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Crossovers between functional and proliferative signaling: key to understanding the pathophysiology and management of heart failure

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Failing heart - a clinical drama

William Withering, who discovered the benefits of digitalis, provides several clinical histories that describe the terrible suffering seen in end stage heart failure. His description of a woman "between forty and fifty years of age", who almost certainly had rheumatic heart disease, provides remarkable insights into the pathophysiology that operates in these patients: “I found her nearly in a state of suffocation; her pulse extremely weak and irregular, her breath very short and laborious, her countenance sunk, her arms of a leaden colour, clammy and cold. She could not lye down in bed, and had neither strength nor appetite but was extremely thirsty. Her stomach, legs and thighs were greatly swollen; her urine very small in quantity, not more than a spoonful at a time, and that very seldom.” [1] Similar descriptions, which can be found in the many meticulously documented case reports published up to the middle of the 20th Century [reviewed in 2-4], illustrate a patho-physiology whose complexity has only recently been appreciated [5].

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Direct and indirect consequences of impaired pump function

Several of the clinical problems in Withering's patient can be attributed directly to the pump dysfunction. These include the weak pulse and peripheral cyanosis, which tell us that she had a low cardiac output, and the irregular pulse, which is almost certainly due to atrial fibrillation. Her dyspnea and orthopnea are attributable to pulmonary congestion, most likely caused by mitral stenosis that impeded blood flow out of her lungs. Other clinical findings, however, are not direct consequences of the defective cardiac pump, but instead reflect a more subtle etiology. Her sunken countenance and anorexia are characteristic of cardiac cachexia, which is due in part to elevated cytokine levels, while her lack of strength probably results from the skeletal muscle myopathy commonly seen in heart failure. Other features noted by Withering are almost certainly caused by the neurohumoral response to her low cardiac output [6-7]. The latter include the cold, damp extremities, the result of peripheral vaso-constriction and sympathetic activation of her sweat glands; fluid retention and oliguria, due in large measure to renal vasoconstriction and aldosterone; and thirst, which almost certainly reflects a central action of vasopressin. Both the impaired ability of the heart to pump and the neurohumoral response to the low cardiac output occur when the function of existing body systems is altered. For this reason, these clinical features in Withering's patient can be viewed as *functional* abnormalities.

A very different type of response in patients with heart failure became apparent when autopsy examinations revealed changes in the size and shape of the diseased hearts. Understanding of these structural changes became possible in 1628, when Harvey discovered that blood flows in a circle. Mayow, in 1674, appears to have been the first to recognize that obstruction to blood flow out of the heart causes ventricular dilatation [for review, see ref. 4]. An even more important insight was published by Morgagni, who in describing a patient with mitral stenosis, notes the causal link between chronic hemodynamic overloading and cardiac hypertrophy: "…for the valvulae mitrales being become bony, and greatly diminishing the orifice by which blood goes into the left ventricle… the columnae, and fibres, of the [right] ventricle, were become very thick… because a greater thickness of the muscles is the consequence of their more frequent and stronger actions. Without doubt, these parts of the heart must have been constantly and vehemently contracted, and exercis'd, in their effort to thrust on so great a quantity of stagnating blood into the pulmonary vessels, which, by reason of the very difficult entrance into the left ventricle, did not readily admit it…" [8]

These and other observations initiated more than a century of discovery that highlighted changes in the size and shape of the failing heart. Corvisart, in 1801, contrasted the clinical manifestations associated with dilatation (eccentric hypertrophy) of the left ventricle and those caused by concentric hypertrophy. It quickly became apparent that dilatation is a progressive condition, now referred to as remodeling. Concentric hypertrophy, on the other hand, was initially thought to be an adaptive response that protects the patient from the adverse effects of dilatation. However, toward the end of the 19th Century, it became clear that hypertrophy, like dilatation, is associated with progression, and so can be deleterious.

Architectural changes in the failing heart, like the neurohumoral response, represent indirect consequences of the pump abnormality. However, unlike the *functional* responses described above, hypertrophy and remodeling are not due simply to changes in preexisting cells, but instead are caused when transcriptional signaling alters the composition, size, shape, and structure of cardiac myocytes and non-myocytes. These architectural changes, therefore, represent *proliferative* (*transcriptional*) responses.

Functional and proliferative responses of the failing heart

Functional and proliferative signal transduction cascades operate over different time courses [9]. The former rapidly stimulate chronotropy, inotropy and lusitropy, thereby facilitating short-term "fight and flight" responses by increasing cardiac output. In contrast, proliferative signaling activates more slowly developing mechanisms that allow the overloaded heart literally to "grow its way out of trouble" (Fig. 1).

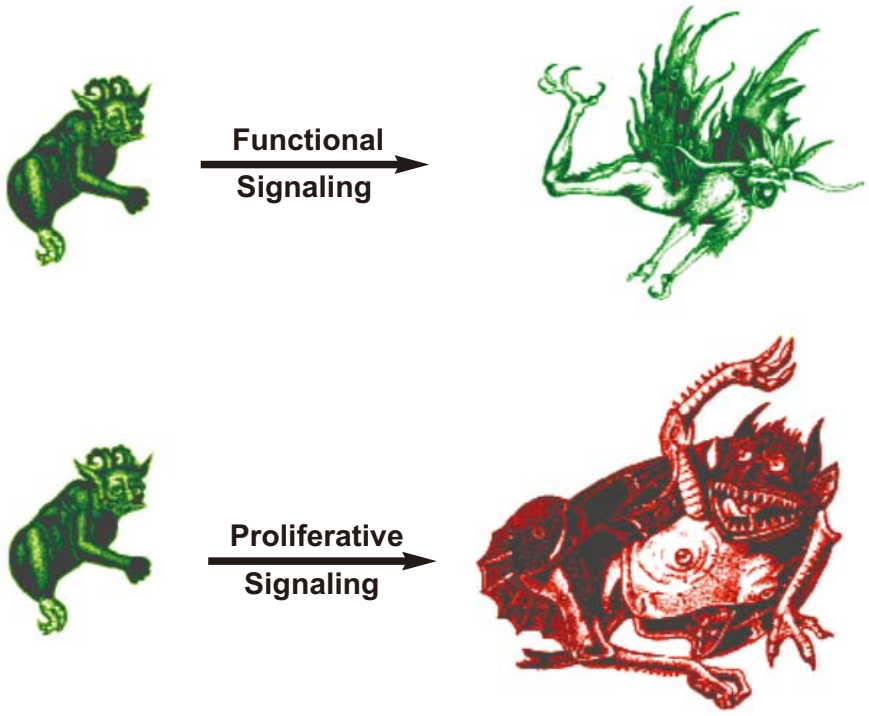

Fig. 1 Functional signaling, which modifies the behavior of preexisting structures by post-translational modifications, enables an organism to survive using such responses as "fight or flight". In the case of proliferative signaling, transcriptional changes allow organisms to "grow their way out of trouble". Modified from Katz, Physiology of the Heart (3rd Ed), Philadelphia, Lippincott/Williams & Wilkins, 2001.

Although β_1-adrenergic stimulation, by increasing heart rate, contractility and relaxation, is the major mediator of the functional response that increases cardiac output, sustained adrenergic drive in the patient with heart failure worsens long-term prognosis (see below). A similar dichotomy is seen in the case of proliferative signaling; whereas the hypertrophic response to sustained overload initially normalizes wall stress and so is beneficial, over the long-term this response shortens survival. It is noteworthy that the maladaptive features of the growth response to overload came as a surprise to many modern investigators, even though this fact was clearly understood by the great clinical pathologists of the 19th Century [for review, see ref. 4].

The cardiomyopathy of overload

The deleterious consequences of cardiac hypertrophy had attracted little notice during the first half of the 20th Century, due largely to developments in hemodynamic physiology. It was not until the role of ventricular architecture in determining wall tension (the Law of Laplace) was rediscovered in the 1950s [10] that efforts were made to determine whether developed stress is abnormal in patients with valvular heart disease. These studies, which showed that overload-induced hypertrophy could normalize wall stress [11-13], appeared to confirm the then prevalent (and early 19th Century) view that this growth response is beneficial. However, Meerson's confirmation of the late 19th Century view that overload-induced hypertrophy shortens survival [14] and the finding that myofibrillar ATPase activity is reduced in failing human hearts, a change that would reduce myocardial contractility [15], showed that hypertrophy can also be maladaptive.

Evidence that the same signaling processes which stimulate hypertrophy might also accelerate myocardial cell death indicates that the hypertrophic response to chronic overload has features that are similar to a cardiomyopathy [16]. This concept, of a

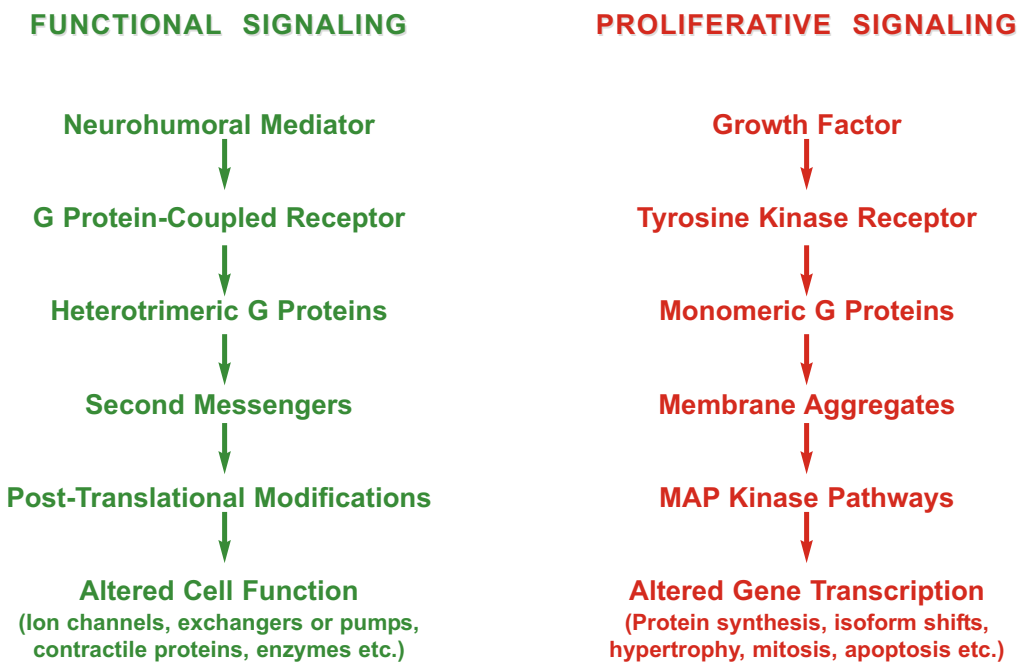

Fig. 2 Functional and proliferative signaling, once believed to be mediated by two entirely different mechanisms as shown in this figure, are now recognized to involve many "crossovers" between steps in these signal transduction cascades. Modified from Katz, Physiology of the Heart (3rd Ed), Philadelphia, Lippincott/Williams & Wilkins, 2001.

"cardiomyopathy of overload", states that proliferative signaling initiates a vicious cycle by causing myocardial cell death, which increases the load on surviving myocytes, which stimulates further proliferative signaling, which causes more cell death. Mechanisms that initiate this vicious cycle in the failing heart include cell deformation, caused by increased stretch and wall stress, which can stimulate cell adhesion molecules and cytoskeletal proteins to activate proliferative signal transduction cascades [for review, see ref. 5]. Maladaptive consequences of these proliferative signals include architectural changes that exacerbate energy starvation, cell elongation which accelerates remodeling, and stimulation of pathways that induce apoptosis. The practical importance of the concept of a "cardiomyopathy of overload" lies in the fact that most mediators of the neurohumoral response, in additional to stimulating functional responses, also activate proliferative responses that contribute to the poor prognosis in patients with heart failure. This means that neurohumoral inhibitors can help alleviate the vicious cycle initiated by chronic overload.

Crossovers between functional and proliferative signaling in the failing heart

As recently as the early 1990s, functional and proliferative responses were believed to be effected by entirely different signaling pathways (Fig. 2) [17]. It is now apparent, however, that a number of signaling molecules initiate both types of response, so that there are many crossovers between functional and proliferative signaling. Neurohumoral mediators like norepinephrine and angiotensin II, which bind to G protein-linked receptors, were initially identified as mediating functional signals. It is now clear, however, that these extracellular messengers also modify proliferative responses once believed to be under the "exclusive" control of enzyme-linked receptors that activate transcriptional responses [for review, see 18]. Conversely, tyrosine kinase receptors once thought to mediate only proliferative responses are now recognized to have

functional effects, such as modifying myocardial contractility. These overlaps are amplified by crossovers between many of the signal transduction cascades that operate within cells.

The importance of abnormal proliferative signaling in the failing heart was recognized only recently, when long-term clinical trials that examined the treatment of heart failure made it clear that efforts to correct the obvious hemodynamic disorders often worsen long-term prognosis. Vasodilators, introduced to unload the failing heart, were found in virtually every short-term clinical study to increase cardiac output and improve energetics; however, most direct acting arteriolar dilators, including α-adrenergic blockers, short-acting L-type calcium channel blockers, minoxidil, prostacyclin, ibopamine, moxonidine, flosequinan, and phosphodiesterase inhibitors worsen long-term prognosis [for review, see refs. 5, 19]. The explanation may be that although providing an immediate clinical improvement, by lowering blood pressure these vasodilators also increase levels of neurohumoral mediators like norepinephrine, angiotensin II, and endothelin, all of which can evoke deleterious long-term proliferative responses. Among the vasodilators, only angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and a drug combination that includes isosorbide dinitrate, all of which have antiproliferative effects, have so far been shown to have a survival benefit [19]. This benefit, therefore, appears to be due to the antiproliferative effects of these drugs, rather than their ability to reduce afterload [20-21].

Additional evidence for the importance of proliferative signaling initiated by the neurohumoral response is provided by the finding that β blockers improve long-term prognosis [22-25]. In spite of their negative inotropic action, which initially worsens the hemodynamic abnormality, these neurohumoral inhibitors inhibit proliferative signaling and so slow, and often reverse transiently, progressive dilatation (remodeling) of the failing heart [for review, see refs. 5, 26-28]. Conversely, in addition to a proarrhythmic effect, the deleterious effects of phosphodiesterase inhibitor inotropes [29-30] may include their ability to stimulate maladaptive proliferative responses. Another neurohumoral inhibitor recently found to prolong survival in patients with heart failure is spironolactone, which was introduced for the treatment of heart failure because of its short-term diuretic effect [31]. The long-term benefit may occur when this drug inhibits aldosterone-induced proliferative signaling in cardiac myocytes [32] and matrix cells [33].

Conclusions

It is now clear that heart failure is much more than a pump disorder. In most patients, the hemodynamic abnormalities are exacerbated by the neurohumoral response to reduced cardiac output, which increases fluid retention, peripheral vasoconstriction and cardiac stimulation. In addition to the clinical worsening caused by these functional responses, survival of patients with heart failure is limited by the deleterious consequences of cardiac hypertrophy. Maladaptive features of this growth response, which is initiated by chronic hemodynamic overloading, can be viewed as a "cardiomyopathy of overload".

The cardiomyopathy of overload, which is an important determinant of survival in patients with heart failure, can be activated by a number of proliferative stimuli; these include chronic mechanical deformation of the cardiac myocytes, cytokines, and peptide growth factors. This cardiomyopathy can also be exacerbated by mediators of the neurohumoral response, such as norepinephrine and angiotensin II. These extracellular messengers, once viewed mainly as activators of functional responses such as increased heart rate and contractility, also activate proliferative responses. Crossovers involving many steps of the intracellular signaling pathways also activate proliferative responses that, by stimulating remodeling, apoptosis and other features of maladaptive growth, play an important role in determining the poor prognosis in these patients. The improved survival observed in clinical trials of neurohumoral blockers like ACE inhibitors, angiotensin II receptor blockers, β blockers, and spironolactone can therefore be attributed in part to their ability to block deleterious proliferative signal transduction pathways.

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