Mechanisms of physiological and pathological cardiac hypertrophy

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Abstract | Cardiomyocytes exit the cell cycle and become terminally differentiated soon after birth. Therefore, in the adult heart, instead of an increase in cardiomyocyte number, individual cardiomyocytes increase in size, and the heart develops hypertrophy to reduce ventricular wall stress and maintain function and efficiency in response to an increased workload. There are two types of hypertrophy: physiological and pathological. Hypertrophy initially develops as an adaptive response to physiological and pathological stimuli, but pathological hypertrophy generally progresses to heart failure. Each form of hypertrophy is regulated by distinct cellular signalling pathways. In the past decade, a growing number of studies have suggested that previously unrecognized mechanisms, including cellular metabolism, proliferation, non-coding RNAs, immune responses, translational regulation, and epigenetic modifications, positively or negatively regulate cardiac hypertrophy. In this Review, we summarize the underlying molecular mechanisms of physiological and pathological hypertrophy, with a particular emphasis on the role of metabolic remodelling in both forms of cardiac hypertrophy, and we discuss how the current knowledge on cardiac hypertrophy can be applied to develop novel therapeutic strategies to prevent or reverse pathological hypertrophy.

Laplace's law
A physical law stating that the wall stress (WS) of a sphere (ventricle) is proportional to the intracavity (ventricular) pressure (P) and the chamber radius (R), and inversely proportional to the ventricular wall thickness (T), given by the formula WS = P*R/2T.

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The major function of the heart is to maintain perfusion of peripheral organs, matching their demand during both normal and stress conditions. To accomplish this task in the presence of increased preload or afterload, the heart and the individual cardiomyocytes often undergo enlargement, a condition termed hypertrophy. Cardiac hypertrophy increases contractility, at least initially, through the addition of sarcomere units in parallel. In addition, increases in left ventricular wall thickness decrease left ventricular wall stress following Laplace's law, thereby maintaining cardiac efficiency. Cardiac hypertrophy is also accompanied by qualitative changes, namely, changes in gene expression, which induce changes in metabolism, contractility, and cardiomyocyte survival. There are two types of hypertrophy: physiological and pathological (FIG. 1). Both hypertrophy types initially develop as an adaptive response to cardiac stress, but they differ greatly in terms of the underlying molecular mechanisms, cardiac phenotype, and prognosis. Physiological hypertrophy maintains cardiac function over time, whereas pathological hypertrophy is accompanied by adverse cardiovascular events, including heart failure, arrhythmias, and death. The cardiac phenotype of pathological hypertrophy varies and can manifest as either heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF)[1].

In this Review, we summarize the characteristics of physiological and pathological hypertrophy and discuss the underlying signalling pathways, with particular emphasis on the emerging mechanisms described in the past decade that mediate the two forms of cardiac hypertrophy. Better understanding of the underlying mechanisms of physiological and pathological hypertrophy might lead to novel therapeutic approaches for reversing pathological hypertrophy and preventing detrimental outcomes.

Characteristics of cardiac hypertrophy

Both physiological and pathological hypertrophy involve enlargement of individual cardiomyocytes, but the characteristics of each type of hypertrophy are distinct (FIG. 1; TABLE 1). Physiological hypertrophy, except for postnatal hypertrophy, is characterized by a mild (10–20%) increase in cardiac mass and individual cardiomyocyte growth in both length and width (FIG. 1). Hearts with physiological hypertrophy have preserved or increased contractile function with no interstitial or replacement fibrosis or cell death, and except for postnatal hypertrophy, physiological hypertrophy is fully reversible and does not progress to heart failure. In addition, expression of fetal genes such as those encoding natriuretic peptide A (ANP; also known as atrial natriuretic peptide); natriuretic peptide B (BNP; also known as

Key points

- The heart initially undergoes hypertrophy in response to haemodynamic overload to increase contractility and reduce ventricular wall stress, but this adaptive hypertrophy transitions to heart failure through pathological remodelling.
- There are two types of hypertrophy, physiological and pathological, which differ in their underlying molecular mechanisms, cardiac phenotype, and prognosis.
- The type of hypertrophic stimuli and the nature of the downstream signalling mechanisms largely determine the fate of cardiac hypertrophy, which is either physiological or pathological.
- Prioritizing the regulators of pathological hypertrophy on the basis of their clinical relevance for therapeutic targeting is important to improve the outcomes in patients with pathological hypertrophy and heart failure.

brain natriuretic peptide); myosin heavy chain, cardiac muscle β-isoform (MYHCβ; also known as myosin 7 or MYH7); and skeletal muscle α-actin, which is commonly observed in pathological hypertrophy, is either unchanged or decreased in physiological hypertrophy. Conversely, even though pathological hypertrophy is initially induced as a compensatory response with concentric growth of the ventricle, this type of hypertrophy progresses to ventricular chamber dilatation with wall thinning through lengthening of individual cardiomyocytes, contractile dysfunction, and heart failure[2]. In HFpEF, heart failure develops even in the absence of systolic contractile dysfunction, but is often associated with concentric cardiac hypertrophy and diastolic dysfunction with microvascular rarefaction and myocardial fibrosis[3–5]. Genes encoding Ca^{2+}-handling proteins are altered during pathological hypertrophy but not during physiological hypertrophy. Pathological hypertrophy is usually accompanied by interstitial and perivascular fibrosis and cardiomyocyte death, with increased levels of type I collagen and myofibroblast activation.

Development of either physiological or pathological hypertrophy depends on the nature of upstream stimuli and signalling mechanisms rather than the duration of cardiac stress per se[6–10]. For example, even intermittent pressure overload induces pathological hypertrophy, whereas exercise training, which is also an intermittent stimulus, induces physiological hypertrophy[11]. Physiological growth of the heart is observed during normal postnatal growth, pregnancy, and repetitive endurance exercise in athletes (TABLE 1). Although power and strength training, such as power lifting, results in pressure overload and concentric physiological hypertrophy[12], endurance training, such as swimming or running, results in volume overload and eccentric physiological hypertrophy. Stimuli inducing physiological hypertrophy often reverse the progression of pathological hypertrophy to cardiac remodelling and heart failure[13,14]. Pathological hypertrophy is induced by chronic hypertension, aortic stenosis, mitral or aortic regurgitation, myocardial infarction (MI), storage diseases (such as lipid, glycogen, and misfolded-protein storage diseases), and genetic cardiomyopathy resulting from mutations in genes encoding sarcomere proteins, such as hypertrophic cardiomyopathy (HCM). Obesity and diabetes mellitus are important comorbidities associated with the development of pathological hypertrophy in developed countries[15,16].

Cardiac remodelling
Process of structural and functional changes in the heart in response to mechanical stress, neurohormonal activation, and myocardial injury that lead to progressively dilated hearts and impaired contractile function.

Mechanisms of physiological hypertrophy

The initial hypertrophic stimuli, such as exercise and hypertension, largely influence the development of either physiological or pathological hypertrophy. The responses that occur concurrently with cell growth clearly differ between the two types of hypertrophy and ultimately determine the physiological or pathological nature of the hypertrophied heart (FIG. 2). For cardiac hypertrophy to be fully adaptive, activation of the following responses is necessary: cell survival signalling, increased energy production and efficiency, angiogenesis proportional to the ventricular wall growth, antioxidant systems, mitochondrial quality control, and cardiomyocyte proliferation and regeneration. These pathways actively antagonize pathological responses; therefore, ventricular wall thickening accompanied by these properties is generally considered to be physiological.

Insulin and IGF1

Insulin and insulin-like growth factor 1 (IGF1) regulate a broad range of cellular processes in the heart, including cell growth, proliferation, differentiation, apoptosis, contractility, and metabolism[17] (FIG. 3). Insulin resistance is commonly observed in heart failure. IGF1 is structurally similar to insulin and is synthesized mostly in the liver in response to growth hormone, but other organs, including the heart, also synthesize and secrete IGF1. Physiological cardiac hypertrophy in athletes is associated with an exercise-induced increase in IGF1 levels in serum[18]. Women with perimenopausal hypertension have significantly lower serum levels of insulin-like growth factor-binding protein 2 (IGFBP2), but not IGF1 or IGFBP3, than normotensive women, and the IGFBP2 level is significantly associated with the increased heart mass accompanying diastolic dysfunction, suggesting the potential importance of IGFBP2 in maintaining physiological hypertrophy during pregnancy[19].

Insulin binds to and activates the insulin receptor, a tyrosine kinase receptor that recruits and phosphorylates the adaptor proteins insulin receptor substrate 1 (IRS1) and IRS2. These proteins in turn activate PI3K–AKT1 (phosphoinositide 3-kinase–RAC-α serine/threonine-protein kinase) signalling to promote physiological cardiomyocyte growth[6]. Cardiac-specific deletion of *Irs1* or *Irs2* in mice causes resistance to exercise-induced physiological hypertrophy[20]. Similarly, IGF1 activates canonical and noncanonical signalling pathways through the binding and activation of the IGF1 receptor (IGF1R), another tyrosine kinase receptor, which is required for exercise-induced physiological hypertrophy[21]. The canonical IGF1 pathway involves the RAS–RAF–MEK–MAPK signalling axis through docking to growth factor receptor-bound protein 2 and the PI3K–AKT1–mTOR (mechanistic target of rapamycin) signalling axis through docking to IRS1 (REF.[22]). The noncanonical IGF1 pathway includes PLC–IP3R3 (phospholipase C–inositol 1,4,5-triphosphate receptor type 3) signalling through docking to a pertussis toxin-sensitive heterotrimeric G_i protein[23].

PI3Ks are heterodimeric lipid kinases that catalyse the formation of phosphatidylinositol 3,4,5-trisphosphate (PIP_3), which is inactivated by phosphatidylinositol

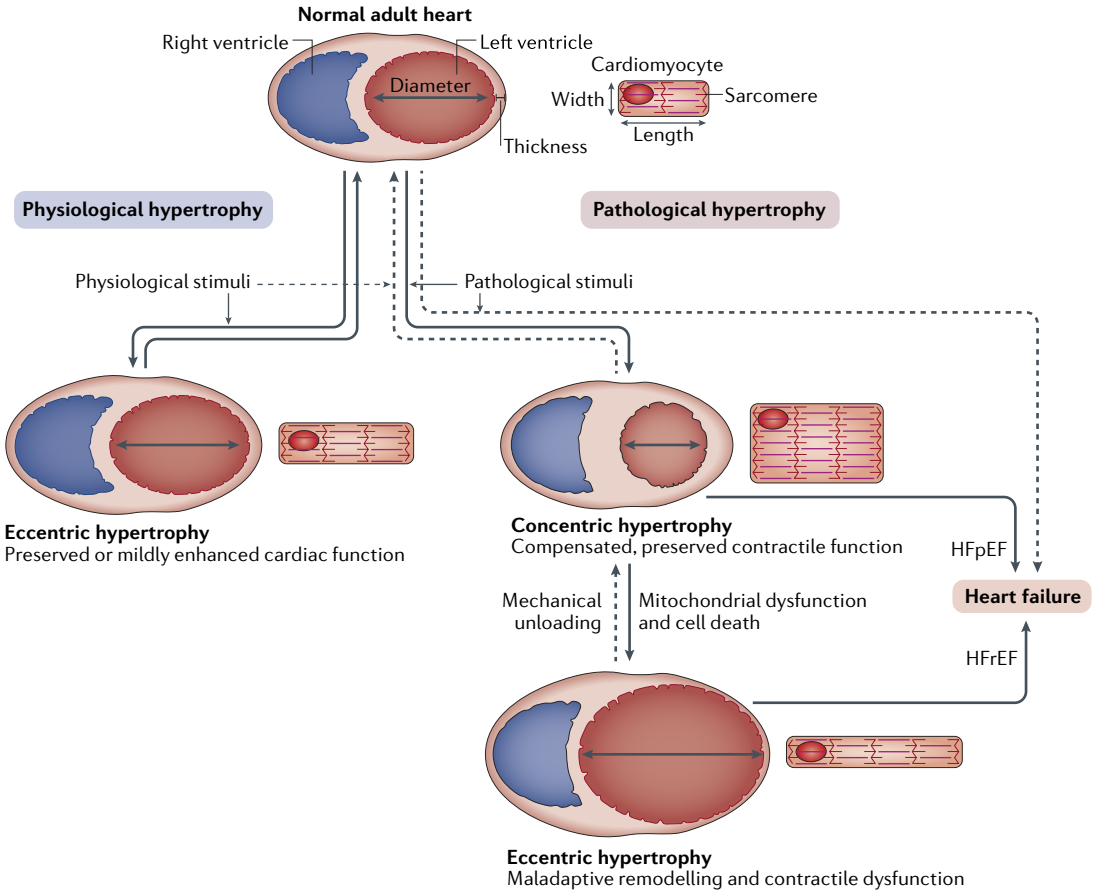

Fig. 1 | **Overview of physiological and pathological hypertrophy.** The heart undergoes physiological or pathological enlargement of cardiac mass, termed hypertrophy, to decrease ventricular wall stress in response to various stimuli according to Laplace's law. Physiological hypertrophy can occur during pregnancy and endurance training, and is mainly identified by a mild (10–20%) increase in ventricular volume with a coordinated increase in wall thickness (eccentric hypertrophy) and individual cardiomyocyte growth in both length and width. After relief of the stimulus, physiological hypertrophy is reversed and the heart returns to its original dimensions. Conversely, pathological hypertrophy is observed in patients with myocardial infarction, valvular diseases, and metabolic syndrome and is initially identified by a reduction in ventricular chamber dimension with increased wall thickness (concentric hypertrophy), where cardiomyocytes typically increase in thickness more than in length. Pathological hypertrophy leads to ventricular chamber dilatation (eccentric hypertrophy) with impaired contractile function (maladaptive remodelling), with lengthening of individual cardiomyocytes. Pathological hypertrophy often results in heart failure with either preserved or reduced ejection fraction (HFpEF or HFrEF). Solid arrows indicate proven pathways; dashed arrows indicate hypothetical or controversial pathways. Figure adapted from REF.[6], Macmillan Publishers Limited.

3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase and tensin homologue (PTEN). The PI3K catalytic subunit p110α is critical for physiological, but not pathological, hypertrophy[24]. Activation of PI3K p110α in the heart is sufficient to induce physiological hypertrophy and antagonize pathological hypertrophy[13,25]. AKT1 is a crucial downstream serine/threonine-protein kinase, activated by PIP_3-mediated membrane recruitment and phosphoinositide-dependent protein kinase 1 (PDK1). *Akt1*-knockout mice have decreased physiological hypertrophy in response to exercise and increased maladaptive hypertrophy[26]. AKT1 phosphorylates and inhibits the downstream glycogen synthase kinase 3β (GSK3β), a kinase that suppresses the translation initiation factor eIF2Bε. AKT1 also inhibits forkhead box protein O3 (FOXO3), which reduces general protein turnover and the catabolism mediated by F-box only protein 32 and E3 ubiquitin-protein ligase TRIM63, thereby promoting cardiomyocyte growth[27]. Suppression of PI3K signalling, but not of AKT1 activation, inhibits physiological mitochondrial adaptations, suggesting that an AKT1-independent pathway downstream of PI3K mediates the mitochondrial adaptations to physiological hypertrophy[28]. Among the three main mitogen-activated protein kinase (MAPK) cascade pathways, MAPK3 and MAPK1 (also known as ERK1 and ERK2, respectively) are activated by MAPK/ERK kinases MEK1 and MEK2 in response to physiological stimuli and are thought to promote physiological hypertrophy[29].

CCAAT/enhancer binding protein-β (C/EBPβ) is a transcription factor that negatively regulates cellular proliferation. C/EBPβ also interacts with serum response factor to downregulate the expression of the genes encoding the transcription factors peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α), transcription factor GATA4, and homeobox

Table 1 | **Triggers and characteristics of physiological and pathological hypertrophy**

Triggers and characteristics	Physiological hypertrophy	Pathological hypertrophy
Triggers	• Normal postnatal growth • Pregnancy • Exercise	• Pressure overload owing to hypertension or aortic stenosis • Volume overload induced by mitral and aortic regurgitation and chronic kidney disease • Myocardial hypoxia as a result of myocardial infarction, obesity, diabetes mellitus, ageing, chronic obstructive pulmonary disease, or anaemia • Storage diseases (lipid, glycogen, or misfolded protein diseases) • Inherited diseases such as hypertrophic cardiomyopathy
Reversibility	Yes	Might be possible with treatment
Adaptivity	Adaptive	Adaptive (initially) and maladaptive (advanced)
Cardiomyocyte size	Increased	Increased
Contractility	Preserved or increased	Preserved or decreased
Heart failure	No	Yes (heart failure with preserved ejection fraction, or with reduced ejection fraction at end stage)
Fibrosis	No	Yes (advanced)
Type I collagen levels	Unchanged	Increased
Myofibroblast activation	Unchanged	Yes (such as increased smooth muscle α-actin)
Cardiomyocyte death	No	Yes (advanced)
Capillary network	Increased and sufficient for nourishment	Insufficient for nourishment and oxygenation
Concentric or eccentric	Eccentric greater than concentric and/or mild growth	Concentric or eccentric (advanced) and/or severe wall thickness growth
Maladaptive remodelling	No	Yes
Fetal genes	Unchanged or decreased	Increased (for example, *ACTA1*, *MYH7*, *NPPA*, and *NPPB*)

protein Nkx-2.5 (REF.[30]). Exercise-induced activation of the PI3K–AKT1 pathway inhibits C/EBPβ expression, which enhances CBP/p300-interacting transactivator 4 (CITED4)-induced cell growth and proliferation, thereby promoting physiological hypertrophy[30]. Cardiac-specific *Cited4* transgenic mice have physiological hypertrophy at baseline, and in these mice, maladaptive hypertrophy after MI is mitigated through the mTOR complex 1 (mTORC1) pathway[31].

Thyroid hormone

T_3 (3,5,3′-triiodothyronine), the active form of thyroid hormone, is critical for postnatal hypertrophy[32]. Blood T_3 and T_4 (thyroxine) levels increase dramatically after birth[33]. T_3 binding to the thyroid hormone receptors TRα and TRβ acts as a transcriptional switch, downregulating the expression of *MYH7* (which encodes MYHCβ) and upregulating the expression of *MYH6* (which encodes MYHCα)[34]. Interaction with the retinoic acid receptor stimulates transcription of the genes encoding sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2), β_1-adrenergic receptor, sodium and potassium channels, and the sodium/calcium exchanger 1 (NCX), but suppresses transcription of the gene encoding cardiac phospholamban (PLN). Therefore, T_3 contributes to improved myocardial performance and to physiological hypertrophy and protects the heart against pressure overload and MI-induced pathological hypertrophy and cardiac dysfunction[35–38].

Nitric oxide

Nitric oxide (NO) is a mediator of exercise-induced cardiac hypertrophy. Exercise stimulates β_3-adrenergic receptors in endothelial cells[39], which in turn increase phosphorylation of endothelial NO synthase (eNOS; also known as NOS3), which generates NO. eNOS-deficient mice have systemic hypertension and age-related cardiac dysfunction with impaired angiogenesis and smooth muscle cell proliferation[40–42], suggesting that eNOS has an important role in vasodilatation, angiogenesis, remodelling, and contractility. NO activates soluble guanylate cyclase (sGC) to increase the levels of cGMP, thereby activating cGMP-dependent protein kinase G (PKG)[43]. PKG in turn activates regulator of G protein signalling 2 (RGS2) and RGS4, which inhibit G protein-coupled receptor (GPCR) signalling and suppress pathological hypertrophy[44–46]. Genetic deletion of *Rgs2* increases susceptibility to pressure overload but has no effect on physiological hypertrophy in response to swimming exercise, which is not accompanied by G_q activation[46]. Deficiency of either eNOS or β_3-adrenergic receptors disrupts the cardioprotective effect of exercise after MI[39,47]. These results suggest that exercise-mediated stimulation of eNOS and NO attenuates pathological hypertrophy through stimulation of β_3-adrenergic receptors and PKG.

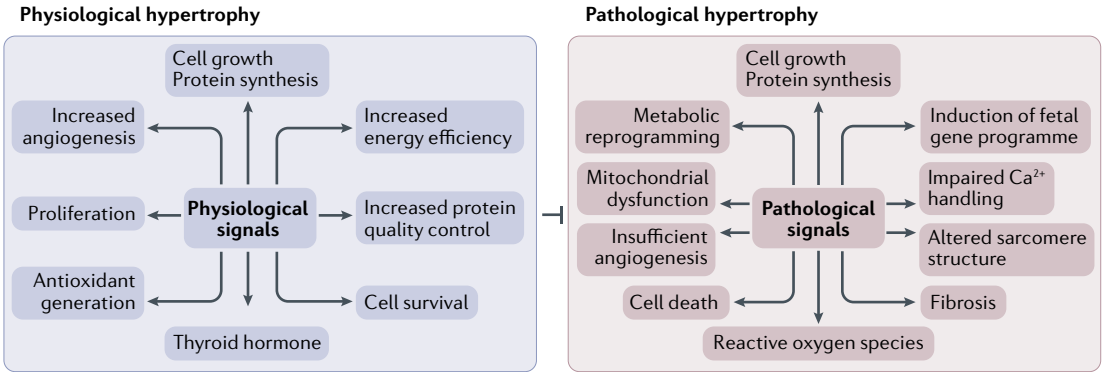

Fig. 2 | **General features of physiological and pathological hypertrophy.** Cardiomyocyte growth and increased protein synthesis induce enlargement of the heart in both types of hypertrophy, but induction of distinct concurrent responses ultimately determines the physiological or pathological growth of the hypertrophied heart. In pathological hypertrophy, induction of the fetal gene programme includes an increase in the expression of genes encoding natriuretic peptide A (also known as atrial natriuretic peptide), natriuretic peptide B (also known as brain natriuretic peptide), β-myosin heavy chain (also known as myosin 7), and skeletal α-actin. The signalling pathways triggered by pathological stimuli promote maladaptive cardiac remodelling and dysfunction. Physiological hypertrophy stimulates signalling pathways that antagonize the pathological cardiac remodelling and dysfunction.

Angiogenesis

Capillary density is an important factor controlling the development of either physiological or pathological hypertrophy[48]. Vascular endothelial growth factor (VEGF) is a crucial angiogenic molecule involved in the maintenance of myocardial capillary density. Deletion of *Vegf* impairs myocardial angiogenesis and cardiac function[49]. Inhibitors of VEGF signalling pathways are clinically approved for the treatment of various types of cancer. However, use of these inhibitors is associated with cardiovascular toxicity, including cardiomyopathy[50]. In physiological hypertrophy, the capillary network is increased in proportion to cardiomyocyte growth, thereby providing the myocardium with sufficient nutrients and oxygen. In pathological hypertrophy, capillary density and coronary flow reserve are insufficient to support the myocardial growth, resulting in a mild myocardial hypoxia and nutrient shortage[51,52].

Supine bicycle exercise or moderate-intensity and high-intensity exercise training improves coronary collateral flow in patients with coronary artery disease[53,54]. Angiogenesis is also associated with the development of pregnancy-related cardiomyopathy. Peripartum cardiomyopathy, which develops in the last months of pregnancy or within 5 months after giving birth, is one of the major causes of maternal morbidity and mortality[55]. Although peripartum cardiomyopathy is a heterogeneous condition, an increase in the circulating levels of soluble VEGF receptor 1 (sVEGFR1; also known as sFLT1), an endogenous VEGF inhibitor, and a decrease in the circulating levels of VEGF are significantly correlated with the development of and poor recovery from peripartum cardiomyopathy[56–58]. These findings support the importance of stimulating angiogenesis for the development of physiological rather than pathological hypertrophy.

Hypoxia-inducible factor 1α (HIF1α) is a major transcription factor that controls oxygen homeostasis by regulating angiogenesis, vascular remodelling, and glucose metabolism[59]. Exercise training upregulates mTOR and stimulates the production of HIF1α-responsive angiogenic factors, including VEGF, which in turn contribute to well-coordinated cardiomyocyte growth and angiogenesis, whereas inhibition of VEGF signalling promotes transition to heart failure during pressure-overload stimulation[60–62]. In pathological hypertrophy, the cellular tumour antigen p53 is upregulated to promote ubiquitylation and proteasomal degradation of HIF1α, probably through the E3 ubiquitin-protein ligase MDM2, leading to a mismatch between myocardial growth and capillary density, thereby promoting maladaptive cardiac hypertrophy[63,64].

Vegfa expression is also directly stimulated by the transcription factor GATA4 in cardiomyocytes in response to pressure overload, which leads to the promotion of angiogenesis in a paracrine fashion[65]. Pressure overload-induced cardiac dysfunction in *Gata4*-null mice is partially rescued by gene delivery of *Vegf* and *Angpt1* (REF.[65]). PGC1α is another regulator of *VEGF* expression. In skeletal muscle, exercise training upregulates PGC1α, which activates oestrogen-related receptor-α (ERRα; also known as ESRRA) and stimulates *VEGF* expression independently of the HIF1α pathway[66]. Cardiac-specific *Pgc1a*-knockout female mice have reduced cardiac microvascular density and develop peripartum cardiomyopathy after one or two pregnancies, which can be rescued by administration of VEGF[56]. In cardiomyocytes, overexpression of *Pgc1a* stimulates expression of angiogenic genes, including *Vegfa*, and increases the migration of adjacent human umbilical vein endothelial cells in a co-culture in vitro system, which is antagonized by addition of sFLT1 (REF.[56]). These results suggest that PGC1α regulates angiogenesis by promoting secretion of VEGF in the heart.

Placental growth factor (PGF) is a member of the VEGF subfamily whose levels are increased in rodent and human ischaemic hearts[67,68]. Transgenic mice with cardiac-specific *Pgf* overexpression have cardiac hypertrophy with well-maintained cardiac function[68]. In these mice, capillary density is increased through the action of

Coronary flow reserve
The ratio between maximal and resting coronary flow, which is thought to reflect the capacity of the coronary arteries to dilate and increase coronary flow in response to metabolic demand.

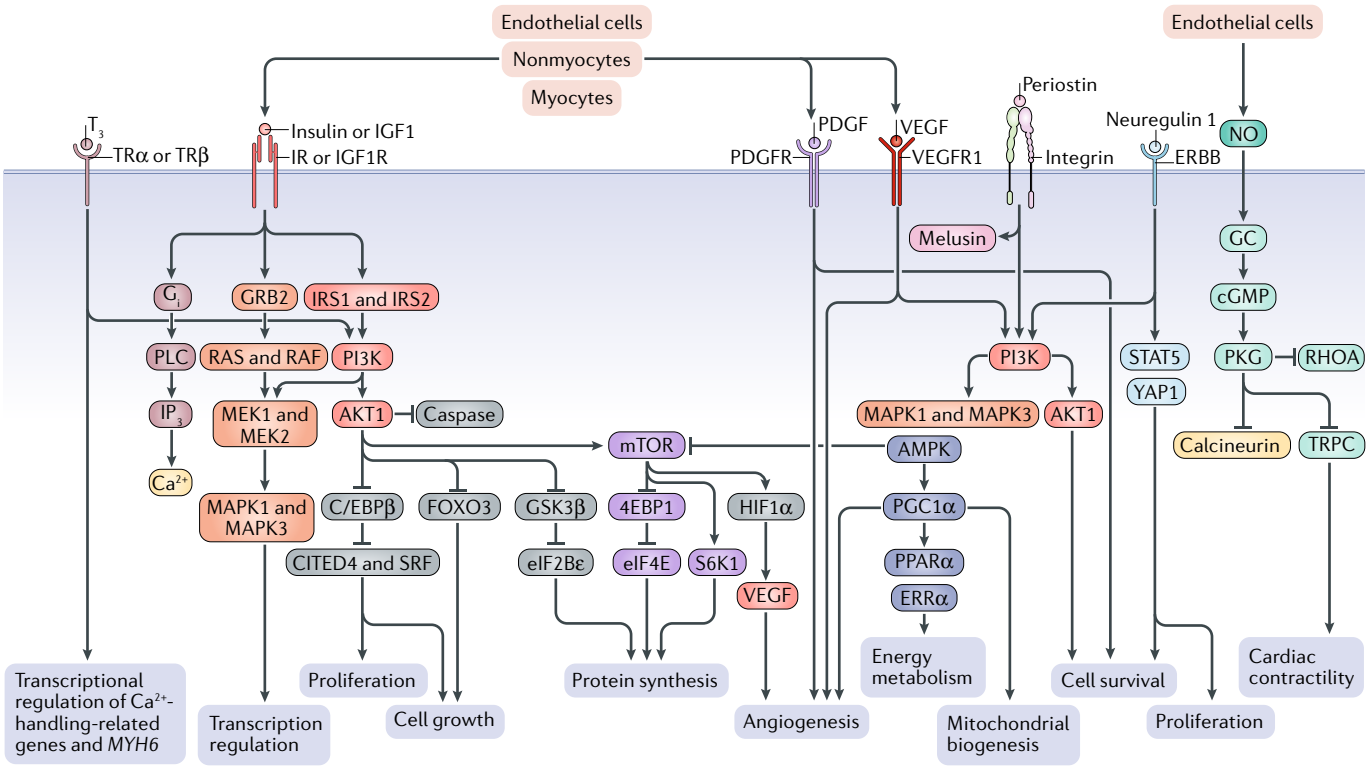

Fig. 3 | **Physiological hypertrophy signalling pathways.** Physiological stimuli, such as exercise and pregnancy, stimulate physiological signalling pathways, such as those involved in cell growth, proliferation, survival, and angiogenesis. Insulin and insulin-like growth factor 1 (IGF1) activate protein synthesis, cell growth, and survival signalling pathways. Thyroid hormone (T_3) is critical for postnatal hypertrophy and regulation of contractility and electrophysiology. Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) increase angiogenesis and cell survival. Nitric oxide (NO) activates protein kinase G (PKG) through an increase in cyclic GMP (cGMP) levels. AMP-activated protein kinase (AMPK) enhances mitochondrial biogenesis and energy metabolism through peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α) and prevents the aberrant activation of mechanistic target of rapamycin (mTOR) to maintain a physiological level of autophagy. 4EBP1, eIF4E-binding protein 1; AKT1, RAC-α serine/threonine-protein kinase; C/EBPβ, CCAAT/enhancer binding protein-β; CITED4, CBP/p300-interacting transactivator 4; eIF2Bε, translation initiation factor eIF2Bε; eIF4E, translation initiation factor eIF4E; ERBB, erythroblastic leukaemia viral oncogene homology; ERRα, oestrogen-related receptor-α; FOXO3, forkhead box protein O3; GC, guanylate cyclase; GRB2, growth factor receptor-bound protein 2; GSK3β, glycogen synthase kinase 3β; HIF1α, hypoxia-inducible factor 1α; IGF1R, IGF1 receptor; IP_3, inositol 1,4,5-triphosphate; IR, insulin receptor; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; MEK, MAP/ERK kinase; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinase; PLC, phospholipase C; PPARα, peroxisome proliferator-activated receptor-α; RAF, RAF proto-oncogene serine/threonine-protein kinase (also known as RAF1); RAS, GTPase RAS; RHOA, transforming protein RHOA; S6K1, ribosomal protein S6 kinase-β1; SRF, serum response factor; STAT5, signal transducer and activators of transcription 5; TR, thyroid hormone receptor; TRPC, transient receptor potential channel; VEGFR1, vascular endothelial growth factor receptor 1; YAP1, Yes associated protein 1.

endothelial cells and fibroblasts in response to pressure overload and neuroendocrine stimulation. By contrast, *Pgf*-knockout mice die rapidly owing to the development of heart failure with impaired angiogenesis in response to pressure-overload stimulation[68].

Platelet-derived growth factor (PDGF) and PDGF receptor (PDGFR) levels are also increased in the heart in response to pressure overload, in part through activation of Krüppel-like factor 5 (KLF5)[69,70]. Mice with cardiomyocyte-specific deletion of *Pdgfrb* are more susceptible to pressure overload stimulation and develop more severe heart failure with impaired angiogenesis than control mice[70]. Therefore, impaired expression of myocardial angiogenic growth factors results in vascular rarefaction. Importantly, findings from clinical studies published in the past 3 years suggest a significant correlation between vascular rarefaction and HFpEF[5,71]. Autopsy data show more cardiac hypertrophy, epicardial coronary artery atherosclerosis, microvascular rarefaction, and myocardial fibrosis in patients with HFpEF than in age-matched control individuals[5]. An angiogenesis-related marker, neuropilin, is predictive for all-cause mortality and heart-failure-related rehospitalization in patients with HFpEF but not in patients with HFrEF[71]. Collectively, these results suggest a critical role of paracrine growth factors from cardiomyocytes and nonmyocytes in maintaining angiogenesis and the importance of the balance between growth and angiogenesis in the adaptation of the hypertrophied heart.

Neuregulin 1

Neuregulin 1–4 are members of the epidermal growth factor family, with neuregulin 1 being the most abundant in the cardiovascular system[72]. Signalling via neuregulin 1 and its receptors — the receptor tyrosine-protein kinase ERBB2 family — has critical roles in heart development and in adaptations to physiological

and pathological stimuli. The endocytic adaptor proteins NUMB and numb-like protein (NUMBL) degrade ERBB2 through interaction with the RAS-related protein RAB7A, which promotes cell-cycle withdrawal[73]. Troponin T-Cre-mediated deletion of either *Numb* alone or both *Numb* and *Numbl* results in sustained ERBB2 signalling and activation of signal transducer and activator of transcription 5 (STAT5), which promotes nuclear translocation of Yes associated protein 1 (YAP1), leading to aberrant cardiomyocyte proliferation and ventricular noncompaction[73]. Endurance exercise increases levels of neuregulin 1, which activates ERBB2 and ERBB4 to stimulate PI3K signalling[74,75]. Neuregulin 1–ERBB signalling induces cardiomyocyte dedifferentiation and proliferation that protects the heart from ischaemic injury[76–79]. Postnatal overexpression of *Erbb2* in mice induces cardiac hyperplasia with increased cardiomyocyte hypertrophy, dedifferentiation, and proliferation, but with preserved cardiac contractile function similar to the phenotype of HCM[77].

Integrins and melusin

Proteins involved in mechanotransduction regulate physiological hypertrophy, and mutations in these proteins result in pathological hypertrophy, including HCM and dilated cardiomyopathy (DCM), as reviewed previously[80]. Overexpression of melusin, a muscle-specific β1 integrin-interacting protein, induces prolonged physiological concentric hypertrophy with preserved contractile function and protects the heart from transition towards a pathological state in response to prolonged pressure overload[81]. Conversely, melusin deficiency in mice impairs the hypertrophic response and accelerates the development of DCM in response to pressure overload induced by transverse aortic constriction (TAC)[82]. These findings suggest that the integrin–melusin complex is involved in the development of physiological hypertrophy and antagonizes the progression of pathological hypertrophy.

MicroRNAs and RNA-binding proteins

MicroRNAs (miRNAs) are differentially expressed in hearts with aerobic exercise-induced physiological hypertrophy[83]. For example, miRNA-222 is upregulated in physiological hypertrophy and has been shown in mice to inhibit four targets potentially relevant to the hypertrophic response: *p27* (which encodes a cell-cycle inhibitor), *Hipk1* and *Hipk2* (which encode protein kinases), and *Hmbox1* (which encodes a transcriptional repressor), thereby promoting cardiomyocyte growth and proliferation[84]. Inhibition of miRNA-222 blocks exercise-induced hypertrophy, whereas cardiac-specific overexpression of miRNA-222 attenuates MI-induced maladaptive cardiac remodelling.

Both physiological and pathological hypertrophy require de novo protein synthesis. During development of hypertrophy, the eIF4F complex and mTORC1 are activated to initiate mRNA translation, thereby increasing the rate of protein synthesis. Poly(A) tail-based translation control is also involved in cardiomyocyte growth[85]. Translation of *PABPC1* mRNA, which encodes an RNA-binding protein that promotes mRNA translation, is upregulated through elongation of its poly(A) tail in the heart in response to both physiological and pathological stimuli. Polyadenylate-binding protein 1 (PABPC1) interacts with eIF4G to stimulate global mRNA translation, and cardiac-specific overexpression of *Pabpc1* is sufficient to induce physiological hypertrophy[85]. Whether PABPC1 also has a functional role in the development of pathological hypertrophy is unknown.

Mechanisms of pathological hypertrophy

Cardiac hypertrophy becomes maladaptive decompensation when, in addition to cell growth and protein synthesis, the following processes occur: cell death, fibrosis, dysregulation of Ca^{2+}-handling proteins, mitochondrial dysfunction, metabolic reprogramming, reactivation of fetal gene expression, impaired protein and mitochondrial quality control, altered sarcomere structure, and insufficient angiogenesis (FIG. 2). The signalling mechanisms that induce these responses promote maladaptive cardiac remodelling and dysfunction and ultimately induce heart failure. Therefore, the heart enlargement accompanying the above responses is generally considered pathological, and inhibiting the concurrent signalling pathways could conceivably be important therapeutically. Pathological conditions, such as hypertension and MI (TABLE 1), promote pathological hypertrophy mainly through neuroendocrine hormones and mechanical forces, accompanied by downstream signalling pathways distinct from those involved in physiological hypertrophy (FIG. 4).

Angiotensin II and endothelin 1

Targeting the renin–angiotensin–aldosterone (RAA) system (using angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers) is a well-recognized clinical approach for reversing maladaptive cardiac hypertrophy independently of blood pressure. Angiotensin II and endothelin 1 are peptide hormones that bind to the GPCRs angiotensin II receptor and endothelin 1 receptor, respectively, which then activate G proteins such as $G_{q/11}$ (FIG. 4). $G_{q/11}$ signalling activates PLC, which then catalyses the synthesis of diacylglycerol (DAG) and inositol trisphosphate (IP_3). Perinuclear PLCε, scaffolded to muscle-specific A kinase-anchoring protein 6 (mAKAP), generates DAG from phosphatidylinositol 4-phosphate (PI4P) in the Golgi apparatus to activate nuclear protein kinase D (PKD; also known as PRKD1) and cardiac hypertrophy[86].

IP_3 promotes release of intracellular Ca^{2+} from the endoplasmic and sarcoplasmic reticulum through IP_3 receptors, which then activates the Ca^{2+}–calmodulin complex and calcineurin. The Ca^{2+}–calmodulin complex activates protein kinase Cα (PKCα) and the serine/threonine kinase calcium/calmodulin-dependent protein kinase type II (CaMKII). Activated PKCα regulates cardiac contractility by phosphorylating protein phosphatase inhibitor 1 (also known as PPP1R1A), which activates serine/threonine-protein phosphatase 1 (PP1A) to decrease phosphorylation of PLN. Dephosphorylated PLN inhibits SERCA2 activity[87]. PKCα deficient mice have cardiac hypercontractility

and are resistant to pressure-overload-induced heart failure, whereas cardiac-specific overexpression of *Prkca* induces contractile dysfunction[88]. In addition, cardiac-specific overexpression of *Pln* inhibits sarcoplasmic reticulum Ca^{2+} uptake and contractile function without affecting heart size[89], whereas *Pln*-knockout mice have improved Ca^{2+} cycling and myocardial contractility[90]. As mentioned above, CaMKII is activated by the Ca^{2+}–calmodulin complex, but also by exchange proteins directly activated by cAMP (EPACs) and by reactive oxygen species through oxidation. Of the four CaMKII isoforms (α, β, γ, and δ), CaMKIIδ is the major isoform in the heart and promotes the progression to maladaptive pathological hypertrophy and heart failure by inducing ryanodine receptor 2-mediated Ca^{2+} leak from the sarcoplasmic reticulum in response to pressure overload[91,92]. CaMKII also induces the nuclear exit of class II histone deacetylase 4 (HDAC4) through

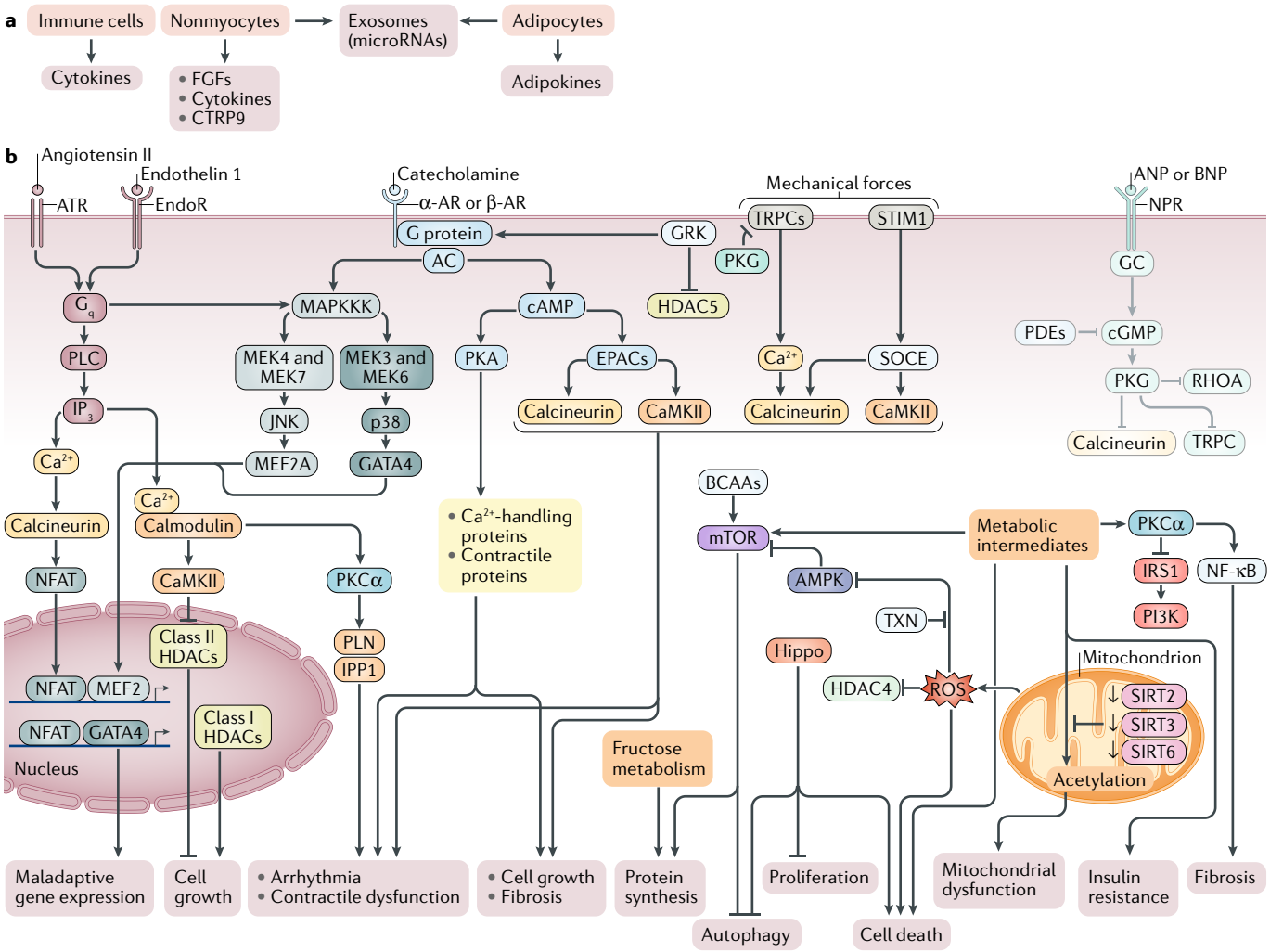

Fig. 4 | **Pathological hypertrophy signalling pathways. a** | Pathological hypertrophy stimuli, in addition to affecting cardiomyocytes, can directly or indirectly promote an increase in the secretion of cytokines, fibroblast growth factors (FGFs), and C1q/TNF-related protein 9 (CTRP9) from nonmyocytes and immune cells. **b** | Pathological enlargement of the heart is triggered by neuroendocrine hormones (such as angiotensin II, endothelin 1, and catecholamines) and by mechanical forces. These triggers directly or indirectly increase reactive oxygen species (ROS) production and myocardial accumulation of metabolic intermediates, inducing cell death, fibrosis, and mitochondrial dysfunction. Natriuretic peptide-mediated increase in cyclic GMP (cGMP) levels activates protein kinase G (PKG) to inhibit cell growth, although the natriuretic peptide receptor (NPR) is desensitized in hypertrophy and heart failure. G protein-coupled receptor kinases (GRKs) are associated with β-adrenergic receptor (β-AR) desensitization, hypertrophy, insulin resistance, cell death, and mitochondrial dysfunction. Sustained activation of mechanistic target of rapamycin (mTOR) is detrimental as a result of suppression of autophagy and consequent deterioration of protein quality control mechanisms. AC, adenylyl cyclase; AMPK, AMP-activated protein kinase; ANP, natriuretic peptide A; ATR, angiotensin II receptor; BCAA, branched-chain amino acid; cAMP, 3′,5′-cyclic AMP; BNP, natriuretic peptide B; CaMKII, calcium/calmodulin-dependent protein kinase type II; EndoR, endothelin 1 receptor; EPACs, exchange proteins directly activated by cAMP; GATA4, transcription factor GATA4; GC, guanylate cyclase; HDAC, histone deacetylase; IP_3, inositol 1,4,5-triphosphate; IP3R3, inositol 1,4,5-triphosphate receptor type 3; IPP1, protein phosphatase inhibitor 1 (also known as PPP1R1A); IRS1, insulin receptor substrate 1; JNK, JUN N-terminal kinases; MAPKKK, mitogen-activated protein kinase kinase kinase; MEF2A, myocyte enhancer factor 2A; MEK, MAP/ERK kinase; NF-κB, nuclear factor-κB; NFAT, nuclear factor of activated T cells; p38, mitogen-activated protein kinase 11; PDE, phosphodiesterase; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKCα, protein kinase Cα; PLC, phospholipase C; PLN, phospholamban; RHOA, transforming protein RHOA; SIRT, NAD-dependent protein deacetylase sirtuin; SOCE, store-operated Ca^{2+} entry; STIM1, stromal interaction molecule 1; TRPC, transient receptor protein channel; TXN, thioredoxin.

phosphorylation[92]. The nucleocytoplasmic shuttling of HDAC4 is also regulated by oxidative stress in a thioredoxin (TXN)-sensitive manner, which is critical for the development of pathological hypertrophy[93]. Class II histones HDAC4, HDAC5, and HDAC9 act as repressors of cardiac hypertrophy, whereas class I histones HDAC1, HDAC2, and HDAC3 are prohypertrophic[94,95]. Class I HDAC inhibitors suppress cardiac hypertrophy and heart failure[96].

Calcineurin is a Ca^{2+}-activated serine/threonine-protein phosphatase that dephosphorylates nuclear factor of activated T cells (NFAT) and promotes NFAT nuclear localization. NFAT interacts with transcriptional cofactors, such as GATA4 or myocyte-specific enhancer factor 2 A (MEF2A), to stimulate expression of hypertrophy-related genes[97]. The calcineurin–NFAT pathway does not mediate physiological hypertrophy during exercise or pregnancy[98].

p38 kinases and JUN N-terminal kinases (JNKs) comprise the MAPK cascade and are activated by MEK3/MEK6 and MEK4/MEK7, respectively. p38 kinases and JNKs phosphorylate and activate GATA4-mediated transcription to promote pathological hypertrophy. MAPK signalling has been extensively reviewed previously[99].

Catecholamines

Increased sympathetic nerve activity in patients with heart failure induces an increase in blood catecholamine levels, which is inversely correlated with survival[100]. Targeting β-adrenergic receptors using β-blockers is a commonly used approach to reverse β-adrenergic receptor desensitization in clinical settings. Catecholamines are neuroendocrine hormones that activate adenylyl cyclase to increase cAMP levels through binding to the seven-transmembrane α-adrenergic receptor and β-adrenergic receptor, a subclass of GPCRs. cAMP activates protein kinase A (PKA), which promotes an increase in cytosolic Ca^{2+} levels by directly phosphorylating Ca^{2+}-handling proteins and contractile proteins. Under pathological conditions, such as hypertension, MI, and heart failure, chronic stimulation of β-adrenergic receptor signalling leads to pathological hypertrophy and receptor desensitization, which is modulated by GPCR kinase (GRK)-mediated β-arrestin signalling[101]. GRK2 and GRK5 are predominantly expressed in the heart and are upregulated in heart failure[102,103]. Cardiac-specific overexpression of *Grk5* in mice exacerbates TAC-induced pathological hypertrophy through phosphorylation and nuclear export of HDAC5[104] or through kinase-independent regulation of NFAT signalling[105]. By contrast, swimming-induced physiological hypertrophy was unaffected by *Grk5* overexpression[106]. Cardiac-specific *Grk5*-knockout mice have significantly less hypertrophy and maladaptation in response to pressure-overload stimulus than wild-type mice[107].

EPAC1 and EPAC2 are also directly activated by cAMP, with distinct subcellular localizations and functions. EPAC1 is predominantly expressed in the heart and is upregulated in response to pressure overload and in heart failure through an increase in cAMP levels induced by β-adrenergic receptor stimulation. Overexpression of *Epac1*, but not *Epac2*, induces pathological hypertrophy through activation of the calcineurin–NFAT and the CaMKII–MEF2A pathways, independently of PKA[108,109]. Downregulation of *Epac1* does not attenuate TAC-induced cardiac hypertrophy, but prevents the transition to maladaptive remodelling and heart failure through suppression of PLC–PKCε-dependent phosphorylation at serine 16 of PLN[110,111]. EPAC1 is mainly located at the nuclear envelope and mediates nuclear export of HDAC5 (REF.[112]). Conversely, EPAC2 is located at the transverse tubules[112]. These results suggest that EPAC1 is involved in contractility and hypertrophy in cardiomyocytes, whereas EPAC2 is involved in β-adrenergic-receptor-induced arrhythmias.

mTOR signalling

Cardiomyocyte growth is accompanied by elevated protein synthesis or decreased degradation of proteins. mTOR is a serine/threonine-protein kinase that functions as part of two distinct complexes, mTORC1 and mTORC2, to coordinate growth factor signalling and nutrient (amino acid) availability with cell metabolism and growth by controlling protein synthesis and degradation[113]. mTORC1 activity is increased during development of both physiological (FIG. 3) and pathological (FIG. 4) hypertrophy in response to biochemical, mechanical, and metabolic signals. mTORC1 promotes ribosomal protein production (mRNA translation) by directly activating ribosomal protein S6 kinase-β1 (S6K1) and inhibiting eIF4E-binding protein 1 (4EBP1), which allows unrestrained, cap-dependent translation by eIF4E[114]. Although increasing protein synthesis and mitochondrial quality control through mTOR are essential adaptive mechanisms for the heart during acute pressure overload[115], sustained activation of mTOR is detrimental, in part as a result of suppression of autophagy and consequent deterioration of protein quality control mechanisms. AMP-activated protein kinase (AMPK) inhibits mTORC1, and pharmacological suppression of mTORC1 attenuates angiotensin II-induced and pressure-overload-induced pathological hypertrophy and heart failure[116,117].

Although S6K1 is one of the most studied substrates of mTORC1 and is activated by mTORC1 during hypertrophy[117], S6Ks might not be involved in the pro-hypertrophic effects of mTORC1. Cardiac-specific overexpression of the gene encoging S6K1, *Rps6kb1,* induces a modest degree of hypertrophy, whereas overexpression of the gene encoding S6K2, *Rps6kb2,* is not associated with a cardiac phenotype[118]. By contrast, genetic deletion of *Rps6kb1*, *Rps6kb2*, or both has no effect on cardiac hypertrophy induced by pressure overload, exercise, or IGF1R–PI3K signalling[118]. Therefore, S6Ks are not essential for the induction of either physiological or pathological hypertrophy. 4E-BPs probably have a more important role in mediating mTORC1-induced cardiac hypertrophy[115]. Of note, mTORC2 is also activated in response to pressure overload, thereby inhibiting cell death through suppression of the pro-apoptotic mammalian STE20-like protein kinase 1 (MST1; also known as STK4)[119]. Therefore, mTORC1 and mTORC2 have opposing functions during pathological hypertrophy.

Natriuretic peptides

Expression of genes encoding natriuretic peptides, including ANP and BNP, is induced in response to pathological stimuli. Cardiac-specific deletion of the gene encoding ANP receptor 1 (*NPR1*) leads to mild hypertrophy that is exacerbated by pressure-overload stimulus, leading to pathological hypertrophy and cardiac remodelling[120]. These results indicate that natriuretic peptides serve as antihypertrophic and cardioprotective molecules. Natriuretic peptides bind to natriuretic peptide receptors and activate guanylate cyclase to generate cGMP, thereby activating PKG. PKG has antihypertrophic effects through inhibition of calcineurin–NFAT, canonical transient receptor potential channels (TRPCs), and RHOA–RHO kinase pathways[43]. cGMP-specific 3′,5′-cyclic phosphodiesterase (PDE5A) and high affinity cGMP-specific 3′,5′-cyclic phosphodiesterase 9 A (PDE9A) degrade cGMP and antagonize the actions of NO and natriuretic peptides. The levels and activities of PDE5A and PDE9A are increased with pathological hypertrophy in mice and humans. PDE5A is located at myofilaments and is activated by cGMP, whereas inhibition of PDE5A increases the level of cGMP and suppresses pathological hypertrophy[121]. PDE9A is located at transverse tubules and mainly degrades natriuretic-peptide-stimulated cGMP[122]. Genetic or pharmacological inhibition of PDE9A attenuates pathological responses to neurohormones and sustained pressure overload independently of the NO pathway[122].

Nonmyocytes and immune cells

Cardiac fibroblasts constitute approximately 15% of nonmyocytes in the adult mouse heart[123] and communicate with other cell types in the heart, such as immune cells, endothelial cells, and cardiomyocytes[124]. Growth factors, including fibroblast growth factors (FGFs), transforming growth factor-β1 (TGFβ1), and IGF1 regulate cardiomyocyte growth and death, as well as cardiac fibrosis[125]. For example, global deletion of *Fgf2* in mice leads to the development of DCM without compensatory hypertrophy in response to angiotensin II stimulation or pressure overload owing to the lack of activation of JNK and p38 MAPK pathways[126,127]. TGFβ is upregulated in response to pathological stimuli, leading to cardiac hypertrophy and fibrosis. Canonical TGFβ–SMAD2/SMAD3 signalling contributes to cardiac fibrosis without inducing hypertrophy in response to pressure overload[128,129], whereas noncanonical SMAD–TAK1 (TGFβ-activated kinase 1; also known as MAP3K7) signalling in cardiomyocytes is involved in the development of pathological hypertrophy and fibrosis[130,131]. A 2017 study identified IL-11 as a critical downstream effector of TGFβ in fibroblasts[132]. Fibroblast-specific overexpression of *Il11* induces cardiac fibrosis and contractile dysfunction. Suppression of angiotensin II-induced or TAC-induced IL-11 signalling by genetic deletion of *Il11ra* inhibits cardiac fibrosis but not hypertrophy[132]. IGF1 locally secreted from cardiac fibroblasts through a KLF5-dependent mechanism suppresses pressure-overload-induced hypertrophy[133]. In addition, cardiac fibroblasts secrete miRNA-enriched exosomes, which contribute to the development of pathological hypertrophy[134]. Fibroblast-derived exosomes containing miR-21-3p promote angiotensin II-induced pathological hypertrophy through suppression of *Sorbs2* and *Pdlim5* in cardiomyocytes[134].

In addition to TGFβ, numerous cytokines associated with cardiac hypertrophy and heart failure are produced by cardiomyocytes, fibroblasts, and resident and circulating immune cells[135]. Circulating levels of the pro-inflammatory cytokines IL-6, IL-1, and tumour necrosis factor (TNF) are elevated in patients with pathological hypertrophy and heart failure[136]. The IL-6 family includes IL-6, IL-11, oncostatin M, leukaemia inhibitory factor, and cardiotrophin 1. IL-6 binds to the IL-6 receptor, which associates with the IL-6 receptor subunit-β (IL-6Rβ) and stimulates the JNK pathway. In mice, infusion of IL-6 or activation of IL-6Rβ induces pathological hypertrophy[137,138], whereas global deletion of *Il6* inhibits the development of TAC-induced hypertrophy, in part through suppression of CaMKII-dependent STAT3 signalling[139]. However, loss of the gene encoding IL-6Rβ in the heart induces acute development of maladaptive remodelling and heart failure in response to pressure overload, without compensatory hypertrophy[140]. Transgenic mice with cardiac-specific *Tnf*-overexpression show cardiac hypertrophy and maladaptive remodelling with mild infiltration of inflammatory cells[141], whereas global deletion of *Tnf* attenuates pressure-overload-induced hypertrophy and cardiac dysfunction with reduced matrix metalloproteinase 9 activity[142]. Cardiac-specific overexpression of human *IL1A* in mice induces cardiac hypertrophy with preserved contractile function[143]. Although *Il1b*-knockout mice have exacerbated contractile dysfunction with lower levels of hypertrophy and fibrosis in response to pressure overload compared with wild-type mice, in part as a result of insufficient JAK–STAT-mediated production of IGF1 in cardiac fibroblasts[144], clinical studies of IL-1 signalling blockade show favourable results. The IL-1 receptor antagonist anakinra improves exercise tolerance in patients with recently decompensated systolic heart failure and in patients with HFpEF[145,146]. The monoclonal antibody targeting IL-1β, canakinumab, lowers the rate of recurrent cardiovascular events in patients with previous MI and a high inflammatory burden (measured by high-sensitivity C-reactive protein levels), independently of lowering of LDL-cholesterol levels[147]. IL-10 is a major anti-inflammatory cytokine that inhibits infiltration of macrophages into the heart. *Il10* knockout in mice exacerbates isoprenaline-induced and TAC-induced cardiac hypertrophy and maladaptive remodelling, whereas IL-10 supplementation inhibits or even reverses TAC-induced cardiac remodelling through activation of STAT3 and inhibition of nuclear factor-κB (NF-κB)[148]. Activation of natural killer T cells with α-galactosylceramide attenuates MI-induced cardiac remodelling[149], and inhibition of T cell immune activity with abatacept ameliorates TAC-induced maladaptive remodelling[150]. Both effects are mediated by increased IL-10 production. These studies set the stage for clinical usage of anti-inflammatory therapy for patients with cardiovascular diseases.

Endothelial cells constitute around 60% of non-myocytes in the adult mouse heart[123], and regulate cardiomyocyte growth in a paracrine manner[151]. IL-33 is predominantly secreted by endothelial cells in response to pressure overload and binds to membrane-bound ST2 (also known as IL-1RL1) in cardiomyocytes[152]. Either endothelial-cell-specific deletion of *Il33* or cardiomyocyte-specific deletion of *Il1rl1* exacerbates pressure-overload-induced hypertrophy[152], whereas infusion of recombinant IL-33 reduces pressure-overload-induced hypertrophy and fibrosis, in part through inhibition of NF-κB activation[153]. Levels of complement C1q/TNF-related protein 9 (CTRP9), which is produced by endothelial cells, are higher in serum from patients with cardiac hypertrophy than in healthy individuals, and are higher in TAC-induced hypertrophic mouse hearts than in healthy hearts[154]. CTRP9 secreted from endothelial cells or cardiomyocytes induces cardiomyocyte hypertrophy in a paracrine and autocrine manner in vitro. *C1qtnf9* deletion attenuates TAC-induced cardiac hypertrophy and dysfunction in mice through decreased activation of the MAPK7–GATA4 signalling pathway[154]. However, CTRP9 supplementation attenuates adverse cardiac remodelling in response to MI, in part via a PKA-dependent pathway[155]. Therefore, CTRP9 might regulate pathological hypertrophy in a stress-dependent manner.

Mechanosensors

Canonical transient receptor potential channels. TRPCs are nonselective cation channels expressed in the heart. The TRPC family includes seven isoforms (TRPC1–TRPC7) that control pathological hypertrophy through signalling effectors, such as calcineurin and NFAT[156]. In particular, TRPC3 and TRPC6 are important for the development of pathological hypertrophy through calcineurin-dependent signalling[157–159]. Deletion of either *Trpc3* or *Trpc6* in mice suppresses maladaptive hypertrophy induced by pressure overload[160]. TRPC3 and TRPC6 are phosphorylated by PKG, which reduces channel conductance, thereby inhibiting TRPC-mediated hypertrophy[161]. Overexpression of a dominant-negative gene variant of certain TRPCs (TRPC3, TRPC4, and TRPC6) protects against TAC-induced pathological hypertrophy[162]. Knockdown of *Trpc4* also attenuates pathological hypertrophy and contractile dysfunction in response to MI[163].

Stromal interaction molecule 1. Stromal interaction molecule 1 (STIM1) is a Ca^{2+} sensor that partners with Ca^{2+}-release-activated Ca^{2+} channel protein 1 to allow Ca^{2+} entry in response to endoplasmic reticulum Ca^{2+} store depletion. TAC-induced upregulation of STIM1 activates the NFAT and CaMKII signalling pathways by enhancing a mechanism known as store-operated Ca^{2+} entry (SOCE), which promotes pathological hypertrophy and arrhythmias[164,165]. Knockdown of *Stim1* inhibits agonist-induced hypertrophy in vitro[166], and *Stim1* silencing by in vivo delivery of specific short hairpin RNAs rapidly induces heart failure without cardiac hypertrophy in response to pressure overload, which is mediated through the suppression of mTORC2–AKT–GSK3β signalling[167]. These findings suggest that STIM1 is critical for the induction of adaptive hypertrophy in the mouse heart by inducing an increase in Ca^{2+} flux in the initial phase of cardiac hypertrophy, but that STIM1 promotes pathological hypertrophy during the chronic phase in response to pressure overload.

Store-operated Ca^{2+} entry
Ca^{2+} influx through the Ca^{2+} channels in the plasma membrane that is triggered when intracellular Ca^{2+} stores are depleted.

Expression regulation

Genetic mutations. Genetic cardiomyopathies are grouped into five morphological subtypes: HCM, DCM, restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction cardiomyopathy (LVNC). Pathogenic mutations causing HCM have been identified in genes encoding sarcomere proteins, including *ACTC1*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *TNNI3*, *TNNT2*, and *TPM1*. Mutations in these sarcomere-related genes lead to altered Ca^{2+}-dependent tension generation in the sarcomeres, although genetic, epigenetic, and environmental modifiers are likely to influence disease development. Pathogenic variants in these genes and the clinical insights have been reviewed elsewhere[168,169]. Genetic cardiomyopathy is commonly accompanied by either fatal ventricular arrhythmias or systolic and/or diastolic cardiac dysfunction; therefore, the cardiac hypertrophy observed in these conditions is categorized as pathological. A 2016 study identified a relationship between the magnitude of myofilament tension developed over time as a result of mutations in sarcomere-related genes and heart growth and showed that this relationship can be used to predict whether the heart will undergo hypertrophic or dilated growth, thereby distinguishing the pathogenesis of HCM and DCM[170]. Although the main pathological effects in HCM result from mutations in sarcomere-related genes in cardiomyocytes, nonmyocytes have been suggested to have an important role in the development of pathological hypertrophy in this condition[171]. For example, in mice, mutations in *Myh6* (Arg403Gln or Arg719Trp) lead to the activation of TGFβ signalling in nonmyocytes, which then promotes fibroblast activation and the induction of diastolic dysfunction and heart failure[171].

Epigenetic modifications. Epigenetic modifications regulate pathological hypertrophy by modulating genome architecture, genome stability, and gene expression. A genome-wide study revealed that trimethylation of histone H3 at lysine (K) 4, K9, or K27 and dimethylation of H3 at K9 and K79 mediate gene reprogramming in pathological hypertrophy[172]. In pathological hypertrophy, levels of the histone lysine-specific demethylase 4A (KDM4A) are elevated; KDM4A upregulates the expression of *Fhl1*, which encodes a crucial component of the mechanotransduction machinery, thereby promoting hypertrophy and heart failure[173]. In addition, miRNA-217-mediated downregulation of *EHMT1* and *EHMT2* mRNA leads to a reduction in the repressive mark H3K9me2 in fetal-type genes, which induces the reactivation of the fetal gene response[174]. Pathological stimuli induce miRNA-217 to suppress *EHMT1* and

EHMT2, and genetic or pharmacological inhibition of histone-lysine *N*-methyltransferases EHMT1 and EHMT2 induces pathological hypertrophy[174]. However, two studies showed that EHMT2 is prohypertrophic during TAC-induced pathological hypertrophy in mice; therefore, the role of EHMT2 in hypertrophy remains controversial[175,176].

The long non-coding RNA (lncRNA) cardiac-hypertrophy-associated epigenetic regulator (Chaer) is enriched in the heart and is required for the development of pathological hypertrophy[177]. Chaer interacts with Polycomb repressor complex 2 (PRC2) in response to hypertrophic stimuli, which leads to the inhibition of H3 K27 methylation in the promoter regions of fetal genes related to cardiac hypertrophy, such as *Acta1*, *Anf*, and *Myh7* in mice, thereby inducing the development of pathological hypertrophy. These studies suggest that epigenetic modifications at H3 are critically involved in fetal gene reprogramming and that targeting these modifications might alleviate the progression of pathological hypertrophy.

Non-coding RNAs. Global transcriptome analyses have identified thousands of lncRNAs aberrantly expressed in cardiac hypertrophy. These lncRNAs might have crucial roles in various cellular processes by affecting cell differentiation, development, growth, and metabolism[178–180]. MiRNAs are involved in a broad range of cardiovascular diseases as well. MiRNAs target mRNAs encoding Ca^{2+}-handling proteins and proteins involved in Ca^{2+}-responsive signalling pathways, thereby mediating the development of pathological hypertrophy and heart failure[181,182].

Interplay between both types of hypertrophy

Many, if not all, signalling mechanisms mediating pathological hypertrophy are initially activated as an adaptive response. For example, inhibition of the calcineurin–NFAT signalling pathway, either with cyclosporine[183] or through deletion of the gene encoding calcineurin subunit B type 1 (*Ppp3r1*)[184], induces acute heart failure and lethality owing to the lack of compensatory hypertrophy in response to pressure overload. Conversely, sustained activation of signalling mechanisms inducing physiological hypertrophy induces heart failure and lethal arrhythmias, especially in the presence of genetic mutations[168]. HCM accounts for around 36% of sudden cardiac deaths in young athletes[185]. Distinguishing HCM from athlete's heart is critical for young athletes and has been reviewed elsewhere[186]. Stimulating insulin signalling in the presence of pathological hypertrophy aggravates the pathology and promotes heart failure[187]. Whereas short-term activation of AKT stimulates physiological growth of cardiomyocytes, sustained activation of AKT leads to pathological hypertrophy and heart failure[60]. These outcomes suggest that the functional consequences of each stimulus and cardiomyocyte response are context-dependent. The balance between cardioprotective and detrimental effects might determine the overall function of the heart and whether the adaptation manifests either physiological or pathological hypertrophy.

Metabolic remodelling in hypertrophy

Cardiac metabolism is differentially regulated in physiological and pathological hypertrophy[188]. Changes in systemic and cardiac metabolism precede the development of heart failure[189,190]. Impaired adaptation of energy metabolism during the hypertrophic response exacerbates pathological hypertrophy and increases cardiomyocyte death. Perturbations in ATP production directly change contractile function and result in heart failure[191,192]. During hypertrophy, ERRα interacts with PGC1α to activate mitochondrial energy metabolism by increasing expression of genes encoding proteins involved in the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. Although deletion of the gene encoding ERRα does not affect the initial development of TAC-induced hypertrophy, ERRα deficiency promotes transition to heart failure[193]. Cardiac-specific deletion of the gene encoding the scavenger receptor CD36 reduces fatty acid uptake and utilization in the heart and exacerbates pressure-overload-induced cardiac dysfunction and heart failure, without affecting the degree of cardiac hypertrophy[194]. These findings suggest that appropriate metabolic adaptation to pathological hypertrophy is required for the maintenance of contractile function. Cardiac-specific deletion of genes encoding insulin receptors promotes mitochondrial dysfunction, oxidative stress, and contractile dysfunction by impairing fatty acid and pyruvate metabolism and TCA flux[195]. Therefore, signalling mechanisms inducing physiological hypertrophy might coordinately regulate mitochondrial metabolism to maintain cardiac function. Altered metabolites also promote pathological hypertrophy and/or heart failure (FIG. 4). Dysregulated fatty acid or carbohydrate metabolism in genetically engineered mouse models directly induces cardiac hypertrophy and/or functional decline by modulating pathological signalling mechanisms[196–201].

Changes in metabolic pathways

During embryonic development, glycolysis is the major form of energy production in proliferating cardiomyocytes. During the perinatal period, cardiomyocytes switch their energy source from carbohydrates to fatty acids, with a concordant increase in mitochondrial oxidative capacity and fatty acid oxidation. During the development of pathological hypertrophy and heart failure, cardiomyocytes remodel the ATP production machinery, reducing energy production from fatty acids and increasing glycolysis, anaplerosis, and other forms of metabolism, such as use of lactate, branched-chain amino acids (BCAAs), and ketone bodies[192,202,203]. This shift towards fetal-type energy production is termed metabolic reprogramming and is accompanied by downregulation of genes encoding proteins involved in mitochondrial energy transduction and respiratory pathways[204]. Fatty acid oxidation and enzymes involved in fatty acid utilization are downregulated during early stages of hypertrophy and continuously decrease during maladaptive hypertrophy and heart failure in response to pressure overload[205]. By contrast, glucose oxidation is maintained, with a slight initial increase during the early stage of hypertrophy, but eventually decreases

Athlete's heart
Dilated and hypertrophied heart observed in athletes, particularly those engaged in endurance training, that is mostly adaptive and benign.

Glycolysis
Metabolic process in which glucose is converted into pyruvate in the cytosol, generating two molecules of ATP.

Fatty acid oxidation
Catabolic processes in which fatty acyl-CoA is sequentially oxidized to generate acetyl-CoA, which is then used in the tricarboxylic acid cycle.

Anaplerosis
Chemical reactions that replenish the tricarboxylic acid cycle intermediates that were extracted for biosynthesis (cataplerosis).

during maladaptive remodelling[205,206]. However, these changes in glucose oxidation during the development of hypertrophy are less consistent than the changes in fatty acid utilization[191]. Glycolysis and anaplerosis are increased in pressure-overload-induced pathological hypertrophy[207]. Glycolysis and utilization of other substrates, such as lactate, BCAAs, and ketone bodies, might not sufficiently compensate for the decreased fatty acid and glucose oxidation, thereby leading to energy deficiency and the development of heart failure. Deletion of *Acacb* (which encodes acetyl coenzyme A carboxylase 2) in mice increases fatty acid oxidation and attenuates the development of pathological hypertrophy and diastolic and systolic dysfunction, while preserving the substrate utilization profile in the presence of pressure overload or angiotensin II stimulation[207,208]. Therefore, metabolic reprogramming can be a direct cause of pathological hypertrophy.

Conversely, fatty acid and glucose oxidation are increased in physiological hypertrophy, which is accompanied by increased expression of genes encoding fatty acid transporters, fatty acid binding proteins, lipid metabolic pathways, and respiratory pathways[20,209]. Metabolomic analysis shows that the levels of acylcarnitines in the heart are increased in pathological hypertrophy and heart failure, whereas acylcarnitine levels are decreased in physiological hypertrophy[202].

The nuclear receptors peroxisome proliferator-activated receptor-α (PPARα) and PPARγ regulate fatty acid metabolism in the heart, whereas PPARβ and PPARδ regulate both fatty acid and glucose metabolism[210]. ERRα also regulates fatty acid metabolism, as well as stimulating gene expression related to mitochondrial oxidative phosphorylation[211,212]. PPARs and ERRs are regulated by the PGC1 family of transcriptional cofactors[213]. Exercise activates PGC1α and PPARα in the heart, whereas these activities are downregulated in pathological conditions[214].

Exercise increases the levels of AMP and NAD^+, which in turn activate the metabolic sensors AMPK and NAD^+-dependent sirtuins[215], respectively. AMPK directly regulates PGC1α through phosphorylation at T177 and S538 to control mitochondrial biogenesis and energy metabolism[216]. AMPK, PPARβ, and PPARδ coordinately mediate expression changes in exercise-induced metabolic genes[217]. These metabolic changes might be regulated in part by exercise-induced NO production. *Nos3* knockout in mice blunts the upregulation of PGC1α and mitochondrial transcription factor 1 (TFAM) induced by swimming, suggesting that eNOS mediates exercise-induced cardiac metabolic changes and hypertrophy[218].

Pathological effects of altered metabolism

Altered cellular metabolism directly induces or contributes to the development of pathological hypertrophy. Furthermore, reduced energy production and increased oxidative stress result in cardiomyocyte death and fibrosis, leading to transition from adaptive to maladaptive hypertrophy and heart failure. Mitochondrial dysfunction is a well-accepted underlying mechanism of this process.

Metabolic intermediates. Accumulation of metabolic intermediates induces cardiac storage diseases — including lysosomal storage disease, glycogen storage disease, and lipid storage disease — leading to cardiomyopathy. Diabetic cardiomyopathy, also known as lipotoxic cardiomyopathy, is frequently observed in individuals with obesity or patients with insulin resistance or diabetes[219,220], and this condition has been shown to induce hypertrophy and heart failure[221]. Clinical studies show altered cardiac metabolism (increased fatty acid uptake and oxidation with reduced glucose uptake) in patients with diabetes and reduced diastolic but preserved systolic function[222]. Intramyocardial lipid accumulation is a hallmark of diabetic cardiomyopathy[220] and is an independent predictor of diastolic dysfunction in patients with type 2 diabetes[223]. However, cellular and rodent studies show that triglyceride accumulation is not associated with cardiac and cardiomyocyte toxicity, suggesting that triglycerides themselves might not be toxic[224]. Alternatively, accumulation of specific lipid intermediates (such as some ceramides, acylcarnitines, and DAG), their cellular compartmentalization, and how they are stored could affect a broad range of biological process, including cellular metabolism, growth, proliferation, and mitochondrial function. However, how the accumulation of intermediates signals to downstream effectors to promote cell growth in the heart remains largely unknown.

Ceramides belong to a family of lipid molecules composed of sphingosine and a fatty acid. Ceramides are synthesized de novo from fatty acid acyl-CoA, particularly palmitoyl-CoA. Although ceramides are mostly localized on cell membranes, their cytosolic accumulation induces insulin resistance and apoptosis[225–228]. In the heart, ceramides are lipotoxic. C6-ceramide reduces AKT activity and increases fetal gene expression in human cardiomyocyte cell lines in vitro, and inhibition of ceramide biosynthesis improves diabetic cardiomyopathy in transgenic mice with cardiac-specific overexpression of the gene encoding glycosylphosphatidylinositol-anchored human lipoprotein lipase[229]. Furthermore, increased sphingolipid metabolism and ceramide accumulation are involved in the development of hypertrophy and diabetic cardiomyopathy[230]. However, the functional relevance of the increased level of ceramides in diabetic cardiomyopathy is controversial[231].

A lipidomic analysis of human failing hearts revealed an increased level of total ceramides and very long-chain ceramides in the myocardium and serum of patients with advanced heart failure, which was reversed after cardiac unloading[232]. In rodent studies, ischaemia–reperfusion injury or chronic ischaemia activates serine palmitoyltransferase (SPTLC), a rate-limiting enzyme of the de novo pathway of ceramide synthesis, and increases ceramide accumulation in the heart[232]. Pharmacological inhibition of SPTLC or genetic deletion of *Sptlc2* preserves cardiac function after ischaemia–reperfusion injury or MI[232,233]. Overexpression of *SPTLC1* and *SPTLC2* is sufficient to increase ceramide accumulation and cell death and to decrease oxidative metabolism in cardiomyocytes in vitro[232]. However, pressure overload also increases the activity of SPTLC

in the heart, although inhibition of SPTLC attenuates TAC-induced pathological hypertrophy and contractile dysfunction[234]. Furthermore, cardiac-specific deficiency of SPTLC reduces the level of ceramides in the heart but induces age-dependent DCM[235]. These results suggest that de novo ceramide synthesis is critical for maintaining contractile function and that increased de novo ceramide synthesis and subsequent ceramide accumulation or changes in myocardial lipid profile contribute to the progression of maladaptive hypertrophy in a stress-dependent fashion.

In cardiomyocytes, long-chain fatty acids are converted to their respective acyl-CoA ester by acyl-CoA synthetases. Long-chain acyl-CoAs are converted into acylcarnitines and free CoA by carnitine *O*-palmitoyltransferase 1, muscle isoform (CPT1M) at the outer mitochondrial membrane. Acylcarnitines are transported across the inner mitochondrial membrane into the mitochondrial matrix through carnitine/acylcarnitine carrier protein. In the matrix, CPT2 reconverts acylcarnitines into free carnitine and long-chain acyl-CoAs, which undergo β-oxidation. Acylcarnitines are associated with insulin resistance in muscle[236]. Metabolomic analyses showed that the level of acylcarnitines in the heart is increased in pathological hypertrophy and decreased in physiological hypertrophy[202,237]. However, acylcarnitine levels are decreased in the heart 8 weeks after TAC or MI[238]. In patients with chronic heart failure, the serum level of long-chain acylcarnitines is independently associated with adverse clinical outcomes[239]. In patients with end-stage heart failure, the serum long-chain acylcarnitines level is significantly higher than in patients with chronic heart failure, but is significantly decreased after mechanical circulatory support[239]. These results suggest that acylcarnitines serve as a prognostic marker and are potential targets for therapeutic intervention. However, the mechanism underlying acylcarnitine level changes and their functional importance in cardiac pathophysiology need to be clarified.

DAG is a lipid metabolite and acts as a second messenger in activating PKC isoforms, which in turn promote insulin resistance through suppression of IRS1 phosphorylation and inflammation through activation of NF-κB in the muscles of patients with diabetes and in rodent models of diabetes[240,241]. Although patients with heart failure have a lower overall fatty acid content in their heart than healthy individuals, DAG levels are increased, accompanied by increased membrane localization of PKC and decreased AKT activity in the myocardium[242]. However, mechanical unloading reduces levels of these lipid intermediates, reversing the associated effects on PKC and insulin–PI3K–AKT signalling. Therefore, the level of cardiac DAG significantly correlates with cardiac insulin signalling in the human heart. DAG is converted to triglycerides via diacylglycerol acyltransferase 1 (DGAT1). In mice, cardiac-specific deficiency of DGAT1 significantly increases the levels of DAG and ceramides and PKCα activation in the heart[243]. Cardiac-specific DGAT1-deficient mice have reduced contractile function and premature death.

BCAAs, including leucine, isoleucine, and valine, are critical for protein synthesis through activation of mTOR and contribute to mitochondrial oxidation and energy production in the heart. BCAAs and related metabolites contribute to insulin resistance[244,245]. In heart failure, BCAA catabolism is impaired through KLF15-mediated transcriptional reprogramming, which elevates branched-chain α-keto acid levels to suppress respiration and induce superoxide production[246]. A defect in BCAA catabolism due to a deficiency in the mitochondrial isoform of protein phosphatase 1 K promotes TAC-induced heart failure in mice[246].

Glucose metabolism. In pathological hypertrophy, insulin-independent HepG2 glucose transporter GLUT1 (also known as SLC2A1) levels are increased, but insulin responsive glucose transporter type 4, (GLUT4; also known as SLC2A4) levels are decreased, accompanied by an increased rate of glucose uptake and glycolysis, but not of glucose oxidation[247]. As a result, glycolysis and glucose oxidation rates are mismatched, leading to the accumulation of glycolytic intermediates. Among these, glucose-6-phosphate regulates carbohydrate-mediated and insulin-mediated cell growth by activating mTORC1 (REFS[248,249]), indicating a link between glycolytic intermediates and cardiomyocyte growth. Accumulation of glycolytic intermediates enhances the hexosamine biosynthetic pathway and the pentose phosphate pathway, which promote biosynthesis of glycoproteins, protein *O*-GlcNacylation, and excessive accumulation of NADPH, all of which contribute to pathological hypertrophy[247,250,251].

Fructose metabolism. Clinical studies have shown a link between excess fructose and a higher incidence of diabetes and cardiovascular diseases. In pathological hypertrophy, fructose metabolism is upregulated in the heart. Pressure overload increases expression of HIF1α, which stimulates expression of *SF3B1* (which encodes the splicing factor 3B subunit 1) to promote an isoform shift from ketohexokinase (KHK)-A to KHK-C[252]. This isoform shift enhances fructose uptake into cardiomyocytes via stimulation of *SLC2A5* (which encodes GLUT5) expression and conversion of fructose to fructose-1-phosphate. The metabolites of fructose-1-phosphate, such as dihydroxyacetone phosphate, glyceraldehyde, and glyceraldehyde-3-phosphate, serve as precursors for glycerol synthesis and nucleic acid and amino acid biosynthesis, thereby increasing the macromolecular biosynthetic capacity for hypertrophic growth[252].

Ketone body metabolism. Ketone bodies consist of three water-soluble molecules, acetoacetate, β-hydroxybutyrate, and acetone, which are produced in the mitochondria of the liver from fatty acids (ketogenesis) during intake of a low-carbohydrate (ketogenic) diet, fasting, prolonged and intense exercise, or untreated diabetes. The heart, brain, kidneys, and skeletal muscles use ketone bodies as an alternative fuel source. In the heart, ketone bodies are converted into acetyl-CoA (termed ketolysis) in mitochondria in three steps involving three enzymes: D-β-hydroxybutyrate dehydrogenase, mitochondrial (BDH1); succinyl-CoA:3-ketoacid

Mechanical unloading
Clinical interventions to reduce ventricular pressure and/or volume with the help of circulatory assist devices in patients with heart failure.

CoA transferase 1, mitochondrial (SCOT; also known as OXCT1); and acetyl-CoA C-acetyltransferase, mitochondrial (ACAT1). Acetyl-CoA is then used for energy production via the TCA cycle and oxidative phosphorylation[253]. Ketone body oxidation contributes to around 10% of total energy production in the normal heart[254].

In patients with heart failure, the level of blood ketone bodies is increased, which is significantly associated with contractile dysfunction and higher serum level of free fatty acids, in part owing to increased neurohormonal stimulation[237,255,256]. In the failing heart, levels of enzymes regulating ketone body metabolism are increased[237,256]. In experimental animals, SCOT deficiency accelerates TAC-induced pathological remodelling[257]. These results suggest that increased ketone body metabolism is an adaptive response in the context of pathological hypertrophy. In clinical studies reported in the past 3 years, the antidiabetic drug empagliflozin, a sodium–glucose cotransporter 2 inhibitor, increased the serum level of β-hydroxybutyrate and was cardioprotective in patients with diabetes at high risk of cardiovascular disease[258–260], supporting the potential benefit of increasing serum levels of β-hydroxybutyrate in cardiac diseases. Of interest, β-hydroxybutyrate inhibits class I HDACs through histone acetylation and increases resistance to oxidative stress[261]. Therefore, in the context of pathological hypertrophy, ketogenic-diet-mediated increases in serum β-hydroxybutyrate might inhibit cardiac hypertrophy through suppression of class I HDACs and increased energy production. However, a study using an isolated, working rat heart model showed that ketone bodies inhibit the TCA cycle by sequestering CoA and induce acute contractile dysfunction that is reversed by supplementation with glucose or TCA-cycle intermediates[262]. Furthermore, the hyperacetylation of mitochondrial proteins found in heart failure[263] might be in part a result of the increased level of mitochondrial acetyl-CoA generated by chronic utilization of ketone bodies beyond the capacity of acetyl-CoA to enter into the TCA cycle. Therefore, further studies are required to determine whether increasing ketone body levels or intake of a ketogenic diet is protective against pathological hypertrophy and, if so, what the underlying mechanisms are.

Metabolic crosstalk between the heart and peripheral organs. Accumulating evidence suggests that the heart controls the metabolism of other organs through cardiokines, factors secreted by the heart[264,265]. For example, cardiac natriuretic peptides regulate not only natriuresis, diuresis, and vasodilatation but also lipolysis, mitochondrial biogenesis, and energy expenditure in adipocytes[266]. The heart also controls systemic energy metabolism, fat mass, and body weight via cardiac miR-208a and mediator of RNA polymerase II transcription subunit 13 (MED13) signalling[267], which targets white adipose tissue and the liver to upregulate metabolic gene expression and increase the number of mitochondria, most probably through regulation of cardiokines[268].

Conversely, obesity-induced adipose tissue dysfunction is linked to cardiovascular diseases, in part through adipokines, factors secreted by adipose tissue[269]. Obesity and diabetes promote low-grade inflammation that contributes to systemic metabolic dysfunction via increased pro-inflammatory adipokines and decreased anti-inflammatzory adipokines[270]. By contrast, the adipokine adiponectin directly suppresses pressure-overload-induced hypertrophy and improves survival in mice through activation of AMPK in cardiomyocytes[271]. Adipose tissue also regulates pathological hypertrophy through secretion of exosomes[272]. The antidiabetic PPARγ agonist rosiglitazone induces cardiac hypertrophy and heart failure as an adverse effect. This induction occurs even in mice with cardiomyocyte-specific PPARγ deficiency, but not in mice with adipocyte-specific PPARγ deficiency[272]. Rosiglitazone stimulates secretion of exosomes containing miR-200a from adipocytes, which leads to a decrease in TSC1 levels and subsequent activation of mTOR signalling in cardiomyocytes, resulting in cell hypertrophy[272].

AMPK in metabolic reprogramming. AMPK serves as an energy sensor, increasing mitochondrial biogenesis, promoting ATP production, and inhibiting energy-consuming biosynthetic pathways by negatively regulating mTOR through phosphorylation[273,274]. Under energy depletion conditions, AMP binds to and activates AMPK through liver kinase B1 (LKB1; also known as STK11), calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2), and TAK1, which then promotes glucose metabolism. Pressure-overload-induced cardiac hypertrophy activates AMPKα1, but not AMPKα2, in the heart[275]. AMPK inhibition exacerbates pathological hypertrophy and heart failure, whereas AMPK activation can be protective against pathological hypertrophy. In particular, redox-mediated regulation of AMPK activity contributes to pathological hypertrophy. AMPK is negatively regulated by oxidation of Cys130 and Cys174 in the α-subunit, which interferes with the interaction between AMPK and AMPK kinases. TXN prevents AMPK oxidation, whereas a high-fat diet downregulates *Txn* expression, thereby suppressing AMPK activity[276]. The role of AMPK in regulating heart failure as a therapeutic target has been reviewed previously[277].

Acetylation of mitochondrial proteins. Mitochondrial proteins are hyperacetylated in hypertrophy and heart failure as a result of reduced NAD^+ levels and consequent inactivation of sirtuins[251,263,278], which contributes to the development of energy metabolic derangements and heart failure. Sirtuins are mammalian homologues of the silent information regulator (Sir) proteins in yeast and comprise seven isoforms. NAD^+-dependent mitochondrial protein deacetylase sirtuin 3, mitochondrial (SIRT3) targets mitochondrial proteins, including fatty acid and glucose metabolism enzymes, protein subunits of the electron transport chain, antioxidant proteins, and proteins involved in maintaining mitochondrial integrity in the heart[279,280]. SIRT3 acts as a modifier of physiological hypertrophy through activation of FOXO3A-mediated antioxidant gene expression[281]. Honokiol blocks the development of pathological hypertrophy and ameliorates pre-existing hypertrophy in rats through activation of SIRT3, which reduces acetylation of the mitochondrial proteins superoxide

dismutase, mitochondrial (SOD2) and ATP synthase subunit O, mitochondrial (ATP5O)[282]. Activation of SIRT3 by nicotinamide mononucleotide supplementation restores cardiac function and energy metabolism through deacetylation of mitochondrial proteins in pressure-overload-induced hypertrophy and heart failure, *Klf4*$^{-/-}$, and Friedreich ataxia cardiomyopathy mouse models[278,283,284]. Therefore, hyperacetylation of mitochondrial proteins through a reduction in SIRT3 activity induces pathological hypertrophy and promotes transition to heart failure.

SIRT6 is also downregulated in pressure-overload-induced cardiac hypertrophy and heart failure[285]. In mice, cardiac-specific deletion of *Sirt6* causes cardiac hypertrophy and fibrosis at baseline, whereas cardiac-specific overexpression of *Sirt6* attenuates pressure-overload-induced hypertrophy and contractile dysfunction[285]. SIRT2, which is primarily localized in the cytoplasm, is downregulated in pathological hypertrophy, whereas cardiac-specific overexpression of *Sirt2* protects the heart against angiotensin II-induced pathological hypertrophy[286]. SIRT2 directly deacetylates LKB1 at lysine 48, which leads to activation of AMPK and attenuates pathological hypertrophy.

Although increased levels of SIRT1, a nuclear protein deacetylase, in the heart attenuate age-related pathological cardiac hypertrophy[287], SIRT1 also serves as a positive effector of pathological hypertrophy in response to pressure overload by suppressing ERR target genes through physical interaction with PPARα[288]. Deletion of *Sirt4*, which encodes an ADP-ribosyltransferase localized in mitochondria, attenuates angiotensin II-induced cardiac hypertrophy and fibrosis, whereas overexpression of *Sirt4* in the heart exacerbates angiotensin II-induced hypertrophy and fibrosis, in part through suppression of SOD2 activity and increased oxidative stress in the heart[289]. These findings suggest that interventions to stimulate SIRT2, SIRT3, or SIRT6 or to inhibit SIRT1 or SIRT4 might prevent pathological hypertrophy.

Cardiac regeneration therapy

Adult cardiomyocytes are terminally differentiated and have only a limited capacity to proliferate, although studies over the past 2 decades have demonstrated a potential to reactivate the proliferative capacity of cardiomyocytes in mammals. Boosting the regenerative capacity of existing cardiomyocytes for the replacement of dead cardiomyocytes with new cardiomyocytes would be an ideal therapy for patients with MI to reduce the risk of progression to heart failure. In experimental mouse models of MI, regeneration therapy has produced beneficial results[290,291].

Cardiomyocyte proliferation

Cardiomyocyte proliferation rates are increased in physiological hypertrophy[30,74,292]. AKT1-mediated inhibition of C/EBPβ increases *CITED4* expression, which leads to stimulation of cardiomyocyte proliferation, thereby promoting physiological hypertrophy instead of pathological hypertrophy[30]. Likewise, exercise-induced upregulation of miRNA-222 increases proliferation of cardiomyocytes[84]. However, the functional importance of increased proliferation in physiological hypertrophy remains to be established. Indeed, some experimental models of physiological hypertrophy show no increase in proliferation. For example, cardiac-specific overexpression of *Parbp1* induces physiological hypertrophy without increases in proliferation[85]. Mice deficient in the cell-cycle inhibitor cyclin-dependent kinase inhibitor 1B (CDKNIB) exhibit cardiac hyperplasia and cardiomyocyte hypertrophy[293–295], with improved contractile function without increased fetal gene expression at baseline[296]. However, these mice are more susceptible to pressure overload or angiotensin II stimulation, with increased hypertrophy and decreased contractile function compared with wild-type mice[296]. Pathological hypertrophic stimuli, such as pressure overload or angiotensin II, increase the activity of casein kinase subunit-α′, which promotes proteasomal degradation of CDKNIB and activates the downstream target cyclin E–cyclin-dependent kinase 2 complex[296]. *Gsk3α*^{Ser21Ala} knock-in mice, which have a form of GSK3α (a crucial regulator of cell growth and death) that cannot be inactivated via phosphorylation, have decreased cardiomyocyte proliferation but increased cardiac hypertrophy and dysfunction during TAC-induced pathological hypertrophy compared with wild-type mice[297]. Therefore, the functional importance of increased proliferation in physiological and pathological hypertrophy warrants further clarification.

Hippo pathway as a therapeutic target

The Hippo signalling pathway is an evolutionarily conserved mechanism that inhibits cell proliferation and survival[298,299]. MST1 (a serine/threonine-protein kinase), a central upstream regulator of the Hippo signalling pathway, phosphorylates various substrates, including the serine/threonine-protein kinases LATS1 and LATS2, beclin 1, and Bcl-2-like protein 1 (BCL2L1), thereby regulating organ size, apoptosis, and autophagy[300–304]. MST1 has an essential role in mediating the progression of heart failure, because MST1 is activated by cardiac stress and promotes cell death and induces dysfunction of individual cardiomyocytes through inhibition of autophagy and mitophagy[302]. Excessive activation of MST1 in the heart inhibits compensatory hypertrophy and/or cardiomyocyte proliferation, thereby inducing wall thinning and heart dilatation, which in turn increases wall stress and further dilatation of the heart[300,302].

The crucial downstream effector of canonical Hippo signalling is YAP1, a transcriptional cofactor that promotes cardiomyocyte growth and survival. YAP1 stimulates both hypertrophy and proliferation in cardiomyocytes[305–308]. YAP1 activates the IGF and Wnt signalling pathways to increase cardiomyocyte proliferation and embryonic heart size through inactivation of GSK3β and increased β-catenin levels, a positive regulator of cardiac growth[309]. Forced expression of a constitutively active form of YAP1 in the adult heart stimulates cardiac regeneration and improves contractility after MI[307,310,311]. In addition to MST1, α-catenin is also a negative regulator of YAP1, and inhibition of α-catenin improves cardiac function after MI[312]. Activation of YAP1 through deletion of *Salv* attenuates pathological hypertrophy and

Biased ligands
Ligands that selectively affect some, but not all, of the many signalling pathways of a given receptor.

heart failure by activating cardiomyocyte proliferation in response to pressure overload or MI[313,314]. Therefore, regeneration of cardiomyocytes through regulation of Hippo–YAP signalling seems a promising strategy for treating pathological hypertrophy.

YAP1 is inactivated by glucose deprivation[315,316]. Energy deprivation activates AMPK, which in turn directly phosphorylates YAP1 at Ser94 and Ser61 to disrupt the interaction between YAP1 and TEA domain family transcription factors (TEADs)[315] or to inactivate YAP1 transcriptional activity[316]. Cellular energy stress-induced activation of AMPK also negatively regulates YAP1 through the angiomotin-like protein 1 (AMOTL1)–LATS pathway[317]. These results suggest a connection between glucose metabolism and Hippo–YAP pathway-mediated cellular proliferation and survival.

Conclusions

Although much progress has been made in elucidating the underlying mechanisms of physiological and pathological hypertrophy, many issues remain unsolved. First, the list of identified molecular factors that contribute to hypertrophy keeps growing, and the field is becoming incremental. In this regard, the different regulators of hypertrophy should be prioritized on the basis of clinical relevance. To this end, identifying several proximal mechanisms commonly altered in many forms of pathological and physiological hypertrophy in humans is important. For example, integrative bioinformatic analyses of data obtained from multiple types of analyses, including RNA sequencing and proteomic analyses, in several different forms of pathological hypertrophy might allow the identification of the crucial common mechanisms of pathological hypertrophy and heart failure. Such mechanisms could then be targeted with higher priority for treatment of heart failure.

Second, given that the heart can tolerate pressure overload even without hypertrophy under some conditions[107], and that the level of cardiac hypertrophy does not necessarily correlate with the extent of cardiac dysfunction[81], what is the role of cardiac hypertrophy per se? Although cardiac hypertrophy is a well-established risk factor for heart failure, cardiac hypertrophy alone might not be appropriate as a direct target for heart failure treatment. Better understanding of the role of cardiac mass in mediating cardiac adaptation and dysfunction is needed.

Conversely, accumulating evidence suggests that specific signalling mechanisms alone can dictate the function and prognosis of patients with cardiac hypertrophy and, therefore, might be the major determinants of physiological and pathological hypertrophy. If this hypothesis is true, selectively inhibiting signalling mechanisms mediating pathological hypertrophy while preserving or even promoting those mediating physiological hypertrophy might help to maintain or improve cardiac function in patients with cardiac hypertrophy. For example, biased ligands selectively activating signalling pathways mediating physiological hypertrophy and/or inhibiting pathological hypertrophy should theoretically be more effective for the treatment of patients with cardiac hypertrophy compared with inhibiting the entire signalling mechanism mediated by angiotensin II receptor type 1 and β_1-adrenergic receptors. Although molecular pharmacology has enabled substantial progress in our understanding of subreceptor signalling mechanisms of GPCRs[318], more research is necessary to improve the selectivity and effectiveness of biased receptor ligands.

Although many studies have aimed to identify biomarkers of physiological versus pathological hypertrophy, predicting the prognosis of cardiac hypertrophy and/or accurately forecasting the timing of decompensation in patients can be difficult. Whether the molecular mechanisms identified through these approaches are the cause or the result of pathological hypertrophy remains to be elucidated. In particular, whether changes in mitochondrial function and metabolism are the primary cause or secondary effects in many forms of hypertrophy is difficult to determine. Detailed time-course studies in patients with hypertrophy before the manifestation of cardiac dysfunction and validation studies using induced pluripotent stem cell-derived human cardiomyocytes might help to clarify these issues.

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