by a hypertrophic increase of the left ventricular wall diameter at the expense of an elevated cardiac oxygen demand. However, the coronary dilator reserve capacity is exhausted in patients with AS and HCM, especially in subendomyocardial regions [44,45]. The blood supply under resting conditions is further altered by several factors including the shortening of the diastole for any given heart rate, since the systolic ejection across the stenotic valve is prolonged [46]. If the calcification of the aortic valve proceeds, the closure of the valve could be impaired leading to aortic regurgitations that increase the stroke volume and further shorten the diastolic phase, reducing the heart's blood supply. Moreover, left ventricular oxygen and nutrient supply are reduced by the elevated left ventricular filling pressure as a major consequence of left ventricular diastolic dysfunction [47]. Finally, the often present coexistence with coronary artery disease leads to a decreased coronary driving pressure beyond the coronary stenosis overstressing the dilator reserve capacity [48]. Thus, in AS, obstruction of the left ventricular outflow tract impairs the systolic and diastolic function of the heart, resulting in a critical shortage of oxygen supply and microenvironmental hypoxia (Fig. 1b).

HCM is distinguished from AS by the massive asymmetric hypertrophy of the ventricular septum and is caused by specific mutations in genes encoding sarcomeric proteins. A common feature in all patients with HCM is the altered diastolic filling [49]. The systolic cardiac function can be according to the type and position of mutation in sarcomeric genes either increased (e.g. R453C mutation in β-cardiac myosin [50]) or decreased (c.2373dupG mutation in myosin binding protein C [51]). In a classical view 'hypocontractile' mutations trigger a compensatory hypertrophy, which results from a systolic and diastolic dysfunction leading to a reduced stroke volume and increased systolic wall stress that activate mechano- and growth factor receptors as well as neurohumoral factors [52], as described above. In other cases, the left ventricle is often hypercontractile. The rapid and forceful blood ejection with increased ejection fraction enables the maintenance of systolic tension, when there is no obstruction [53]. However, the strong ejection might also create a *Venturi* effect on the anterior mitral leaflet, which is drawn rapidly towards the septum [54]. This causes an obstruction of