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Review

Phenotypic plasticity of adult myocardium: molecular mechanisms

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Summary

Cardiac phenotypic plasticity (so-called cardiac remodelling, CR) is characterized by changes in myocardial structure that happen in response to either mechanical overload or a loss of substance such as that occurring after myocardial infarction.

Mechanosensation is a widespread biological process and is inextricably mixed with other transduction systems from hormones and vasopeptides, which ultimately produce post-translational modifications of transcription factors. The expression of the four main transcription factors during cardiogenesis is also enhanced as a link to foetal reprogramming.

CR results from re-expression of the foetal programme, which is mostly adaptive, but also from several other phenotypic modifications that are not usually adaptive, such as fibrosis. (i) The initial determinant is mechanical, and re-expression of the foetal programme includes a global increase in genetic expression with cardiac hypertrophy, re-expression of genes that are normally not expressed in the adult ventricles, repression of genes not expressed during the foetal life, and activation of pre-exisiting stem cells. Microarray technology has revealed a coordinated change in expression of genes pertaining to signal transduction, metabolic function, structure and motility, and cell organism defence. The physiological consequence is a better adapted muscle. (ii) During clinical conditions, the effects of mechanics are modified by several interfering determinants that modify CR, including senescence, obesity, diabetes, ischemia and the neurohormonal reaction. Each of these factors can alter myocardial gene expression and modify molecular remodelling of mechanical origin.

Finally, as compared to evolutionary phenotypic plasticity described in plants and insects in response to variations in environmental conditions, in CR, the environmental factor is internal, plasticity is primarily adaptive, and it involves coordinated changes in over 1400 genes. Study of reaction norms showed that the genotypes from different animal species are similarly plastic, but there are transgenic models in which adaptation to mechanics is not caused by hypertrophy but by qualitative changes in gene expression.

Key words: cardiac remodelling, phenotypic plasticity, foetal programme, myosin, energetics, heart failure, mechanoconversion.

Introduction

Molecular cardiologists, even clinical cardiologists, are familiar with phenotypic plasticity. They call it remodelling*. Myocardial and vascular remodelling have primarily a mechanical origin and an adaptive significance. Cardiac remodelling (CR) occurs in response to chronic mechanical overloading, and arterial remodelling is a response to permanent arterial hypertension (Lompré et al., 1979; Swynghedauw, 1999; Levy and Tedgui, 1999). CR leads to heart failure and, with cancer, is one of the major causes of death in our countries, so cardiac plasticity is a major public health problem. This review will only focus on myocardial remodelling (excluding the remodelling of coronary vessels).

This review will start from the most common clinical conditions†, namely CR occurring after myocardial infarction or chronic essential arterial hypertension, and will consider

*Remodelling qualifies changes that result in the rearrangement of normally existing structures. Although remodelling does not necessarily define a pathological condition, myocardial remodelling is usually restricted to diseased conditions. Remodelling concerns both the myocardium and the vessels. Although 'myocardial remodelling' is now a widely used term, from a historical point of view it was initially used by drug companies to describe the remodelling that occurs following myocardial infarction. The meaning of the word was subsequently extended and used to qualify pure mechanical overload, as well as hypertensive, familial hypertrophic, dilated cardiomyopathy… Transgenic manipulations, experimental or clinical hormonal intoxications are also able to remodel the myocardium (Swynghedauw, 1999).

†Every clinical condition can be experimentally reproduced; the most commonly used models of CR are myocardial infarction obtained by coronary ligation, which results in heart failure, and abdominal aortic stenosis, which creates a rather perfect model of compensatory hypertrophy.

the following. (i) The signals and pathways that inform the nucleus of the changes in mechanical conditions. (ii) The permanent phenotypic modifications that are caused by changes in gene expression; during the first stage of CR these modifications are basically adaptive with a normalized economy and the main trigger is mechanics. This is the compensated cardiac hypertrophy stage. (iii) Later on, other factors, such as susceptibility factors, aetiological parameters and the neurohormonal reaction, are prominent, CR becomes non-adaptive, and the first signs of heart failure appear. (iv) Perfect phenotype–environment matching for greatest adaptive value is always an insuperable strategy (Arnold, 1992), and heart failure is nothing more than an example of how perfect adaptation is never achieved in nature. (v) Finally, CR should be compared to other forms of phenotypic plasticity.

The initial events: sensors and signalling pathways

For the moment, it is impossible to decide whether, whatever the signal (mechanical or hormonal), the same pathways are activated, whether such a multiplicity indicates multiple but specific effectors, or whether specific pathways exist that result in specific gene expression. There are several reasons for such a confused situation. (i) Pure mechanical overload, i.e. a situation during which mechanical stress is not accompanied by a neurohormonal (including vasopeptide) reaction, is a rather rare condition. There are experimental designs in which the neurohormonal reaction has been minimized, but such a situation is quite exceptional in clinical settings, especially during post-myocardial remodelling. (ii) An important confounding factor is the fact that hormones and mechanics were probably activating the same pathways. (iii) Transgenic technology has been extensively utilized in an attempt to clarify the situation (MacLellan and Schneider, 2000). Nevertheless, whatever genes were manipulated, it was impossible to reproduce the entire cascade that follows the mechanical stress. (iv) Finally, there is evidence that during cardiogenesis the different transcription factors act synergistically in a combinatorial way (Bruneau, 2001). Nevertheless, this is, for the moment, not documented in cardiac overload.

Triggers

Mechanosensation is a large, diverse, biological process (e.g. osmotic stress in bacteria, roots growing under the influence of wind, hearing, touch, fluid shear stress) that is known to act through multiple pathways, including (i) changes in ionic fluxes through the activation of several stretch-activated channels (Blount, 2003), (ii) extracellular matrix-sensing receptors such as the integrin family and Z-line proteins; the transmission through the cytoskeleton is known to be stretch-specific and (iii) autocrine/paracrine mechanisms, including stretch activation of growth factors and angiotensin II secretion.

Hormones, vasopeptides, gas (NO, O_2 *via* gasotransmitters) may also directly activate transcription (Semenza, 2004), and mechanotransduction is, for the moment, inextricably mixed with the transduction systems of most hormones and vasopeptides through the G protein family.

Post-translational modifications

The mandatory intermediary step involves post-translational modifications of transcription factors, which include (i) mainly phosphorylations, through the Mitogen-Activated Protein Kinases (MAPK) superfamily (Bogoyevitch, 2000) or the calcineurin pathway, (ii) hydroxylations for Hypoxia-Induced-Factor-1 (HIF), oxygen being a rate-limiting substrate that

Table 1. *Myocardial expression levels or activities of several transcription factors (TF) in pressure overloaded hearts*

Transcription factors	Embryonic and/or foetal changes	Mechanical effects	Hormonal effects
GATA4	Disruption results in lethality	⇑ expression	⇑ under hormonal (α- and β-adrenergic) and vasopeptide (ET-1, angiotensin II) stimuli
MEF-2	Controls cardiac looping and right ventricle formation	⇑ expression	?
Csx/Nkx2-5	Disruption arrested looping morphogenesis	⇑ expression	⇑ under hormonal (α- and β-adrenergic) stimulus
HAND-transcription factors	eHAND plays a role in the differenciation of the left ventricle; dHAND is restricted to the right ventricle	⇓ expression	⇓ under hormonal (α-adrenergic) stimulus

The TFs selected are those known to regulate cardiogenesis during embryonic development [taken in part from information published elsewhere (Akazawa and Komuro, 2003)].

GATA4 regulates: α-MHC, Mlc1/3, cTNC, cTNI, ANP, CARP, cNCX1, cM2 R, A1 R, carnitine palmytoyl transferase expressions.

MEF2-binding sequences exist in CK, α-MHC, Mlc1/3, Mlc2v, sα-actin, SERCA, cTNT, cTNC, cTNI, desmin, dystrophin. MEF2 regulates calcium signalling.

Csx/Nkx2-5 regulates: Mlc2v, ANP, BNP, CARP, MEF2-C, eHAND/HAND1, N-myc, Iroquois homeobox gene 4, HOP, cα-actin, A1R, calreticulin, connexion 40, NCX1.

dHAND induces several expressions synergistically with the other transcription factors.

regulates the degradation of HIF-1 and the DNA binding properties (Semenza, 2004).

Ischemia is a major partner of CR because myocardial infarction is generally preceded by repeated episodes of acute or subacute myocardial ischemia, which modifies gene expression *per se* (Assayag et al., 1998), especially at the level of fibroblasts. The changes in gene expression are quite rapid and the mechanisms are likely to be post-transcriptionally regulated.

Increased expression of transcription factors

The expression of at least four transcription factors, GATA4, MEF2, Csx/Nkx2-5 and e/dHAND, is determinant during cardiogenesis. It is not surprising that these expressions are enhanced in cardiac overload as an intermediary step for the foetal reprogramming (Table 1, Fig. 1). The same activation is also observed in hormone-induced cardiac hypertrophy. Interestingly, the activation of some of these factors seems to be specifically linked to foetal reprogramming (Akazawa and Komuro, 2003) (see also Table 1). Epigenetic changes have not yet been explored, but there are suggestions that at least one of the transcription factors may influence histone acetylation (Bruneau, 2002). In addition, two studies, one on zebra fish, the other on chick embryo, have indicated a specific role of hemodynamics, as an epigenetic factor, during cardiogenesis (Reckova, 2003; Hove, 2003).

Compensatory cardiac hypertrophy

Molecular remodelling of the myocardium results from two groups of factors: (i) re-expression of the foetal programme, which is caused by mechanical overload and participates in the adaptational process during the compensatory phase, and (ii) several other phenotypic modifications, including fibrosis, apoptotic or non apoptotic cell deaths, and the phenotypic consequences of senescence, diabetes, ischemia, hormones or vasoactive peptides, which do not participate in the adaptational process and are major factors causing heart failure (Swynghedauw, 1999; Swynghedauw and Baillard, 2000).

Gene reprogramming

The initial determinant of cardiac remodelling is mechanical. The mechanical factor is equally active on cultured cardiocytes, isolated heart (Schreiber et al., 1970; Bauters et al., 1988) and *in vivo*. Mechanics directly activate protein synthesis and qualitative changes in genetic expression, and a hormonal stimulus is not a prerequisite for the development of cardiac hypertrophy, even if it is of secondary importance.

Mechanoconversion is mainly, and possibly only, caused by the re-expression of the foetal programme (Table 2). The main component of this programme is a global increase in gene expression that leads to hypertrophy. The first report of allelic modifications in cardiac overload was made in our group on

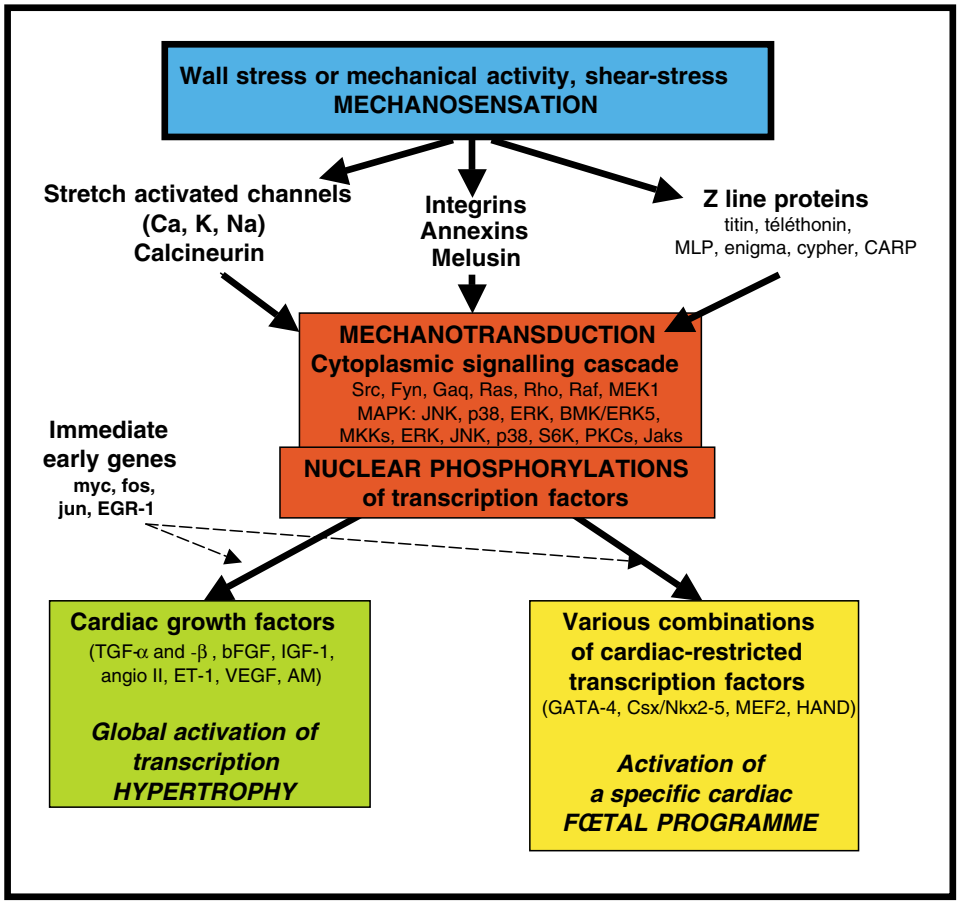

Fig. 1. Working hypothesis summarizing the relationships of molecular events that drive CR. This synopsis is drawn from several recent review articles (Swynghedauw, 1999; Bogoyevitch, 2000; Akazawa and Komuro, 2003; Sugden, 2003; Knöll et al., 2003; Barki-Harrington and Rockman, 2003; Katsumi et al., 2004). The hypothesis is based on the sequence of events proposed elsewhere (MacLellan and Schneider, 2000). It includes a mechanical trigger, a cytoplasmic cascade, and then a series of phosphorylations/dephosphorylations that finally activate several transcription factors. These factors are known to act synergistically in a combinatorial fashion. It is hypothesized that (i) the foetal reprogramming depends upon transcription factors expressed during embryogenesis, and (ii) non-specific gene activation is a consequence of growth factor secretion. The scheme does not include autocrine/paracrine factors. The functions of the immediate early genes are unknown; several of them are not translated into proteins (Snoeckx et al., 1991).

Table 2. *Foetal programme re-expression during cardiac remodelling*

Changes in gene expression	Physiological consequences
Global increase in expression	Hypertrophy;
Including collagen, contractile proteins, channels…(Schreiber et al., 1970) with activation of pre-existing or imported stem cells (Urbanek et al., 2003)	⇑ contractile units Normalized wall stress
Genes re-expressed	
ββ-Myosin Heavy Chain (Lompré et al., 1979)	⇓ myosin ATPase and V_{max}
Anaerobic switch (Taegtmayer and Overturf, 1988)	Better recovery period
Lactate Dehydrogenase M subunits (Revis and Cameron, 1978)	
B subunit of Creatine Kinase (Younes et al., 1985)	
Neuronal NO synthase and caveolin* (Damy et al., 2004)	⇓ in adrenergic response
Ventricular expression of ANF (Mercadier et al., 1989)	⇓ preload
Genes of the apoptotic pathway (Haunstetter and Izumo, 1988)	'eat-me' signal
α3-subunit of Na^+, K^+-ATPase (Charlemagne et al., 1994)	⇓ sodium affinity
Embryonic MLC in ventricles (Sütsch et al., 1992)	?
IVS3A form of calcium channel (Gidh-Jain et al., 1995)	?
Genes whose expression is blunted	
Calcium ATPase of SR (SERCA 2) (Lompré et al., 1991)	⇑ relaxation time
Early transient K^+ current, I_{tO} (Swynghedauw et al., 2003)	⇑ action potential duration
αα-Myosin Heavy Chain (Lompré et al., 1979)	⇓ myosin ATPase and V_{max}
β1-adrenergic, muscarinic receptors (Mansier et al., 1993)	⇓ heart rate variability
Myoglobin (O'Brien et al., 1992)	Anaerobic switch

Major changes are in bold.
*Caveolin is augmented and likely to be responsible for the translocation of nNOS.

myosin heavy chain in 1979 (Lompré et al., 1979). In the rat ventricles (and mammalian atria), cardiac overload rapidly induces a shift from the αα to ββ-MHC isoform, which is responsible for the diminution of both the myosin ATPase specific activity and the maximum shortening velocity (for the unloaded muscle), V_{max} (Swynghedauw, 1986). Most of the other molecular components of the foetal programme are main determinants of the new myocardial function, as summarized in Table 2. (i) Re-expression of genes that are normally not expressed in the adult ventricles, such as the atrial natriuretic factor. (ii) Repression of genes that are normally not expressed or poorly expressed during the foetal stage, such as the Ca^{2+}-ATPase of the sarcoplasmic reticulum. (iii) Many genes responsible for apoptosis are also activated because apoptosis is an important component of the foetal programme and, during cardiac remodelling as during development, acts as an 'eat-me' signal and is the mechanism utilised to eliminate misplaced cells. (iv) Recently, an activation of either pre-existing or imported stem cells has been suggested (Anversa and Nadal-Ginard, 2002).

Applications of genomics and proteomics are still at the early stages. Several studies have been published using such a technology; some, in human, were pilot feasibility studies (Steenman et al., 2005) and others, using rats after myocardial infarction, were more complete (LaFramboise et al., 2005). Fourteen recent study reports pertaining to gene array analysis have been reviewed (Sharma et al., 2005). These techniques may sometimes have important limitations due to lack of sensitivity (for Affymetrix) or cross-hybridizations (for the cDNA microarrays), and the values of the corresponding studies may be seriously limited by the fact that they do not to include data on transcription factors and allelic shifts, both of particular significance in phenotypic plasticity. It is not the goal of this paper to extensively analyse these problems. For the moment, these approaches have only suggested a rather wide and coordinated change in expression of genes pertaining to signal transduction, metabolic function, structure and motility and cell organism defence (Table 3).

The physiological consequences of the foetal reprogramming

In stable cardiac overload, gene expression and the corresponding myocardial phenotype are progressively modified. The physiological consequences of these gene changes are a better adapted muscle with a normal economy, and less heat produced per gram of tension developed. This adaptation is due to the combination of hypertrophy, a slower and prolonged contraction and a more efficient anaerobic metabolism (Alpert and Mulieri, 1982).

Hypertrophy augments the number of contractile units and normalizes the wall stress. Wall stress increases as the load is augmented, but the enhanced intraventricular pressure is compensated by ventricular hypertrophy that decreases the denominator of the formula derived from the Laplace law, thereby maintaining wall stress in the normal range value.

Myocardial economy has been determined using a thermopile that measures the heat produced per gram of tension. Economy returns to normal values (Alpert and

Table 3. *Distribution of several genes significantly altered after an experimental myocardial infarction in rats, by functional classification (into genes regulating growth, contractility and metabolism)*

	Number of genes					
	Day 1 Infarct zone		Day 1 remote zone		Day 28 remote zone	
Functional class	Up	Down	Up	Down	Up	Down
Signal transduction	79	**186**	**101**	25	**10**	0
Transcription	23	**76**	**21**	11	**3**	2
Inflammation	28	**66**	**61**	4	**7**	0
Apoptosis	4	**33**	**10**	2	**3**	0
Protein synthesis	4	**26**	**17**	10	**2**	1
Growth factors	10	**18**	**15**	2	**3**	0
Metabolism	15	**79**	**27**	14	**6**	2
Energy transduction	17	**43**	10	10	1	1
Calcium regulation	12	**29**	**4**	1	**1**	0
Myocardial contraction	1	**13**	**2**	1	/	/
ECM remodelling	5	**8**	**5**	1	**3**	2
Angiogenesis	1	**6**	**4**	2	**1**	0

Infarct zone becomes a scar at day 28.
Numbers in bold = major changes.
Day 1 or 28 indicates the time after surgery (rearranged from LaFramboise et al., 2005).
ECM, extra-cellular matrix.

Mulieri, 1982). This is the first, and major, paradigm. Such an adaptation is caused by a reduction in V_{max}. The slowing of contractility is obtained by an increased action potential and calcium transient durations, and also, during exercising, by a reduced inotropic response. Finally, this is accompanied by a shift from a predominantly aerobic metabolism to a more anaerobic glycolytic metabolism, which allows a better regulation of the recovery period of the contractile cycle. Such a shift has been further confirmed by large-scale analysis of gene expression (LaFramboise et al., 2005).

In acute conditions, mechanical overload worsens the thermodynamic conditions and can immediately produce acute failure. From a purely mechanical point of view, in any muscle, smooth or striated, mechanical overload immediately reduces the instantaneous shortening velocity by using the mechanical properties of the muscle fibre. Muscle fibre economy is adapted to a given shortening velocity and, if the load is greater, the fibre contracts more slowly and economy falls. This is the primary determinant of every sequential event that follows. The re-expression of the fœtal programme will result in a slower V_{max}, which allows the muscle to contract on a different velocity/load curve and then to recover a normal economy (Table 2). These changes will allow the muscles to survive and to adapt to the new loading conditions in terms of thermodynamic status.

Hormones, ischemia, senescence as factors of CR

During clinical conditions, mechanical overload is rarely isolated and the phenotype that is obtained by pure ‘mechanoconversion’ is *de facto* modified by several interfering determinants that modify trophicity (Table 4).

Table 4. *The two biological determinants of cardiac remodelling*

Phenotypic changes	Effects of mechanics	Effects of other factors
Mitochondrial function	=	Altered (ischemia)
Ca *L*-type calcium channel density	=	⇑ (catecholamines)
Ca-ATPase of sarcoplasmic reticulum	⇓	⇑ (ischemia)
Angiotensin II receptor density	⇑	⇓ (plasma angiotensin II)
β1-adrenergic receptor density	⇓	⇓ ⇓ (plasma catecholamines)
Cardiac catecholamine stores	⇑	⇓ (ischemia)
$G_{\alpha i\text{-}2}$	=	⇑ (catecholamines)
Collagen concentration	=	⇑ (multifactorial)
Apoptotic markers	⇑	⇑ (multifactorial)

These are examples of phenotypic changes initially induced by mechanical stretch that can be further modified in a radical manner by interventions generated either by the specific cause of cardiac remodelling, such as ischemia, or by hormones or peptides, thus creating complex and sometimes paradoxical patterns.

These determinants include susceptibility factors, aetiologies, and the neurohormonal reaction.

Susceptibility factors

Heart failure commonly occurs in elderly, diabetic and obese persons. These factors, *per se*, strongly alter myocardial genetic expression and modify the molecular remodelling that is obtained by pure mechanical overload.

(i) The molecular composition of the normal senescent heart is modified as compared to adult hearts. Aged persons have a normal cardiac index at rest and during exercising. Nevertheless, early ventricular filling is hampered and atrial contraction is enhanced. Biological studies have revealed two groups of phenotypic changes that are likely to reflect the general process of senescence directly, namely fibrosis and cell loss. In addition, aging reduces arterial compliance which, in turn, overloads the left ventricle and induces the corresponding phenotypic modifications (Swynghedauw, 1999).

(ii) Diabetic and obesity-associated cardiomyopathy are well documented in both clinical settings and experimental models. Diabetes is responsible for specific vascular changes, cardiac autonomic neuropathy and specific structural changes, mainly fibrosis and microangiopathy (Sutherland et al., 1989). Obesity-associated cardiomyopathy is mainly caused by an excess in blood volume. Left ventricular volume and mass, and cardiac output, increase in a quasi-linear fashion as a function of body weight and enhanced body weight oxygen consumption. In addition, obesity increases the sympathetic nerve-firing rate (Ventura et al., 1983). Then, both obese and diabetic patients already have myocardial structural changes and the modifications produced by an additional arterial hypertension or myocardial ischemia are superimposed onto this pre-existing phenotype.

Aetiologies

Ischemia, the main cause of heart failure in western countries, is also responsible for specific changes in gene expression. (i) Some genes are activated to repair structural damage due to proteolysis. These genes include several calcium regulating proteins and the β-adrenergic receptors (Assayag et al., 1998). (ii) Other genes, such as glycolytic enzymes, vascular endothelial growth factor and erythropoietin, were activated under hypoxia to maintain local and systemic oxygen delivery. This activation is likely to be mediated by HIF-1 (Semenza, 2004). Interestingly, some of these modifications were exactly opposite to those observed during mechanical overloading, which could explain why the results observed in clinical conditions were so frequently controversial (Assayag et al., 1998) (see also Table 4). (iii) In ischemia, cell loss has both an apoptotic and a non-apoptotic origin.

Hormones and peptides

The last source of modifications in genetic expression are the neurohormonal changes that happen in response to the hemodynamic deficit. Angiotensin II, catecholamines, aldosterone, endothelin and cytokines have, besides specific, mostly hemodynamic, functions, pronounced and well-documented trophic effects that alter the myocardial phenotype in a sometimes unexpected way. For example, mechanical overload does not modify the density of Ca^{2+} channels *per se* while in contrast, catecholamines increase their density. In addition, the elevated plasma levels of ligands downregulate the corresponding receptor densities and complicate the framework, especially when the receptors are upregulated under the influence of mechanical overload (Table 4).

Transition to heart failure

The final myocardial phenotype is variable, and depends upon the relative predominance of each factor. Re-expression of the foetal programme, which is caused by mechanical overload, can indeed be radically modified by ischemia or by high plasma levels of catecholamines. Consequently, experimental models or clinical materials utilized to screen new compounds have to be fully characterized, not only in terms of myocardial performances, as usual, but also in terms of susceptibility factors, aetiologies and neurohormonal reactions, which is rarely done. Most of experimental models use young animals, and pharmacological studies with senescent, diabetic or obese animals are exceptions. The same story applies to clinical trials which, for the most part, have been performed in rather young patients with a majority of males, an abnormality that has been frequently emphasized.

The shorter and less controversial definition of heart failure is ‘ventricular dysfunction with symptoms’, which definitively means that heart failure is a disease state with both abnormalities in the myocardial structure and clinical symptoms due to fluid retention. The severity of the disease is commonly appreciated using the New York Heart Association (NYHA) classification, which is entirely based on functional symptoms. Thus, a deficit in myocardial function, without the detection of peripheral symptoms, is not, by definition, heart failure, and a ‘biological marker’ of failure is meaningless.

The functional nature of the definition renders the experimental approach to the transition difficult. It’s not easy to quantify tachypnea in a rat! From a biological point of view, schematically, the heart can fail for three reasons. (i) Failure may indicate the limits of the adaptive process. (ii) Fibrosis plays a crucial role in aggravating systolic dysfunction, myocardial electrical heterogeneity and myocardial stiffness. (iii) Heart failure can be caused by a loss of the muscle mass due to various types of cell deaths. In clinical practice, these reasons are frequently associated, although to variable degrees.

Cardiac plasticity, as compared to other models of phenotypic plasticity

During this last century, primarily through declines in infectious and parasitic diseases, the expected lifespan has dramatically risen in many countries. Most of this increase is the result of various improvements in sanitation, nutrition,

preventive and interventional medicine. For centuries, the only causes of cardiac diseases were infections, including endocarditis, and mostly, rheumatic heart disease. These both result in valve diseases and then in pure mechanical overload. In western countries, population-based prophylaxis has considerably overcome these infectious aetiologies and, consequently, incidences of valve diseases and that of heart failure due to pure mechanical overload have been considerably reduced (Carapetis et al., 2005). The enhanced lifespan results in an increasingly aged population, and aging allows a prolonged contact with cholesterol and glucose levels, blood pressure and various pollutants, facilitating the expression of low penetrance genes and epigenetic factors that finally cause atherosclerosis and coronary diseases. Myocardial infarction is now the main source of cardiac remodelling and heart failure, the pathophysiology of which is much more complicated than previously thought, and includes volume overload, hormone and vasopeptide stimuli, and cardiac senescence.

Cardiac plasticity is organ plasticity and, as such, differs from organism plasticity. Cardiac plasticity, like phenotypic plasticity described in plants and insects in response to variations in environmental conditions, is an 'environmentally sensitive production of alternative phenotypes by given genotypes' (Doughty and Reznick, 2004). Nevertheless, the two groups of environment-induced plasticity differ in many respects.

During CR, the cue is internal and plasticity is, by definition, organ-specific. Mechanics generate signalling in the heart through several sensor pathways. There are also many – too many – signals that are transitorily activated, including transcription factors that are normally involved during embryogenesis. Nevertheless, finally, the cardiac response to mechanics involves changes in expression, including allelic modifications that reproduce the foetal programme (Lompré, 1979). Cardiac remodelling involves the whole organ and genome-wide analyses have revealed significant coordinated changes in over 1400 genes early and 125 genes late in the infarct zone, and nearly 600 genes early and 100 genes late in the non-infarct zone (LaFramboise et al., 2005). As such, it resembles yeast remodelling in response to various changes in the extracellular environment. In yeast, genome-wide analysis has revealed a 'Common Environment Response' (CER), which is characterized by changes in the expression of over ~10% of the entire genome (Causton et al., 2001). Another common feature between the two is the fact that the foetal reprogramming is equally not specific for mechanical overload and does also occur after various hormone treatments

Phenotypic plasticity in plants or insects, for example, is not necessarily adaptive (Doughty and Reznick, 2004), and can even be maladaptive (Price et al., 2003). In comparison, cardiac hypertrophy due to exercising or pure mechanical overload is initially fully adaptive (the compensatory cardiac hypertrophy stage). Prolonged, excessive overload is associated with several additional factors, which induce fibrosis and render the initial favourable process progressively detrimental. Finally, the heart fails to produce sufficient ejection fraction and does not assume normal peripheral oxygenation.

Because the heart contracts permanently, this situation is cardiac specific and never happens in other muscles subjected to mechanical overload. Cardiac remodelling is reversible, overload can be reduced by medical or surgical treatment, and we do not require transplantation to demonstrate reversibility. Such a reversion is far from the rule in other models. Finally, the study of reaction norms, which is central in evolutionary biology (Dewitt and Schneider, 2004), shows different results in normal and in transgenic animals. Comparative experimental cardiology shows that the genotypes from different animal species were similarly plastic with no interaction variance. Nevertheless, there are at least two transgenic models with interaction variance in which the adaptation to mechanics is not caused by hypertrophy but by qualitative changes in gene expression (Esposito et al., 2002).

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