Cardiovascular disease is a leading cause of death worldwide. Nearly 2400 Americans die of cardiac causes each day, 1 death every 37 seconds.1 Thus, the heart still reigns supreme: “[F]oundation of their [animals’] life, the sovereign of everything within them, the sun of their microcosm, that on which all growth depends, from which all power proceeds” (William Harvey, 1628).

Effective myocardial function depends primarily on oxidative energy production. In humans, at a heart rate of 60 to 70 beats per minute, the oxygen consumption normalized per gram of myocardium is 20-fold higher than that of skeletal muscle at rest. As an adaptation to this high oxygen demand, the heart maintains a high level of oxygen extraction of 70% to 80% compared with 30% to 40% in skeletal muscle.2 This is facilitated by the capillary density of 3000 to 4000 compared with 500 to 2000 per 1 mm² in skeletal muscle and a tight regulation of the coronary blood flow.3 In the case of exercise-induced hypertrophy, the heart preserves the oxygen supply/demand, matching the proportional increases in cardiac myocyte size and the extent of coronary microvasculature.3,4 Different forms of hemodynamic stress (hypertension, aortic stenosis, coartation of the aorta, mitral regurgitation, and myocardial infarction, among others) increase intraventricular pressure or volume and lead to a hypertrophic response.5 A prolonged increase in wall stress may result in progressive ventricular dilation and myocardial decapsulation owing to ongoing myocyte death and fibrosis and, ultimately, heart failure and death.5,6,7 This pathological progression demonstrates a mismatch between oxygen supply and demand, as the extent of cardiomyocyte hypertrophy is not matched by a corresponding increase in the arterial blood supply.3

The human heart contains an estimated 2 to 3 billion cardiac muscle cells, but they account for fewer than a third of the total number of cells in the heart. The balance includes a broad array of additional cell types, including smooth muscle and endothelial cells of the coronary vasculature and the endocardium, fibroblasts and other connective tissue cells, mast cells, and immune system–related cells. Recently, pluripotent cardiac “stem cells” have also been identified in the heart.8 These distinct cell pools are not isolated from one another within the heart but instead interact physically and via a variety of soluble paracrine, autocrine, and endocrine factors (summarized in Figure 1). Thus, to fully understand the biology and pathobiology of the heart, the influences of this cellular crosstalk must be considered. In this review, we discuss new insights into molecular regulation of a myocardial hypertrophic response, focusing on the contribution of cell-cell crosstalk in the heart to this process.

Cardiac Myocytes

The differences between exercise- and pressure-induced hypertrophy exemplify the profound importance of extrinsic factors as determinants of myocardial morphology and function. These factors can be either physical (myocardial wall tension, myocyte stretch, etc) or molecular/chemical (growth factors, cytokines, and other circulating or locally produced bioactive molecules). In addition to directly affecting myocytes, the same factors can also affect the nonmyocyte cell populations in the heart. Thus, in cardiac responses to a specific physiological or pathophysiological stimulus, intrinsic signaling pathways within the myocytes and crosstalk between myocytes and other cell populations within the heart play crucial and interdependent roles.

The sine qua non of myocardial hypertrophy is an increase in cardiac myocyte size rather than an increase in cell number.9 This increase in size is generally due to an increase in the number of sarcomere units within each myocyte. The alignment of these additional sarcomeres either in series or in parallel within the cell defines whether thicker or more elongated myocytes result. Multiple intracellular signaling pathways and molecular effectors are involved in the regulation of cardiomyocyte hypertrophy, including G-protein isoforms, calcineurin, insulin-like growth factor (IGF)-I, fibroblast growth factors (FGFs), transforming growth factor (TGF)-β, Ras GTPases, mitogen-activated protein kinase cascades, histone deacetylases, and a repertoire of transcription factors (eg, nuclear factor of activated T cell, GATA motif binding factor 4 (GATA4), nuclear factor-κB, monocyte enhancer factor-2, serum response factor).5 The ultimate result of the action of this panoply of players is the promotion of protein synthesis, assembly of additional sarcomeres, and activation of the fetal cardiac gene program (eg, atrial natriuretic factor, brain natriuretic factor, β-myosin heavy chain).

The type of hypertrophy that results is likely determined by a complex crosstalk between these various intracellular signaling pathways, with a preponderance of specific signaling events directing specific patterns of cardiac hypertrophy. Recently, for example, physiological hypertrophy was linked

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of the connexin family have been shown to play a crucial role in determining impulse conduction and the heart morphogenesis. Global deletion of connexin43 in mice causes neonatal death from conotruncal malformation and outflow obstruction. Both heterozygous and homozygous global deletion of connexin40 in mice results in developmental defects in the heart, including double-outlet right ventricle, tetralogy of Fallot, and various endocardial cushion defects. The specific importance of connexin43 in myocardial gap junctions was further established by cardiomyocyte-specific deletion studies that demonstrated postnatal lethality with no survival of homozygous knockout pups beyond postnatal day 16. Interestingly, although no morphological abnormalities were noted in these mice during embryonic development, ventricular hypertrophy and outflow tract abnormalities were observed after birth.

Gap junction remodeling, a set of molecular and functional changes that occur at the gap junction during myocardial hypertrophy, includes alterations in the expression and phosphorylation of specific connexins and lateralization of the gap junction from the intercalated disk. This results in altered impulse conduction but may also include other, yet undefined, effects on cell-cell communication. Thus, not enough is currently known to prove or disprove the involvement of gap junction communications in myocardial hypertrophy.

Cardiomyocyte-cardiomyocyte communication is clearly not the only context in which gap junctions and connexins play an important role in determining cardiac form and function. The developmental abnormalities associated with the loss of specific connexins during heart embryogenesis have been attributed, for example, to the role of gap junctions in the neural crest and neural tube. In addition, gap junctions in the proepicardium are purported to play a role in coronary development and patterning.

Although the role played by gap junctions in cell-cell communication has been characterized best in terms of communication between cells of the same type, gap junctions may also be involved in crosstalk between diverse cell types. They can form, for example, between cardiac myocytes and fibroblasts and therefore could conceivably play a role in the crosstalk between these 2 cell types in the intact heart. Myoendothelial gap junctions also form between smooth muscle cells and endothelial cells in blood vessel walls. They may play a role in vascular physiology and remodeling and may be involved in specific pathological processes affecting the vasculature such as atherosclerosis or vascular remodeling responses to altered hemodynamic loads.

The third type of cardiomyocyte-cardiomyocyte communication, communication via adhesion complexes, also involves cell-cell contact. Unlike gap junctions in which ions and small molecules are exchanged between cells, adhesion complex communications involve intracellular signaling cascades that are triggered by cell-cell or cell-matrix engagement of specific proteins in these complexes. This type of signaling can alter myocardial responses to growth factors, thereby modulating cardiac growth and hypertrophy. These interactions are complex, and most emphasis currently is on the cell-matrix rather than cell-cell adhesion-based signaling. This subject is discussed further in subsequent sections dealing with myocyte-matrix interactions and crosstalk.
Adhesion complexes, cell-cell interaction, and cell-matrix interaction often involve shared pathways and molecular machinery. For example, cardiac myocyte–specific deletion of vinculin, a multiligand protein that links the actin cytoskeleton to the cell membrane, leads to dilated cardiomyopathy and sudden death. However, it is also involved in connecting matrix adhesion to the intracellular cytoskeleton and in preservation of intercalated disk structure, including organization of gap junctions and the distribution of connexin43.

Myocytes-Endothelium Communications: Monologs or Dialogs?

As secretory cells, cardiac myocytes are the source of multiple paracrine signals that can affect the coronary vasculature. Some of these—ET-1, FGF2, urocortin, adenosine, and the enzyme heme oxygenase, to name a few—regulate the vascular tone coordinating myocardial requirements for oxygen and nutrients with the blood flow. ET-1 is a powerful vasoconstrictor, whereas adenosine and urocortin are equally powerful vasodilators. FGF2, in addition to its growth factor and vasoconstrictor, whereas adenosine and urocortin are equally powerful vasodilators. FGF2, in addition to its growth factor properties, has the ability to regulate vascular tone in an as-yet poorly understood manner. Finally, heme oxygenase can modify vascular tone via regulation of carbon monoxide levels.

In addition to the dynamic regulation of the vasculature, cardiomyocyte paracrine signaling can affect long-term growth and development of coronary arterial, venous, and lymphatic trees. Among these, the most important are probably vascular endothelial growth factors (VEGFs), but others also playing a role include multiple FGF, platelet-derived growth factor (PDGF), and TGFβ family members; monocyte chemoattractant protein-1; hepatocyte growth factor (HGF); midkine; angiopoietins; and others, probably including several yet-to-be-identified factors.

Cardiac myocyte–specific deletion of VEGF-A results in variable embryonic lethality and hypovascular thin-walled hearts, suggesting a need for adequate coronary vasculature to complete myocardial morphogenesis. The mice that survive to adulthood have significant cardiac dysfunction and decreased myocardial vessel density. Of particular interest is the fact that although cardiac myocytes represent fewer than a third of all cells in the heart, cardiomyocyte-specific deletion of the VEGF-A gene results in a decrease in whole-heart VEGF mRNA synthesis to <15% of normal, underscoring the crucial role of cardiomyocytes as sources of this growth factor in the heart. VEGF production is increased substantially in the ischemic myocardium, and the vasculature in ischemic heart exhibits greater sensitivity to VEGF- and other growth factor–induced vasodilation.

Cardiomyocyte–vascular signaling plays a critical role in the vascular adaptations that occur during myocardial hypertrophy, and a failure of the vasculature growth to match the myocyte growth can lead to progressive cardiac dysfunction (Figure 2, left). During hypertrophic growth, for example, there is a requirement for a commensurate growth of the coronary vasculature to provide adequate oxygen and nutrient delivery to the greater cardiac mass. In addition, a decrease in the vascular cell/myocyte ratio could theoretically also modify the biology of cardiac muscle by reducing the availability of paracrine factors derived from vascular cells that “speak to” cardiac muscle (see below).

Exemplifying the importance of a balance between cardiac growth and vascular growth are studies done in genetically engineered mice in which cardiac hypertrophy was induced by expression of Akt1. During postnatal development, heart growth is significantly modulated by nutritional status and Akt1 signaling in response to growth factors. Transgenic overexpression of activated Akt1 in cardiomyocytes resulted
in a varied spectrum of phenotypes, from cardiac hypertrophy with preserved systolic function to cardiac dilatation and failure.\textsuperscript{36} A crucial determinant of whether cardiac function is preserved during Akt1-induced hypertrophy is the ability of coronary angiogenesis to keep pace with the increase in cardiac mass. To demonstrate this in a more direct manner, a tetracycline-inducible cardiac myocyte–specific Akt1 transgenic mouse model was used. Short-term (2 weeks) cardiac myocyte–specific induction of Akt1 expression resulted in physiological hypertrophy that was accompanied by commensurate myocardial angiogenesis, driven in part by myocyte-derived VEGF and angiopoietin-2.\textsuperscript{37} Akt1 activation for longer periods of time, however, resulted in a disproportional increase in cardiac mass relative to the extent of angiogenesis. This disproportion growth was associated with the development of heart failure, presumably on the basis of an inadequate blood supply to support the hypertrophic ventricle. This exemplifies the importance of coordination between cardiac muscle and the coronary vasculature in the maintenance of cardiac function and suggests that angiogenic adaptation is not limitless.\textsuperscript{38} Whether this limitation is due to a hypertrophy-associated diminution in myocyte production of specific growth factors and cytokines or, perhaps, to increased production of molecules with antiangiogenesis activity remains unclear.

Myocardial infarction is another clinical setting in which the importance of cardiac myocyte–derived factors influencing the vasculature is in evidence. In fact, there is strong evidence that an important mechanism whereby cell therapy may be beneficial after the infarction is by providing and replenishing growth factors and cytokines that can no longer be made by those cardiac myocytes that have been lost during infarction.

Paracrine and autocrine factors are involved in many aspects of cardiac repair after infarction, including maintenance and reparative growth of the coronary vasculature, remodeling of the extracellular matrix (ECM), and possibly maintenance of the viability of those cardiomyocytes that have survived in the infarct and peri-infarct zones. Exemplifying this is follistatin-like 1 (fstll), a secreted cardioprotective factor that is highly expressed in the myocardium in response to pressure overload and myocardial infarction.\textsuperscript{39} Fstll acts in an autocrine/paracrine manner in a positive feedback loop that promotes myocyte survival through an Akt-mediated signal. Interestingly, Fstll expressed in skeletal muscle in the setting of hind-limb ischemia enhanced angiogenesis via an Akt–endothelial nitric oxide (NO) synthase pathway.\textsuperscript{40} Fstll is different from other members of follistatin family that act as extracellular binding partners of TGFβ superfamily. Instead, Fstll exerts its cardiovascular protective effects by a receptor-mediated mechanism. A recent in vitro study identifies DIP2A (Disco-interacting protein 2 homolog A), a novel cell-surface receptor, as binding partner for Fstll and a mediator of Fstll-induced Akt activation in endothelial cells and cardiomyocytes.\textsuperscript{41} These data suggest that Fstll–DIP2A signaling is involved in cell communication in the heart and may also play an important role in mediating postinfarction coronary angiogenesis.

### Transcriptional Coregulation of Cardiomyocyte Growth, Metabolism, and Coronary Vascular Growth

The many cellular “conversations” in the heart must be coordinated to ensure that cell–cell cross talk directs appropriate biological responses, and that various cell types respond in a harmonious fashion to altered environmental factors to which the heart may be exposed. Transcription factors can act as the orchestral conductors in this context, responding to external stimuli and paracrine messages from other cells and altering the expression of paracrine and autocrine factors produced by the cell in which they reside. One example of such a transcription factor is the hypoxia-inducible factor 1α (HIF1α). HIF levels increase in response to hypoxia and ischemia, altering the expression of numerous proteins, including angiogenic factors, vasomotor tone–determining peptides, proteins that can alter the adhesion characteristics of the endothelium, those that regulate cardiac myocyte glucose uptake and metabolism, and even those that promote cardiomyocyte survival.\textsuperscript{42,43} Genes under transcriptional control by either HIF1 or HIF2α include all the glycolytic enzymes, the Glut1 glucose transporter, VEGF, PDGF-B, HGF, TGFβ1, inducible NO synthase, ET-1, heme oxygenase, connective tissue growth factor (CTGF), and many others. As such, HIF-mediated transcriptional responses coordinate a broad array of vascular and myocyte responses to ischemia.

Another example of a broad transcriptional regulator is GATA4, a transcription factor that modulates cardiomyocyte differentiation and adaptive hypertrophic response in the adult heart. Conditional transgenic expression of GATA4 in cardiomyocytes led to an augmentation of myocardial angiogenesis, increased coronary flow, and perfusion-dependent cardiac contractility.\textsuperscript{44} Interestingly, GATA4 transgene expression induced angiogenesis even at a low level of expression, but only mice with high GATA4 expression showed increases in cardiac mass and myocyte size. This suggests that GATA4-induced angiogenesis was independent of hypertrophic response and that the absolute levels of GATA4 expression determined whether concomitant angiogenesis and hypertrophic cardiac growth occur together or angiogenesis occurs alone. The angiogenic effect was mediated in large measure by GATA4-enhanced VEGF-A expression in cardiomyocytes through direct regulation of the VEGF-A promoter and was reversible with GATA4 cessation, indicating that a constant elevation of GATA4 was required.\textsuperscript{45}

### The Endothelium

The vasomotor control of coronary arteries plays a critical role in maintaining an adequate supply of oxygen to the myocardium in response to physical exercise or hemodynamic stress. The ability of coronary vasculature to dilate and increase the blood flow in the heart results from a plethora of vasodilator and vasoconstrictor factors generated under neurohumoral, endothelial, and metabolic influences. Endothelium releases NO, ET-1, AngII, prostaglandins, procoagulant and anticoagulant factors, and various growth factors, including FGF, VEGF, and PDGF-BB, that can affect numerous parameters of myocardial and vascular function. VEGF, in particular, is a powerful vasodilator.\textsuperscript{46}

In addition to its well-understood role in the regulation of vasomotor tone and thrombosis, endothelium plays a role in regulation of the heart size.\textsuperscript{47} Several studies support the notion that the increase in heart vasculature not only may support cardiomyocyte hypertrophy but also may actually induce this process (Figure 2, right). For instance, thyroid hormone admin-
istration in rats increased vessel density in the heart, which was later followed by an induction of a physiological hypertrophy and enhancement of ventricular systolic function. This angiogenic response to thyroxine treatment was related in part to an early upregulation of FGF2 expression.

The link between angiogenesis and myocardial hypertrophy was addressed in another study in which an angiogenic peptide (PR39) conditionally expressed in myocardium induced myocardial hypertrophy in the absence of any external stimuli. PR39 transgene expression for 3 weeks in the adult mouse heart led to a significant increase in endothelial cell mass and endothelium/myocyte ratio with no changes in heart size. However, 3 weeks later, there was a significant increase in heart size that returned the endothelium/myocyte mass ratio to prestimulation levels. The heart enlargement was due to an increase in cardiomyocyte size, and it was significantly but not completely prevented by concurrent treatment with the endothelial NO synthase inhibitor N-nitro-l-arginine methyl ester, thus indicating that an NO-dependent endothelium paracrine signal is responsible for about a half of the observed effect.

The mechanism by which NO induces cardiomyocyte hypertrophy is not clear and is the subject of active investigations. One likely possibility is the role played by NO in the “N-end rule pathway,” a ubiquitin-dependent proteolytic degradation of intracellular proteins in which destabilization of N-terminal residues functions as an essential determinant of signal degradation. Recently, a negative regulator of G proteins type 4 (RGS4) was identified as a substrate for the N-end rule pathway that suggests that NO may control Gαq-protein–induced hypertrophic signaling by changes in RGS4 levels. It would be reasonable to hypothesize that low NO levels favor RGS4 stabilization by preventing ubiquitin-dependent degradation and thereby blunting Gα-mediated signaling, whereas high NO levels, as a result, for example, of an increased endothelial cell mass, would favor RGS4 ubiquitination and derepression of the hypertrophic program.

Transgenic overexpression of VEGF-B in the heart induced an increase in vessel diameters rather than an increase in vessel density that was accompanied by increases in cardiomyocyte size and heart mass. The total myocardial endothelial mass appears to be an important regulator of heart function. A reduction in cardiac VEGF levels by a conditional cardiomyocyte-specific expression of a VEGF trap reduced vessel density, leading to hypoperfusion and myocardial hibernation. The effect was reversible, with the heart fully recovering once the VEGF trap expression was discontinued and the coronary vessel density returned to normal.

It is now well accepted that an increase in capillary density is important for the development of physiological cardiac hypertrophy, whereas a reduction in the capillary bed size underlies the transition from a compensated to an uncompensated heart failure. VEGF trap administration during pressure overload accelerates heart failure progression, presumably because of inhibition of compensatory growth of the vascular bed or possibly a reduction in the size of the existing vasculature. Similarly, reduced VEGF expression during sustained pressure overload as a result of p53 expression–induced inhibitory effect on HIF1α activity, contributes to functional decompensation of myocardial hypertrophy. On the other hand, p53-deficient mice exposed to pressure overload demonstrate a robust compensatory hypertrophic response, improved systolic function, and increased capillary density.

Endothelium is also capable of secreting factors that support cardiomyocyte compensatory response to hemodynamic stress. One of these is neuregulin-1 (NRG-1), a member of the EGF family. The role played by NRG-1 in adult heart accidentally came to light when trastuzumab (Herseptin), an inhibitory antibody against the NRG receptor erythroblastic leukemia viral oncogene homolog 2 (ErbB2) used to treat mammary carcinomas, was discovered to induce cardiomyopathy in treated patients. NRG/ErbB signaling is indispensable during cardiac and neuronal development. In the adult heart, NRG-1 expression is restricted to the endothelial cells adjacent to cardiomyocytes, whereas its tyrosine kinase receptors ErbB2 and ErbB4 are expressed on cardiomyocytes. In response to pressure overload, NRG-1/ErbB expression first increases during the compensatory stage of concentric growth and then decreases as the heart begins to fail.

The link between these changes in NRG-1/ErbB expression and hypertrophy/hemiation progression is not clear. Potential mechanism include direct stimulation of cardiomyocyte hypertrophy via Erk1/2 and PI3K/Akt pathways, direct myocardial toxicity via mitochondrial and reactive oxygen species pathways, or possibly effects on the vasculature. A newly described mechanism of Erk1/2 autophosphorylation at Thr188 integrates a crosstalk between G-protein signaling and the NRG-1/ErbB pathway in response to pressure overload. As result of NRG-1 stimulation, activated ErbB recruits Gβγ to Raf1-Mitogen-activated protein kinase (MAPK) cascade, which in turn causes intermolecular autophosphorylation of Erk1/2 at Thr188, Erk1/2 nuclear translocation, and activation of the hypertrophic growth program. Interestingly, increasing NRG-1/ErbB4 signaling by NRG-1 injection or ErbB4 expression may induce cardiomyocyte proliferation and promote myocardial regeneration after myocardial infarction.

Another recently identified important neurohumoral regulator secreted by the endothelium is apelin. Apelin acts via its G-protein–coupled receptor apelin receptor (APJ) and likely plays an important role in cardiovascular physiology and pathology by opposing actions of the rennin-angiotensin system. Thus, whereas AngII increases vascular tone and raises blood pressure, apelin promotes vasodilatation through an NO-dependent mechanism, and its expression is induced in response to hypoxia in the ischemic heart. In the heart, apelin is expressed primarily in the endothelium and APJ is expressed on cardiomyocytes, smooth muscle cells, and endothelial cells, suggesting a paracrine mode of signaling.

Several reports suggest a contribution of apelin to the pathophysiology of human heart failure and associate its deficit with myocardial decompensation. Interestingly, in hypertensive cardiac hypertrophy, the levels of apelin and APJ are maintained during the compensated stage and decline as heart failure sets in. This may be due to an inhibitory effect of AngII because the Angiotensin II receptor type 1 (AT1R) blocker telmisartan restores apelin/APJ expression.

The Fibroblasts Cardiac fibroblasts account for two thirds of the cell mass of the heart and produce the majority of ECM proteins, including...
fibronectin, laminin, and collagen I and III in the interstitium and around the blood vessels. Fibroblasts can sense and respond to biomechanical stress. A number of humoral factors can affect fibroblast activation and deposition of ECM, including AngII, ET-1, TGFβ, FGF2, and IGF-1.77–79 The resultant fibrosis can alter intercellular crosstalk and impairs myocyte contractility, oxygenation, and metabolism. It can also result in fibroblasts differentiating into myofibroblasts, cells that express smooth muscle-type contractile proteins and exhibit increased proliferative and secretory properties.80

In addition to stimulation of proliferation of resident fibroblasts, cardiac fibrosis may result in endothelial cells undergoing endothelial-mesenchymal transformation and contributing in this manner to the total pool of cardiac fibroblasts.81 This process is mediated by TGFβ1 and can be inhibited by bone morphogenic protein 7, a TGFβ superfamily member known to antagonize TGFβ signaling.81,82

Bidirectional fibroblast-cardiomyocyte crosstalk plays a pivotal role in myocardial hypertrophy. AngII, via the AT1 receptor, induces TGFβ expression by cardiomyocytes and cardiac fibroblasts. TGFβ, in turn, promotes cardiac hypertrophy by activation of Smad proteins and TGFβ-activated kinase-1. At the same time, it induces fibroblast proliferation and deposition of ECM proteins, leading to fibrosis as described above.71 Recently, CTGF, a TGFβ-activated factor, was associated specifically with fibroblast proliferation and ECM production in the setting of myocardial fibrosis.83 CTGF is expressed by cardiac fibroblasts and cardiomyocytes, and its expression is negatively regulated by 2 cardiac microRNAs, miR-133 and miR-30.84 Although miR-133 is expressed specifically in cardiomyocytes, miR-30 is expressed in both cardiac fibroblasts and myocytes. MiR-133 knockout mice develop excessive fibrosis and heart failure, whereas miR-133 knockdown also causes cardiac hypertrophy with impaired cardiac function.85,86 These findings suggest that the reduction of miR-133 expression derepresses the prohypertrophic program in cardiomyocytes and supports cardiomyocyte–cardiac fibroblast crosstalk in promoting fibrosis in the heart.

Interestingly, although communication between cardiac fibroblasts and myocytes promotes myocyte hypertrophy in the adult heart, it promotes myocyte proliferation during embryonic development. The latter is thought to be mediated in part by embryonic cardiac fibroblast secretion of fibronectin, collagen, and heparin-binding EGF-like growth factor that collaboratively interact and promote cardiomyocyte proliferation via β1-integrin signaling.87 Thus, a switch in the fibroblast genetic program allows them to drive cardiomyocyte proliferation during embryonic development and myocyte hypertrophy in postnatal life.

Cell-Matrix Interaction and Adhesion-Associated Molecules in Cardiac Crosstalk

One of the most important ways of transducing a mechanical load to the ventricle is by altering cell adhesion to the ECM.88 Integrins, together with a number of associated cytoskeletal proteins, connect the sarcomeric contractile apparatus to the ECM across the plasma membrane and trigger intracellular signaling pathways that activate the cardiomyocyte hypertrophy program. Overexpression of a muscle-specific integrin isoform β1D in neonatal cardiomyocytes in vitro can augment the hypertrophic response induced by α1 adrenergic stimulation, whereas suppression of integrin signaling inhibits it.89 Moreover, cardiac myocyte–specific deletion of β1 integrin results in an abnormal cardiac function and impaired compensatory response to pressure overload–induced stress.90

Integrins work in concert with an array of effectors, including focal adhesion kinase, tyrosine phosphatases such as Shp2, and small GTPases such as Ras and Rho that can activate Akt and mitogen-activated protein kinase signaling pathways. Thus, Shp2 negatively controls focal adhesion kinase activation and limits hypertrophic growth by modulating the Akt/mTOR signaling pathway91,92 whereas Cdc42, a member of the Rho family of small GTPases, can act as an antihypertrophic switch by activating Jun N-terminal kinase signaling, thereby reducing nuclear factor of activated T-cell transcriptional activity in response to pressure overload.93 Integrins can also signal via a focal adhesion kinase–related nonkinase, which has the ability to buffer focal adhesion kinase signaling, attenuating cardiac hypertrophy.94 Several adaptor molecules involved in integrin-mediated signal were shown to be essential for hypertrophic response. For example, melusin interaction with the integrin β1 cytoplasmic domain is required for phosphorylation of glycogen synthase kinase-3β, which is needed for the prevention of heart failure in response to sustained pressure overload.95

As the result of crosstalk between integrins and growth factor signaling pathways, a complex synergistic mechanism controls the hypertrophic process.96 Thus, AngII and TGFβ stimulate integrin expression and localization97; in turn, integrins regulate TGFβ expression.98 Furthermore, angiopoietin-1 (an endothelial cell–specific regulator of vessel maturation) reduces cardiac hypertrophy by binding to integrins and activating integrin-linked kinase and Akt/ mitogen-activated protein kinase pathways in cardiomyocytes.99

In addition, integrin-mediated cell adhesion can be modulated by membrane-associated proteins such as the ADAMs (a desintegrin and metalloprotease) that can cleave specific matrix proteins and mediate adhesion complex shedding. ADAMs can also modulate expression and function of growth factor receptors and thus affect a wide variety of biological processes that are important in the heart, including angiogenesis and cardiac hypertrophy. Inhibition of ADAM12 function by a specific metalloproteinase inhibitor, for example, attenuates cardiac hypertrophy in mice, likely by inhibition of ADAM12-mediated shedding of heparin-binding epidermal growth factor receptor.100

Long-Distance Cell-Cell Communications

A myocardial hypertrophic response and the transition to heart failure are not determined solely by cell-cell communication in the heart and are controlled by endocrine signaling. Although some of these such as aldosterone and the renin-angiotensin system are well known, others are just beginning to be understood.
Adiponectin
Adiponectin, a circulating adipose tissue–derived cytokine that is downregulated in patients with obesity, has recently been described as a cardioprotective factor. This function of adiponectin in a hypertrophy-induced response to hemodynamic stress in the heart is related to increased AMP-activated protein kinase signaling and reduced activation of the Erk pathway. Although adiponectin may induce angiogenesis in the hind-limb ischemia model, no comparable effect has been observed in the myocardium, suggesting that the protective effect of adiponectin in this setting is related to its effect on cardiomyocytes.

From a clinical standpoint, the role of adiponectin in preventing heart failure is controversial. Although obesity is a risk factor for the development of heart failure, a higher body mass index and lower adiponectin levels were associated with an improved prognosis in patients with established chronic heart failure, whereas higher levels of plasma adiponectin were associated with a lower risk of myocardial infarction in men.

Calcitonin Gene–Related Peptide
Recent studies have begun describing important roles played by endogenous regulatory peptides members of calcitonin gene-related peptide family, adrenomedullin and intermedin/adrenomedullin-2. The calcitonin/calcitonin gene-related peptide family of peptides, widely distributed in various peripheral tissues, induces multiple biological effects. Adrenomedullin is secreted primarily by vascular cells and functions as a local autocrine or paracrine mediator, as well as a circulating hormone capable of inducing vasodilation, diuresis, and cardioprotection. In mouse embryos, adrenomedullin deficiency leads to lethality caused by vascular fragility, severe hemorrhage, and edema. In vivo and in vitro studies have shown that adrenomedullin inhibits myocyte hypertrophy, fibroblast proliferation, and ECM production and improves heart contractility, whereas systemic infusion of adrenomedullin is protective and beneficial in myocardial infarction, heart failure, and renal failure.

Intermedin/adrenomedullin-2 shares similar cellular and tissue distribution with adrenomedullin, and its predominant localization in hypothalamus, pituitary, and kidney is consistent with the role in central and peripheral regulation of water-electrolyte homeostasis. Intermedin/adrenomedullin-2 gene expression is upregulated in the failing heart, suggesting a possible antihypertrophic effect.

Conclusions
It is becoming clear that in solid organs different cell types sense different stimuli and integrate their responses to them. Thus, no cell is an island, particularly in the heart. The many cellular “conversations” in cardiac tissues must be coordinated to ensure that the cell-cell crosstalk directs integrated biological responses to various stimuli. Cells in the heart use a number of communication channels to communicate with their neighbors. Of these, the most extensively studied are paracrine and autocrine signaling, which uses a long list of secreted factors such as VEGF, FGF, TGFβ, ET-1, AngII, PDGF, IGF, HGF, angiopoietins, NO, NRG-1, apelin, and Fstl-1. The cell-cell endocrine crosstalk from beyond heart boundaries using molecules such as adiponectin...
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Disclosures

None.

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