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CARDIAC HYPERTROPHY AT THE CELLULAR LEVEL: LITERATURE REVIEW

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Abstract

Cardiac hypertrophy (CH) is an adaptive increase in myocardial mass that initially serves to normalize wall stress and preserve cardiac output in response to chronic hemodynamic overload. However, persistent stimulation transforms this compensatory process into pathological remodeling, characterized by cardiomyocyte dysfunction, fibrosis, and eventual heart failure. This comprehensive review explores CH at the cellular and molecular levels, emphasizing distinctions between physiological and pathological hypertrophy, as well as the microstructural, metabolic, and signaling alterations underlying disease progression.

Physiological hypertrophy—observed in athletes and pregnancy—is reversible, maintains capillary density, and preserves function. In contrast, pathological hypertrophy (pressure- or volume-induced) involves unbalanced sarcomere addition, altered calcium handling, extracellular matrix expansion, and irreversible fibrosis. Recent advances in imaging, such as diffusion tensor MRI (DTI), enable in vivo visualization of myofiber disarray and extracellular remodeling, improving differentiation from conditions like hypertrophic cardiomyopathy (HCM).

At the molecular level, maladaptive CH is driven by activation of Calcineurin/NFAT and MAPK pathways, neurohumoral signaling (AngII/GPCR), redox imbalance, and epigenetic dysregulation involving HDACs and non-coding RNAs. Mitochondrial dysfunction and metabolic reprogramming toward glycolysis precede contractile failure, linking energetic impairment to structural decline. Genetic insights reveal that sarcomeric mutations, particularly in *MYBPC3* and β-myosin heavy chain, alter contractility and energy utilization, fueling debates over mechanisms like haploinsufficiency and hypercontractility.

Ultimately, CH represents a convergence of biomechanical stress, molecular signaling, and metabolic disturbance. Future directions should focus on integrative omics, genotype-specific therapies, and earlier imaging-based detection of irreversible fibrosis. These approaches may enable precision interventions that halt or reverse pathological remodeling before the onset of heart failure.

Keywords: cardiac hypertrophy, fibrosis, mitochondria, MAPK pathway, NFAT, heart failure.

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YURAK GIPERTROFIYASI HUJAYRA DARJASIDA: ADABIYOTLAR TAHLILI

Annotatsiya

Yurak gipertrofiyasi (CH) — bu yurak mushak massasining adaptiv oshishi bo‘lib, u dastlab devor stressini normallashtirish va uzoq muddatli gemodinamik yuklamaga javoban yurak chiqishini saqlab qolishga xizmat qiladi. Biroq, stimulyatsiyaning uzoq davom etishi bu kompensator jarayonni patologik qayta tuzilishga olib keladi. Bu holat kardiomiyositlar disfunktsiyasi, fibroz va oxir-oqibat yurak yetishmovchiligi bilan tavsiflanadi. Ushbu keng qamrovli sharh CHning hujayra va molekulyar darajadagi xususiyatlarini yoritadi, fiziologik va patologik gipertrofiya o‘rtasidagi farqlar hamda kasallik rivojlanishiga asos bo‘luvchi mikrostrukturaviy, metabolik va signal o‘zgarishlarini tahlil qiladi.

Fiziologik gipertrofiya — sportchilar va homiladorlikda kuzatiladigan holat — qaytuvchan bo‘lib, kapillyar zichligini va yurak funksiyasini saqlab qoladi. Aksincha, patologik gipertrofiya (bosim yoki hajm ortishi natijasida) sarcomerlarning nomutanosib qo‘shilishi, kaltsiy muvozanatining buzilishi, hujayra orasidagi matritsaning kengayishi va qaytmas fibroz bilan kechadi. Tasvirlash texnologiyalaridagi yangi yutuqlar, xususan diffuzion tenzorli MRT (DTI), mushak tolalari tartibsizligi va ekstrasellyulyar qayta tuzilishni jonli aniqlash imkonini beradi, bu esa gipertrofik kardiomiopatiya (HCM) kabi holatlarni farqlashni osonlashtiradi.

Molekulyar darajada maladaptiv CH — bu Kalsineurin/NFAT va MAPK yo‘llarining faollashuvi, neyrogumoral signalizatsiya (AngII/GPCR), redoks muvozanatining buzilishi va HDAC hamda kodlanmagan RNKlarni o‘z ichiga olgan epigenetik o‘zgarishlar natijasidir. Mitoxondrial disfunktsiya va metabolik qayta dasturlanish (glikoliz tomonga siljish) kontraktil yetishmovchilikdan oldin yuz beradi va energiya tanqisligini tuzilma buzilishi bilan bog‘laydi. Genetik tadqiqotlar MYBPC3 va β-myozin og‘ir zanjiri kabi sarkomer oqsillaridagi mutatsiyalar qisqarish kuchi va energiya sarfini o‘zgartirishini ko‘rsatadi, bu esa giperkontraktilitet va haployetishmovchilik kabi mexanizmlar bo‘yicha bahslarni keltirib chiqarmoqda.

Yakunda, CH — bu biomexanik stress, molekulyar signalizatsiya va metabolik buzilishlarning birlashgan natijasidir. Kelajakdagi tadqiqotlar integrativ omika, genotipga asoslangan terapiya va fibrozni erta tasvirlash orqali aniqlash usullariga yo‘naltirilishi kerak. Ushbu yondashuvlar yurak yetishmovchiligiga olib keluvchi patologik qayta tuzilishni to‘xtatish yoki qaytarish imkonini berishi mumkin.

Kalit so‘zlar: yurak gipertrofiyasi, fibroz, mitoxondriya, MAPK yo‘li, NFAT, yurak yetishmovchiligi.

СЕРДЕЧНАЯ ГИПЕРТРОФИЯ НА КЛЕТОЧНОМ УРОВНЕ: ОБЗОР ЛИТЕРАТУРЫ

Аннотация

Сердечная гипертрофия (CH) представляет собой адаптивное увеличение массы миокарда, которое изначально направлено на нормализацию стеночного напряжения и сохранение сердечного выброса в ответ на хроническую гемодинамическую перегрузку. Однако длительная стимуляция превращает этот компенсаторный процесс в патологическое ремоделирование, характеризующееся дисфункцией кардиомиоцитов, развитием фиброза и, в конечном итоге, сердечной недостаточностью. Данный обзор всесторонне рассматривает CH на клеточном и молекулярном уровнях, уделяя особое внимание различиям между

физиологической и патологической гипертрофией, а также микроструктурным, метаболическим и сигнальным изменениям, лежащим в основе прогрессирования заболевания.

Физиологическая гипертрофия — наблюдаемая у спортсменов и во время беременности — обратима, сохраняет плотность капилляров и функциональность миокарда. В противоположность этому, патологическая гипертрофия (вызванная давлением или объемной перегрузкой) сопровождается несбалансированным добавлением саркомеров, нарушением кальциевого гомеостаза, расширением внеклеточного матрикса и необратимым фиброзом. Новейшие методы визуализации, такие как диффузионно-тензорная МРТ (DTI), позволяют проводить in vivo визуализацию дезорганизации мышечных волокон и ремоделирования внеклеточного матрикса, что способствует более точной дифференциации СН от состояний, таких как гипертрофическая кардиомиопатия (HCM).

На молекулярном уровне развитие патологической СН обусловлено активацией путей Calcineurin/NFAT и MAPK, нейрогуморальной сигнализацией (AngII/GPCR), нарушением редокс-баланса и эпигенетической дисрегуляцией, включающей HDAC и некодирующие РНК. Митохондриальная дисфункция и метаболическое перепрограммирование в сторону гликолиза предшествуют сократительной недостаточности, связывая энергетические нарушения со структурной деградацией. Генетические исследования показывают, что мутации в саркомерных белках, особенно MYBPC3 и β-тяжёлой цепи миозина, изменяют сократимость и энергетический обмен, что вызывает дискуссии о механизмах гаплонедостаточности и гиперконтрактильности.

Таким образом, СН представляет собой результат взаимодействия биомеханического стресса, молекулярной сигнализации и метаболических нарушений. Будущие исследования должны быть направлены на интегративные «омикс»-подходы, разработку генотип-специфических терапий и раннее выявление необратимого фиброза с помощью современных методов визуализации. Эти стратегии могут позволить осуществить прецизионные вмешательства, способные остановить или обратить патологическое ремоделирование до развития сердечной недостаточности.

Ключевые слова: сердечная гипертрофия, фиброз, митохондрии, сигнальный путь MAPK, NFAT, сердечная недостаточность.

Introduction

Cardiac hypertrophy (CH) represents an increase in cardiac muscle mass that develops in response to chronic increases in cardiac workload, such as those caused by increased preload or afterload. This enlargement serves initially as an adaptive and compensatory mechanism intended to reduce ventricular wall stress (as predicted by Laplace’s law) and maintain cardiac function and output. However, if the underlying stimulus persists, this compensatory response often transitions into a pathological remodeling process, culminating in ventricular chamber dilatation, contractile dysfunction, and ultimately chronic heart failure (CHF). Pathological hypertrophy is recognized as an independent predictor of adverse cardiovascular outcomes, including heart failure, arrhythmia, and sudden death (Haider et al., 1998; Vakili et al., 2001; Martin et al., 2023).

At the cellular level, CH involves the enlargement of individual cardiomyocytes, as the adult myocardium possesses a limited capacity for cell proliferation (Tham et al., 2015; Carbone et al., 2017). The pathological progression is characterized by profound alterations in fundamental cellular systems, including modified gene transcription, mitochondrial function, calcium handling, protein synthesis, metabolism, inflammation, and oxidative stress (Caturano et al., 2022; Tham et al., 2015). This review aims to provide a comprehensive and critical analysis of the microstructural characteristics, morphological subtypes, and key molecular signaling pathways that govern cardiac hypertrophy and its progression toward clinical failure.

Normal Myocardial Microstructure

The myocardium is a complex structure primarily composed of cardiac muscle cells (cardiomyocytes), fibroblasts, endothelial cells, and immune cells (Tham et al., 2015). Although cardiomyocytes account for 70–80% of the heart's mass, they represent only approximately 30% of the total cell number (Tham et al., 2015).

The fundamental contractile unit is the sarcomere, formed by interdigitating thick filaments (primarily myosin) and thin filaments (primarily actin), along with tension-sensing titin and regulatory proteins like cardiac myosin-binding protein C (cMyBP-C) (Squire, 1997; van der Velden & Stienen, 2018; Lehman et al., 2023). Contraction is initiated through excitation-contraction (EC) coupling: the action potential propagates into the cell interior via the T-tubular network, triggering Ca^{2+}-induced Ca^{2+} release (CICR) from the sarcoplasmic reticulum (SR) through the ryanodine receptor (RyR) (van der Velden & Stienen, 2018).

The structural integrity and mechanics of the heart depend heavily on the complex three-dimensional organization of myocardial fibers. Within the normal left ventricle (LV), myofibers are arranged in counter-directional helices, with the helix angle (HA) continuously varying from the subendocardium (positive HA/right-handed helix) to the subepicardium (negative HA/left-handed helix) (Beyhoff et al., 2019). This intricate microstructural geometry can be non-invasively characterized using Diffusion Tensor Magnetic Resonance Imaging (DT-MRI) (Bueno-Orovio et al., 2016; Nielles-Vallespin et al., 2017).

Physiological Hypertrophy

Physiological hypertrophy is an adaptive response induced by stimuli such as endurance exercise ("athlete's heart") or healthy pregnancy (Sag et al., 2014; Nakamura & Sadoshima, 2018; Martin et al., 2023). It is characterized by a mild (10–20%) increase in cardiac mass and a coordinated growth of individual cardiomyocytes in both length and width, resulting in preserved or enhanced contractile function. Crucially, physiological hypertrophy is reversible upon removal of the stimulus and avoids the detrimental hallmarks of pathological remodeling: no interstitial or replacement fibrosis, no cell death, and no adverse fetal gene expression reactivation (e.g., ANP, BNP, β-MHC). Furthermore, physiological hypertrophy maintains or increases myocardial capillary density, ensuring adequate oxygen supply to the enlarged cardiomyocytes (Oldfield et al., 2020; Shiojima et al., 2005).

Pathological Hypertrophy

Pathological hypertrophy develops due to chronic disease stress, such as chronic hypertension, valvular disease (e.g., aortic stenosis or regurgitation), or myocardial infarction (Sag et al., 2014; Caturano et al., 2022).

1. Concentric Hypertrophy (Pressure Overload): This is typically induced by chronic pressure overload (e.g., hypertension, aortic stenosis). Cardiomyocytes primarily increase in width, achieved by adding new sarcomeres in parallel to existing ones. Anatomically, this leads to increased wall thickness and a reduction in ventricular chamber dimension (Nauta et al., 2020; Nakamura & Sadoshima, 2018).

2. Eccentric Hypertrophy (Volume Overload): This pattern is typically induced by chronic volume overload (e.g., valvular regurgitation). Cardiomyocytes increase predominantly in length, achieved by adding new sarcomeres in series, leading to ventricular chamber widening (dilation) and potential wall thinning (Nauta et al., 2020; Li et al., 2020).

Pathological hypertrophy (both types) involves significant gene expression changes, altered Ca^{2+}-handling protein expression, fibrosis, and cardiomyocyte death, ultimately progressing to heart failure (Nakamura & Sadoshima, 2018; Caturano et al., 2022).

Clinical Differential Diagnosis

Differentiating physiological hypertrophy from pathological conditions like Hypertrophic Cardiomyopathy (HCM), the most common cause of sudden cardiac death in young athletes (Das et al., 2020), is a major clinical challenge. HCM is primarily a genetic disease caused by mutations in sarcomere proteins. Echocardiographic criteria aid differentiation: athletes often have larger LV cavities, aortic roots, and left atria compared to HCM patients (Caselli et al., 2014). A definitive LV cavity size cutoff of <54 mm was highly reliable in distinguishing HCM from athlete's heart in the "gray zone" (Caselli et al., 2014). Furthermore, HCM often presents with lower e′ velocity by tissue Doppler imaging, indicative of diastolic dysfunction (Caselli et al., 2014; Ho et al., 2002).

Cardiomyocyte and Sarcomere Alterations

In pathological hypertrophy, cardiomyocytes undergo substantial reorganization. Electron microscopy in feline HCM revealed ultrastructural aberrations of the myocardial cytoarchitecture, including myofibril disorganization and depletion of sub-sarcolemmal mitochondria in severely affected cats (Pires et al., 2015). Pathological signaling often leads to cytoskeletal and myofibrillar abnormalities and depressed cardiac function (Oldfield et al., 2020). For instance, exposure to volume overload (mitral regurgitation model) triggers eccentric remodeling characterized by cardiomyocyte elongation and extracellular matrix loss (Ryan et al., 2007). In volume overload, this lengthening involves the weaving hypothesis of sarcomeres and changes in titin isoforms, which modulate cellular stiffness (Yoshida et al., 2010; Hutchinson et al., 2015; Cazorla et al., 2000).

Extracellular Matrix Remodeling and Fibrosis

Fibrosis is a prominent and prognostic feature of pathological remodeling. It is primarily mediated by cardiac fibroblasts that proliferate and differentiate into myofibroblasts, secreting collagens (Type I and III) and fibronectin (Schiattarella & Hill, 2015).

• Detection and Classification: Fibrosis can be categorized as reactive (interstitial or perivascular) or replacement (at the site of cardiomyocyte loss). Cardiac Magnetic Resonance (CMR) accurately detects this remodeling: Late Gadolinium Enhancement (LGE) reveals replacement fibrosis, while T1 mapping measures the extracellular volume (ECV), which correlates with the burden of diffuse interstitial fibrosis (Everett et al., 2018; Flett et al., 2010). In HCM, LGE is an important prognostic marker linked to mortality and sudden cardiac death (O’Hanlon et al., 2010; Raman et al., 2019).

• Irreversibility: A key finding in aortic stenosis studies is that while cellular hypertrophy and diffuse interstitial fibrosis initially increase in a balanced manner and can partially reverse following aortic valve replacement, midwall replacement fibrosis accumulates rapidly once established and seems irreversible (Everett et al., 2018; Treibel et al., 2018). This persistence suggests that the myocardial scar burden developed prior to surgery remains long-term and reinforces the need for prompt intervention.

Myocardial Microstructural Disarray (DTI Insights)

Advanced non-invasive imaging provides high-resolution insights into myofiber and sheetlet organization.

• HCM vs. Athlete: Diffusion Tensor Imaging (DTI) distinguishes HCM from physiological hypertrophy by quantifying water molecule diffusion. HCM patients show significantly higher global Mean Diffusivity (MD) and lower Fractional Anisotropy (FA) compared to athletes and healthy volunteers (Das et al., 2020). These changes indicate an increase in the amplitude and isotropy of water diffusion, which is characteristic of myocyte disarray and expansion of the extracellular space (Das et al., 2020).

• Sheetlet Orientation: The secondary eigenvector angle (E2A), reflecting laminar sheetlet orientation, is significantly higher in both athletes and HCM patients compared to volunteers, indicating steeper configurations. However, in HCM patients, E2A values are highest in the thickest segments, correlating directly with LGE and ECV (fibrosis), suggesting that the expansion of the extracellular space coupled with cardiomyocyte disarray leads to localized hypercontracted states (Das et al., 2020; Nielles-Vallespin et al., 2017). Conversely, in athletes, E2A values are uniform across the myocardium, reflecting a concentric spread of hypercontraction.

• Localized Damage: Even circumscribed subendocardial damage (often present early in hypertension) can cause microstructural remodeling in remote regions, manifesting as a left-shift in the helix angle (HA) towards lower values, mainly determined by subepicardial myofibers (Beyhoff et al., 2019).

Signaling and Transcriptional Regulation

Calcineurin/NFAT and MAPK Pathways: The stress response pathways diverge significantly between physiological and pathological CH (Nakamura & Sadoshima, 2018). The Calcineurin/NFAT pathway is a calcineurin-dependent transcriptional mechanism specifically engaged during pathological, but not physiological, CH (Molkentin et al., 1998; Wilkins et al., 2004; Martin et al., 2023).

Mitogen-activated protein kinases (MAPKs), including Extracellular signal-regulated kinase (ERK), are also critical mediators (Nakamura & Sadoshima, 2018). ERK signaling exhibits context-dependent duality: it can induce adaptive concentric hypertrophy and prevent cell death during early chronic pressure overload (Mutlak et al., 2018; Sala et al., 2016). Conversely, specific phosphorylation of ERK at threonine 188 (ERK^Thr188) and activation of ERK5 are associated with maladaptive and pathological hypertrophy (Rachmin et al., 2014; Sala et al., 2012).

Neurohumoral Activation and Redox Signaling: The Angiotensin II (AngII) system, working through the AT1 receptor, is a potent inducer of pathological cardiac cell growth and hypertrophy, often activating ERK (Huang et al., 2018; Suzuki et al., 1993). Activation of G-protein coupled receptors (GPCRs), particularly the Gαq family, promotes hypertrophy (Wettschureck et al., 2001).

The use of beta-blockers and ACE inhibitors/ARBs in heart failure management provides a mechanism for reverse remodeling by inhibiting these neurohumoral systems (Martin et al., 2023).
Redox signaling, involving the generation of reactive oxygen species (ROS), is intrinsically linked to CH (Sag et al., 2014). ROS modify cellular proteins and signaling, potentially leading to apoptosis or activating NFkB-mediated gene transcription, contributing to pathological progression (Sag et al., 2014; Zima & Blatter, 2006). For instance, NOX4-derived ROS enhance cardiomyocyte HIF1 activation, mediating protective effects through enhanced capillarization in response to chronic pressure overload (Sag et al., 2014).

Epigenetic Modifiers and Non-Coding RNAs: Epigenetic mechanisms, including histone modification, play key roles. Histone Deacetylases (HDACs), particularly Class II HDACs, are typically transcriptional repressors of hypertrophy, and their inhibition can attenuate CH (Kong et al., 2006; Zhang et al., 2002; Xie & Hill, 2013). Certain histone dimethyltransferases, such as EHMT1/2 (H3K9 dimethyltransferases), protect against pathological CH (Thienpont et al., 2017).

MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are integral regulators of cardiac remodeling. MiRNAs function by targeting pro-hypertrophic signaling pathways, such as calcium signaling and cell cycle regulation (Chuang et al., 2018). For example, miR-1 suppresses CH by targeting NFATc3 (Yin et al., 2015) and regulates the mitochondrial calcium uniporter (MCU) (Zaglia et al., 2017). Conversely, other miRNAs like miR-22 and miR-29a promotes hypertrophy by targeting PTEN or pathways involved in proliferation and fibrosis (Nie et al., 2018; Shi et al., 2019; Zhang et al., 2019). Macrophage miRNA-155 has been shown to promote cardiac hypertrophy and failure (Heymans et al., 2013; Schiattarella & Hill, 2015).

Metabolic Reprogramming

Pathological hypertrophy is linked to profound metabolic changes, including mitochondrial dysfunction and a shift away from fatty acid oxidation toward glycolysis, mirroring the fetal metabolic gene program (Caturano et al., 2022; Doenst et al., 2013; Houser et al., 2012; Wang et al., 2013). This metabolic remodeling occurs early, preceding systolic heart failure in pressure-overload hypertrophy (Zhang et al., 2013).

Mitochondrial quality control is impaired. The shift in substrate preference is linked to decreased mitochondrial energy production and insulin resistance (Caturano et al., 2022; Liew et al., 2017). Specific lipid disturbances, such as increased *de novo* ceramide synthesis, are observed in failing myocardium (Ji et al., 2017). Conversely, preserving myocardial fatty acid oxidation can prevent diastolic dysfunction in models of Angiotensin II infusion (Choi et al., 2016). Mechanical unloading via LV assist devices (LVADs) can induce reverse metabolic remodeling, increasing fatty acid utilization and decreasing glucose dependence, though some glycolytic pathway upregulation persists (Gupte et al., 2014; Diakos et al., 2016).

Sarcomere Genetics and Mechanistic Debates

HCM is primarily caused by variants in sarcomeric protein genes, leading to altered Ca^{2+}-dependent tension generation. These mutations generally result in increased force generation or hypercontractility, which compromises efficiency and leads to energetic impairment (Lehman et al., 2023; Spudich, 2019; Crilley et al., 2003).

Conflicting Findings and Debates

1. Mechanism of Sarcomeric Mutations: A significant debate centers on the exact mechanism by which truncating mutations in cardiac myosin-binding protein C (MYBPC3) cause HCM. One theory is haploinsufficiency (insufficient wild-type protein product) (Marston et al., 2009; Glazier et al., 2019). However, Helms et al. (2014), analyzing human surgical samples, provided evidence against haploinsufficiency as the unifying explanation, observing a nine-fold increase in MYBPC3 mRNA and equivalent total MYBPC3 protein levels in hypertrophic MYBPC3 mutant hearts compared to controls. They argued that assumptions of gain or loss of function based purely on mutation type fail to capture the complex responses, such as alterations in splicing, protein stability, or sarcomere incorporation.

2. Hypertrophy as a Target: A critical debate concerns the utility of inhibiting hypertrophy itself in treatment. Some researchers argue that blunting load-induced hypertrophy, even when the afterload stress persists, can ameliorate LV dysfunction (Schiattarella & Hill, 2015; Frey et al., 2004). Conversely, others caution that hypertrophy, particularly in its initial compensated phase, is adaptive and blocking it directly can be detrimental, suggesting that therapeutic strategies should instead target the underlying cause (e.g., AngII inhibition) or reorchestrate ventricular components, as maintaining contractile function without allowing wall thickening (hypertrophy) may induce hypercontractility and subsequent ischemia, especially in pre-existing pathologies (Schiaffino et al., 2015).

Conclusion

Cardiac hypertrophy is a complex, multi-faceted cellular response that serves as a pivotal bridge between chronic cardiovascular stress and end-stage heart failure. The microscopic distinction between adaptive (physiological) and maladaptive (pathological) hypertrophy is crucial, marked by differential patterns of cardiomyocyte growth, presence of non-myocyte proliferation, and extensive extracellular matrix deposition (Nakamura & Sadoshima, 2018). Advances in imaging techniques, notably DT-MRI, now allow for *in vivo* assessment of subtle microstructural disarray and the precise mapping of fibrosis (ECV, LGE), which are critical prognostic markers, particularly in HCM and aortic stenosis (Das et al., 2020; Everett et al., 2018). The finding that replacement fibrosis may be irreversible following mechanical unloading strongly suggests that timing interventions based on the presence of microscopic damage is paramount (Everett et al., 2018).

At the molecular level, pathological remodeling involves the activation of distinct pathways (Calcineurin/NFAT, redox signaling, and context-dependent MAPK pathways) and a detrimental metabolic reprogramming characterized by mitochondrial dysfunction. While significant progress has been made in identifying individual molecular factors, the field risks becoming incremental (Nakamura & Sadoshima, 2018).

Future research should prioritize integrative bioinformatic analyses across diverse forms of human pathological hypertrophy to identify crucial common proximal mechanisms that are most clinically relevant, thereby offering higher priority targets for treatment (Nakamura & Sadoshima, 2018). Furthermore, developing genotype-driven therapies for inherited cardiomyopathies, such as those targeting the hypercontractile state caused by sarcomeric mutations (Lehman et al., 2023), necessitates further investigation into the precise consequences of individual mutations, moving beyond simplifying assumptions like uniform haploinsufficiency (Helms et al., 2014). Finally, the clinical utility of advanced imaging markers, such as DTI parameters, requires validation in larger

cohorts to ensure their accuracy in differentiating overlapping clinical phenotypes (Das et al., 2020). Addressing these fundamental questions is essential for translating mechanistic insight into effective strategies for reversing pathological remodeling and preventing heart failure progression (Caturano et al., 2022).

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