Hypertrophy and dilation: a TOTally new story?

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Myocardial hypertrophy is either a primary disease of the heart as found for genetic cardiomyopathies (hypertrophic or dilated), or an adaptive response secondary to, for instance, hemodynamic disturbances (pressure or volume overload) or endocrine dysfunction (hyperthyroidism, diabetes mellitus) [1,2]. Reactive concentric hypertrophy is fundamentally a compensatory response as the enlargement of the ventricular wall maintains normal hemodynamics and therefore allows physiological tissue perfusion. However, hypertrophy does not proceed indefinitely: the maintenance of the initial stress that induced the compensatory response overwhelms, after a variable delay, the hypertrophic capacity of the heart. From a functional standpoint, systolic dysfunction, metabolic exhaustion and insufficient tissue perfusion, i.e. major signs of heart failure, occur and in absence of adequate treatment, lead to premature death. Cardiac hypertrophy is clearly a double-edged sword: on one hand, it is beneficial as it preserves tissue perfusion while, on the other, it is a deleterious process as it predisposes the heart to pump failure [3].

Until now, the biochemical and molecular mechanisms leading to cardiac dilation have been much less studied than those responsible for cardiac hypertrophy [3]. For the latter process, it is becoming clear that the signaling pathways are numerous, complex and interactive. In particular, the hypertrophic role of the protein kinases C, the mitogen-activated protein and Janus kinases family, and the tyrosine kinases has been stressed [4–8]. Their activation has been shown to induce fetal gene reprogramming, to upregulate natriuretic peptide genes and to downregulate the expression of certain genes such as the one encoding the calcium pump of the sarcoplasmic reticulum [3]. More recently, the involvement of phosphatases in the hypertrophic process has been demonstrated, not only as “turn-off” effectors of the kinases action [9,10] but also, more surprisingly, as inducers of hypertrophy [7,11]. Thus, overexpressing a constitutively active form of the calmodulin-regulated phosphatase calcineurin in transgenic mice was sufficient to induce myocardial concentric hypertrophy [11].

Studying the molecular pathways leading to cardiac dilation is a more complicated matter because cardiac dilation is either a cardiomyopathy, i.e. a primary disease of the heart, or secondary to hypertrophy. Data now converge to indicate that primary dilated cardiomyopathy is a disease of the cytoskeletal/myofibrillar apparatus. Thus, proteins that are mutated, either naturally or transgenically, or overexpressed, such as dystrophin [12,13] or β-tropomyosin [2], are associated with a dilated phenotype. More recently, transgenically-induced, cardiac-specific overexpression of tropomodulin in mice generated a new animal model of dilated cardiomyopathy [14]. Interestingly, treating these mice with the calcineurin inhibitors cyclosporine A or FK506 prevented the dilated phenotype, despite the fact that calcineurin activation is a hypertrophic signal [2]. The main conclusion from this work was that the dilated heart was actually, at least in this model, a heart that failed to hypertrophy [14]. It also indirectly suggested that the classical distinction between concentric hypertrophy and dilation might be an oversimplification and that signaling pathways might be common to both processes.

This hypothesis is substantiated by the work published in this issue of Cardiovascular Research by Sussman and coworkers [15]. The authors used transgenic mice cross-breeding to demonstrate the existence of common molecular pathways between hypertrophy and dilation. Three strains of mice were bred: (1) a heterozygous strain, ATOT (Asymptomatic Tropomodulin-Overexpressing Transgenic), which has a normal phenotype (no cardiac hypertrophy and/or dilation) compared to the non-transgenic strain, despite elevated calcineurin activity and
activation) is present. This suggests that strong hypertrophic stimulus (such as permanent cal-
dilated heart was still able to hypertrophy, provided that a
presented both hypertrophy and dilation, indicating that the
whether this myosin switch has any importance in the lack
hybrid strain TOT / CAL the reverse switch [3]. It would be interesting to test
this situation created delayed organ maturation, due to myosin isoform whereas in the adult, hypertrophy induces
litters [16]. This has been accounted for by the fact that delayed tropomodulin accumulation in TOT mice by inducing
hypothyroidism in pregnant TOT mice with 5-propyl 2-
thiouracil, prevented the development of the dilated
phenotype. Secondly, the new transgenic strain obtained by
breeding ATOT or TOT, and CAL mice exhibited a novel
phenotype characterized by earlier mortality than in either
tropomodulin-overexpressing parental strain, as well as
marked dilation and hypertrophy (‘pumpkin-shaped’
heart), the extent of which was more marked in the hybrid
than in the parental strain.

Therefore, the authors show that occurrence of the
dilated phenotype heavily relies on post-natal maturation of
the heart, especially in terms of myofibrillogenesis. This
has been recently exemplified by the same group who
showed that the TOT phenotype was less frequent in large
litters [16]. This has been accounted for by the fact that
this situation created delayed organ maturation, due to
malnutrition. Furthermore, the hybrid strain TOT/CAL
presented both hypertrophy and dilation, indicating that the
dilated heart was still able to hypertrophy, provided that a
strong hypertrophic stimulus (such as permanent cal-
cineurin activation) is present. This suggests that physio-
logical CAL activation, such as detected in TOT and
ATOT hearts may not be sufficient to trigger the con-
centric hypertrophy phenotype.

This work has several important implications. For
instance, for the pathogenesis of DCM, it suggests that any
disturbance of myofibrillogenesis is susceptible to lead to a
dilated phenotype. Myofibrillogenesis is a hallmark of the
hypertrophic process, occurring either physiologically in
the young, during post-natal cardiac growth, or in a
pathological context [3]. In fact, addition of new myofibrils
requires the integrity of the myofibrillar apparatus as well
as proper scaffolding conferred by the cytoskeleton [3].
This naturally leads one to wonder whether breeding of
transgenic mice models of DCM based on mutated/over-
expressed, myofibrillar/cytoskeletal proteins, and CAL
mice, would reproduce the same phenotype as found for
ATOT/CAL and TOT/CAL strains. Alternatively, it
would be interesting to test whether hypertrophic stimuli
other than permanent calcineurin activation would also be
able to induce the hypertrophic/dilated phenotype in mice
models of DCM. The feasibility of aortic banding in mice
[17,18] renders this type of experiment possible.

According to the chart presented by Sussman et al. in
Fig. 11, the disturbed contractility secondary to abnormal
myofibrillar/cytoskeletal architecture would provoke
dysfunctional intracellular calcium regulation, leading to
calcineurin activation and hypertrophy/myofibrillogenesis
[7,16]. However, the latter could not proceed normally
because of disturbed cytoskeletal architecture. This impair-
ment would be overwhelmed by excessive calcineurin
activation as encountered in CAL mice. In this context, it
would be interesting to test whether pre- and post-natal
transition of tropomodulin and activation of calcineurin in the
former group, which became similar in TOT and ATOT
strains 10 days post-partum. Conversely, delaying
tropomodulin accumulation in TOT mice by inducing
hypothyroidism in pregnant TOT mice with 5-propyl 2-
thiouracil, prevented the development of the dilated
phenotype. Despite the attractiveness of the hypothesis that the
dilated heart would be a ‘hypertrophic-failed’ heart, some
limitations must be stressed, especially in a clinical
context. In these transgenic mouse models, DCM and
death occur relatively early in the mouse life whereas in
heart failure patients, ventricular dilation, which may or
may not be preceded by concentric hypertrophy, usually
occurs late in life [20–23]. It is therefore unclear whether
the ‘quality’ of the hypertrophic stimulus (physiological
post-natal maturation vs. reactive hypertrophy due to
disturbed hemodynamics, for instance) does matter for the
occurrence of the dilated phenotype. The situation is even
more complicated in rodents in which post-natal hyper-
trophy is accompanied by a switch from a slow to a fast
myosin isoform whereas in the adult, hypertrophy induces
the reverse switch [3]. It would be interesting to test
whether this myosin switch has any importance in the lack
of hypertrophic response in the TOT mouse.

The importance of the animal model is further stressed
by the fact that the activation of calcineurin is considered
to be a critical triggering signal for hypertrophy [7,11]. As
other calmodulin-regulated enzymes, calcineurin is not
sensitive to rapid variations of intracellular calcium (such
as those occurring during the cardiac beat) but rather to
time-averaged and/or basal (diastolic) calcium concen-
tration [24]. The disturbances in intracellular calcium
regulation described in ventricular myocytes isolated from
aged (16 weeks) TOT mice hearts have been considered as
being responsible for activation of calcineurin [16]. How-
ever, this work does not help to distinguish between the
importance of heart rate [7,25] and the altered intracellular
calcium regulation in activating calcineurin and whether
this signaling pathway is indeed found in other animal
models of DCM, which may have more better clinical
relevance. Clearly, the status of calcineurin, its time-de-
pendent activation [16,26] and the effect of inhibitors such as
FK506 and cyclosporin A [2,27] should be studied in
other models in larger species in which no myosin shift
occurs and which exhibit a lower heart rate. One such
model could be transmural myocardial necrosis in the dog
[28]. The rapid ventricular pacing models in pigs or dogs
[1,29,30] which induce dilation without hypertrophy, sug-
gests that calcineurin could also be activated. An interest-

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ing hypothesis would be to study whether its pharmacological inhibition would prevent dilation on this model, as found in mice models of DCM.

In conclusion, the experiments reported by Sussman and coworkers seem to indicate that the dilated heart might actually fail to hypertrophy. The fact that both concentric and dilation may coexist suggests that both processes share common signaling pathways. Uncovering these pathways, especially in the adult heart (most of the studies are presently performed in neonatal myocytes) [8], will open the way to new therapeutic strategies [7] as well as lead to a better understanding of the processes responsible for the transition from compensated hypertrophy to ventricular dilation [3]. Transgenic mouse models will be a powerful tool to achieve these goals but extrapolation to human patients will certainly require the development of models in larger animal species.

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