Hypertrophic defect unmasked by calcineurin expression in asymptomatic tropomodulin overexpressing transgenic mice

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Abstract

Objective: Dilation and hypertrophy often occur concurrently in cardiomyopathy, yet the interaction between these two functionally distinct conditions remains unknown. Methods: Combinatorial effects of hypertrophy and dilation were investigated by cross-breeding of two cardiomyopathic transgenic mouse lines which develop either hypertrophy (calcineurin-mediated) or dilation (tropomodulin-mediated). Results: Altering the intensity of signals driving hypertrophy and dilation in cross-bred litters resulted in novel disease phenotypes different from either parental line. Augmenting the calcineurin-dependent hypertrophic stimulus in tropomodulin overexpressing transgenics elevated heart:body weight ratios, increased ventricular wall thickness, and significantly accelerated mortality. These effects were evident in calcineurin cross-breeding to tropomodulin backgrounds of transgene homozygosity (severe dilation) or heterozygosity (mild dilation to asymptomatic). Molecular analyses indicated that tropomodulin and calcineurin signaling events in the first week after birth were critical for determination of disease outcome, substantiated by demonstration that temporary neonatal inhibition of tropomodulin expression prevents dilation. Conclusions: This study shows that postnatal timing of altered signaling in cardiomyopathic transgenic mouse models is a pivotal part of determining outcome. In addition, intensifying hypertrophic stimulation exacerbates dilated cardiomyopathy, supporting the concept of shared molecular signaling between hypertrophy and dilation. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Specific mutations in contractile proteins have been associated with familial hypertrophic cardiomyopathy [1–3], but molecular defects responsible for dilated cardiomyopathies remain elusive. ‘Idiopathic’ dilated cardiomyopathies characterized by progressive loss of contractility are a significant health problem throughout the world with high morbidity and mortality [4,5]. Epidemiological analyses of human populations have mapped several genetic loci with approximately one third of clinical dilated cardiomyopathies thought to be inherited [6]. Linkage analysis shows dilated cardiomyopathy is a complex disease caused by multiple independent genes with loci scattered throughout the genome [7]. Only two candidate genes, dystrophin and actin, have been associated with dilated cardiomyopathy [8,9], although titin and tropomodulin were implicated from genetic linkage analyses [10,11]. Consistent with human studies, transgenic mice have shown that dilated cardiomyopathy results from...
defects in cytoskeletal or myofibril organization of the cardiomyocyte: deficiency of cytoskeletal-associated muscle LIM protein [12] or loss of myofibril organization caused by tropomodulin (Tmod) overexpression [13]. Previous work by our group has shown that Tmod overexpressing transgenic (TOT) mice develop dilated cardiomyopathy with a `failed' hypertrophic response [13].

Dilation in TOT hearts results from calcineurin activation which is secondary to the myofibril degeneration caused by Tmod overexpression [14]. Calcineurin activation, regulated by increased basal cellular calcium levels, has been hypothesized to be a primary pathway for induction of hypertrophy [15]. Treatment of TOTs with cyclosporin, a calcineurin inhibitory drug, prevents cardiac dilation without rescuing myofibril organization or affecting mortality [14]. Thus, myofibril degeneration in TOTs was not directly responsible for dilation. Instead, Tmod overexpression is indirectly linked to calcineurin activation, and the failure to hypertrophy stems from impaired myofibrillogenesis in the presence of excessive Tmod protein.

To induce dilated cardiomyopathy in TOTs, Tmod expression levels had to be elevated by breeding to transgene homozygosity [13]. TOTs with heterozygous transgene dosage did not develop any external symptoms of cardiomyopathy which were readily apparent in their homozygous siblings. These asymptomatic TOTs (ATOTs) presumably lacked threshold levels of Tmod transgene expression necessary to initiate development of the cardiomyopathic phenotype. In contrast, Tmod accumulation in TOTs unleashes a cascade of structural and molecular effects: after Tmod overexpression causes myofibril disorganization, intracellular basal calcium levels rise to increase contractility, followed by activation of calcineurin which drives cardiac dilation [14,16]. The pathogenesis of TOT dilation depends upon high level Tmod expression to start the chain of molecular events leading to calcineurin activation and eventual dilation. If Tmod protein accumulation is lower in ATOTs and calcineurin is not activated, then it is reasonable to predict that dilation would not occur. Despite their seemingly healthy appearance, the possibility remained that ATOTs were compromised by Tmod transgene accumulation, either evidenced as subtle sarcomeric dysgenesis or a `silent' defect which could be exacerbated by a complicating stimulus. A secondary `hit' to the ATOT heart in the form of a strong hypertrophic stimulus could unmask the presence of elevated Tmod level by inducing rapid myofibril reorganization. Since calcineurin activation is the secondary `hit' which promotes TOT dilation, ATOTs were cross-bred with another transgenic mouse line which expresses activated calcineurin in the myocardium. The calcineurin transgenic (CAL) develops marked hypertrophy within 2–3 weeks after birth [15]. Breeding the ATOT–CAL hybrid combination created a novel lethal cardiomyopathic phenotype different from either parental line. Results presented in this report indicate that ATOTs indeed carry a `silent' defect in myofibrillogenesis (presumably due to accumulation of Tmod) which can be revealed by calcineurin activation. Furthermore, evidence is presented that reaching threshold tropomodulin levels within the first week after birth is critical to initiate pathogenesis. Collectively, the results show that superimposing a hypertrophic stimulus to build myofibrils upon a heart with impaired myofibrillogenesis cannot compensate for loss of contractility, but instead exacerbates pathology. Analogous combinatorial conditions may exist in human cardiomyopathy, in which dilated cardiomyopathies may benefit from attenuation of signals from hypertrophic pathways.

2. Methods

2.1. Creation and breeding of mice

TOTs were created as previously described [13]. TOT litters in this study were the offspring of TOT mating pairs. TOT males and females were housed together until 3–4 weeks of age. ATOT mice were created by breeding of homozygous TOTs to normal nontransgenic animals. CAL mice were bred to TOT mice to create double heterozygote transgenics (CAL–ATOT). CAL–ATOT mice were back crossed to TOT mice to generate TOT–CAL mice which were homozygous for tropomodulin transgene. The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication number 85-23, revised 1996).

2.2. Phenotype tracking and database analysis

Data gathered on the mouse population was analysed using PROGENY v2.0 (Genetic Data Systems, Mishawaka, IN, USA).

2.3. Microscopic analyses

Gross heart photos were taken using a Nikon microscope. Hematoxylin and eosin stained sections were scanned using a Nikon LS-3500 slide scanner. Confocal microscopy and morphometric analyses of heart sections were performed as previously described [13]. Sections were labeled with antibodies to α-actinin to label Z-disks as well as tropomodulin to confirm overexpression of the transgene. Electron microscopy was performed as previously described [17]. All microscopy experiments were performed using three separate individuals analyzed in each group of controls or transgenics at three weeks of age. Confocal and electron microscopy experiments were performed using hearts from different mice.
2.4. Gel electrophoresis, immunoblots, and immunoprecipitations

Equivalent amounts of total protein were separated by SDS–PAGE on a 10% gel and transferred to nitrocellulose. The region corresponding to apparent mobility of Tmod was excised from the blot and labeled with anti-Tmod antibody. Bound antibody was detected by labeling with a Vistra ECF western blot kit (Amersham) as directed by the manufacturer. Signal intensity was quantitated using a Storm 860 fluorimager (Molecular Dynamics, Sunnyvale, CA, USA) and calculated as the product of average pixel intensity in the band multiplied by the area of the band. Immunoprecipitation of calmodulin–calcineurin complexes was performed as previously described [14]. For analysis of Tmod and calcineurin expression level in ATOT versus TOT, four hearts were pooled at each time point to minimize individual variability. Each time point for the Tmod time course represents values derived from two separate groups of pooled hearts that were tested repeatedly on three separate blot experiments. Minor variation in sample loading was corrected by standardization to GAPDH signals from the same blot. Tmod expression level was significantly lower in ATOT relative to TOT samples by comparing the average level from days 1–5 after birth between the ATOT (average = 1.57 ± 0.57, n = 42) and TOT (average = 2.04 ± 1.0, n = 55) groups (P = 0.012). The calcineurin time course was repeated on two different groups of pooled heart samples with comparable results in both experiments.

2.5. 5-Propyl-2-thiouracil (PTU) treatment of TOT mice

PTU treatment was administered by feeding animals a diet containing 0.15% PTU (Teklad Premier, Madison, WI, USA). TOT mothers were switched to food containing
PTU within 1 day of giving birth to the litter. Nursing mothers were maintained on PTU for 1 week and then switched back to normal food. Litters were treated routinely and weaned from the mother at approximately 3 weeks of age. Number of animals for the three time points analyzed in each population were: 21 day untreated (n = 60), treated (n = 9); 77 day untreated (n = 16), treated (n = 11); 120 day untreated (n = 14), treated (n = 5).

2.6. Statistical analysis

Significance values were determined by Student’s t-test using Microsoft Excel. Values of P<0.05 were considered to indicate a significant difference between the sets of data being compared. Tmod levels were consistently lower in neonatal ATOT samples (Fig. 5) as confirmed by two-way analysis of variance where group and time were independent factors and expression level was the dependent factor. An analysis of variance showed that time was not a factor in determining the significant difference between the groups (data not shown).

3. Results

3.1. ATOT heart functional assessments and left ventricular chamber size are normal

TOT mice suffer from severe contractility defects and loss of systolic function [13]. To determine if ATOT hearts suffer any functional impairment, ATOT and nontransgenic control hearts were analyzed by isolated working heart preparation using multiple animals ranging from <5 to >50 weeks of age (Fig. 1, top). Working heart preparations were performed as previously described [18]. Contractility and relaxation of ATOT hearts were indistinguishable from that of age-matched nontransgenic controls. These results indicate that ATOT hearts are not functionally compromised.

Severe ventricular chamber dilation is a defining characteristic of TOT cardiomyopathy [13]. To determine if ATOT hearts exhibit dilation in vivo, ATOT hearts were examined by echocardiography using multiple animals which were followed in a longitudinal study over a period of months (Fig. 1, bottom). Echocardiographic analyses were performed as previously described [19]. Left ventricular end diastolic chamber dimensions did not increase in any of the mice analyzed over the course of the study, and the average size of the ATOT left ventricular chamber (3.9 ± 0.4) is comparable to previously published values for age matched nontransgenic control hearts of 3.7 ± 0.3 [19]. This demonstrates that ATOT hearts do not show chamber dilation under in vivo working conditions and supports the conclusion that ATOT hearts are not functionally compromised.

3.2. Microscopy of ATOT heart sections

Confocal microscopy was performed upon sections from ATOT mice to observe myofibril structure (Fig. 2). Nontransgenic control sections showed myofibrillar pattern of alternating tropomodulin and α-actinin bands as previously described [20]. In comparison, ATOT sections showed abundant tropomodulin reactivity throughout the interior of cardiomyocytes (Fig. 2), similar to previous observations with TOT sections [13]. Unlike TOT sections, α-actinin staining in ATOT sections was well organized compared to the degeneration evident in TOTs [13]. Z-disks of myofibrils viewed by α-actinin staining were regularly spaced, aligned, and straight in both control nontransgenic and ATOT sections.

Subtle sarcomeric abnormalities in neonatal TOTs were not apparent by confocal microscopy, yet electron microscopy revealed subtle sarcomeric abnormalities [16]. Since TOT cardiomyopathy is most severe at 3 weeks after birth [13], myocardial samples were taken from 3-week-old ATOT mice to search for degenerative changes. ATOT samples showed no defects in myofibrils, sarcomeres, mitochondria, or intercalated discs (Fig. 3). The arrangement and packing density of myofibrils was normal in cross-section and sarcomeres showed organized banding. Thick and thin filaments were oriented in parallel as in normal controls, unlike samples from TOT mice [13]. Well-defined mitochondrial membranes and cristae were present, appearing comparable to nontransgenic control samples. Normal myofibril and sarcomeric structure observed by confocal (Fig. 2) and electron microscopy (Fig. 3) supports the idea that myofibril and sarcomeric structure in ATOT hearts is not significantly affected.
3.3. ATOT mice show elevated tropomodulin levels

Tmod protein expression level in TOTs was elevated at birth and remains chronically high [16]. Lack of pathological changes in ATOTs prompted immunoblot analyses to determine if tropomodulin accumulation was decreased relative to TOTs. Tmod expression in ATOTs was estimated relative to control samples (Fig. 4, nontransgenic lanes) and quantitative analysis was standardized against GAP-DH (data not shown). Tmod level in control nontransgenic animals remained constant throughout the time course investigated, so one representative sample was used. ATOTs ranging in age from young (82 days) to middle aged (325 days) show marked elevation of Tmod level relative to the control nontransgenic sample. In comparison, a typical TOT sample with expression comparable to previously published levels [13] showed a higher Tmod level than any ATOT sample tested. This survey showed that Tmod is markedly overexpressed in older ATOTs, although levels always remain below typical levels in TOTs.

Abnormally high Tmod levels in neonatal TOTs rise
3.5. Calcineurin expression exacerbates the pathology of tropomodulin-mediated cardiomyopathy

Cardiomyopathic TOTs described in our previous study were created by selecting for transgene homozygosity [13]. Pathological changes in TOT mice were clearly apparent within two weeks after birth and the majority of TOT early mortality ranges from two to three weeks after birth. In comparison, ATOTs are asymptomatic and show no evidence of cardiomyopathic disease (Figs. 1 and 3). However, both TOT and ATOT lines exhibit comparable
guished from either parental strain in morphology, degree of enlargement, and magnitude of ventricular wall hypertrophy.

3.6. Cross-breeding of CAL to ATOTs or TOTs increases heart:body weight ratios and early mortality

Heart:body weight ratios for CAL–ATOT are elevated approximately 5-fold above normal nontransgenic values as early as postnatal day 10, remaining at this level for at least 3–4 weeks after birth (Fig. 9A). In comparison, heart:body weight ratios for CAL mice between 3–4 weeks after birth are increased 3-fold above normal (average increase for 10 CAL mice versus 12 age matched nontransgenic controls between postnatal days 20–30). Cardiac enlargement was maintained throughout life, and the decrease in ratio with age reflects body weight gain rather than reduction of cardiac mass. Comparable results were obtained in analysis of CAL–TOT heart:body weight ratios (data not shown).

Actuarial data was collected on the population of 49 CAL–ATOT and 12 CAL–TOT mice which died spontaneously. Hybrids died as early as 11–12 days after birth, but peak mortality occurred 2–3 weeks after birth (Fig. 9B). Approximately 70% of CAL–ATOT mice did not survive beyond 3 weeks of age. CAL–TOT mortality peaked in comparable fashion with 75% of the population dead within 3 weeks of birth (data not shown). Mortality of the hybrid lines is markedly higher than parental lines which showed either no difference from nontransgenic controls (in ATOTs), initial mortality occurring only after 2 months of age (in CAL), or 38% mortality within 3 weeks of birth (in TOTs). Acceleration of mortality in hybrid lines indicated that the cardiomyopathy in crossbred mice was much more severe than the disease in either parental strain. The combinatorial pathologic effect of mixing calcineurin and Tmod transgenes created a novel, more lethal dilated hypertrophic cardiomyopathy.

3.7. Transient inhibition of tropomodulin expression during neonatal life reverses dilation in TOT mice

ATOTs do not develop overt cardiomyopathic disease as observed in TOTs, although both tropomodulin expression level and calcineurin activation in the two lines were
Fig. 7. Introduction of the CAL into ATOT and TOT causes severe dilated hypertrophic cardiomyopathy. Bisected hearts show the relative degree of cardiomyopathic changes between lines as well as progressive changes over time. All images were processed identically so sizes can be compared between all examples. Postnatal day 16 hearts (top row) from normal nontransgenic and ATOT were comparable in size and shape. In comparison, TOT heart was slightly larger with a dilated ventricular cavity. The hypertrophic CAL heart is larger than normal nontransgenic or TOT hearts. Cross-breeding of either ATOT or TOT to CAL resulted in a novel distorted ‘pumpkin’ shape. Hypertrophic influence of the CAL transgene is evident by enlargement of CAL–ATOT and CAL–TOT hearts. ATOT and CAL–ATOT hearts from postnatal day 18 (middle row) showed comparable size and shape between normal nontransgenic and ATOT which contrasted sharply with the abnormal dilation of the CAL–ATOT of the same age. Hearts from older CAL–ATOT showed marked chamber dilation with varying degrees of ventricular wall thickening. Note similar size of age-matched CAL–TOT and CAL–ATOT hearts. TOT and CAL–TOT hearts from postnatal days 23 (bottom row) showed the characteristic dilation of the TOT heart compared to the normal control, whereas the misshapen CAL–TOT heart has marked chamber dilation. A 36-day-old CAL–TOT heart showed pathology consistent with progressive dilated and hypertrophic cardiomyopathy.

comparable within 10 days of birth (Figs. 4 and 6). Restriction of these transient molecular differences to early postnatal development suggested the heart was particularly sensitive to disturbances during this period. To test this hypothesis, activation of tropomodulin transgene expression in TOTs was delayed by administration of PTU for 1 week after birth. Following PTU withdrawal, TOTs were reared well beyond the age of 1.5–2 weeks when cardiomyopathic disease normally develops in untreated TOTs [13]. Results of TOT heart:body weight comparisons demonstrated a dramatic reduction of heart mass after 1 week of PTU supplementation. PTU-treated TOTs compared to untreated TOTs at three different ages showed highly significant decreases in heart:body weight (Fig. 10). Differences between PTU-treated and untreated TOT ratios were all highly significant \( (P<0.00001) \). The heart:body weight ratios of the PTU-treated TOTs are comparable to normal values for control nontransgenic mice [16]. These

Fig. 8. Histologic sections show chamber dilation and ventricular wall hypertrophy in CAL–TOT and CAL–ATOT. Comparison of postnatal day 15 hearts prior to development of aberrant shape changes. All images were processed identically so sizes can be compared between all examples. (Top row) Nontransgenic control heart section was small compared to hypertrophic CAL heart as evidenced by thickened ventricular walls and decreased chamber size. (Middle row) ATOT heart was comparable to nontransgenic control (shown above, see top row), but CAL–ATOT heart showed combinatorial enlargement and chamber dilation different from either parental line. (Bottom row) TOT heart showed characteristic dilation compared to control nontransgenic or ATOT although CAL–TOT cross resulted in a dilated and hypertrophic heart with pathologic changes similar to the CAL–ATOT heart (shown above, see middle row).
Fig. 9. CAL−ATOT heart:body weight ratios and mortality peak within 3 weeks of birth. Heart:body weight ratios (A) and mortality (B) for a CAL−ATOT population of 43 individuals which spontaneously died. (A) The heart:body weight plot shows the average ratio for every two neighboring points on the line. Ratios for animals between 1.5 and 4 weeks of age clustered between a low of 22 to a high of 35. Declining ratios in older mice between 60 and 120 days of age reflect increasing animal body weight without concomitant heart weight gain. The number of mice used to determine the average heart:body weight ratio for every point is represented as bars with a scale on the right hand axis of the plot. (B) Mortality plot shows number of deaths per day versus age in days for CAL−ATOT population. CAL−ATOT mortality peaked between 2−3 weeks after birth, whereas highest TOT mortality splits into two separate peaks occurring at 2 weeks and 3 weeks after birth [16]. Population size of the CAL−ATOT group was 49 individuals.
myofibrillogenesis undergoes a rapid and intense postnatal hypertrophic response (Fig. 11, adapt). ATOT mice can mount normal postnatal cardiac development but, when challenged with calcineurin activation (CAL–ATOT), cannot adapt to intense hypertrophic signaling and undergo progressive decompensation that leads to accelerated mortality.

The apparent paradox of dilated cardiomyopathy in TOTs versus asymptomatic to mild dilation in ATOTs can be resolved by understanding the importance of early postnatal calcineurin activation in pathogenesis. The cryptic nature of the ATOT phenotype was uncovered by cross-breeding these mice to CAL, which resulted in comparable phenotypes between TOT and ATOT. Since TOT dilation is driven by activated calcineurin, it was reasonable to speculate that levels of calcineurin activation were different in the two lines. Immunoblot analysis confirmed that the time course of calcineurin activation was delayed in ATOT, although by 10 days after birth the levels were comparable between ATOT and TOTs. Similarly, tropomodulin expression in ATOT was lower than in TOT, but only for the first few days after birth. These findings suggest that innocuous ATOT cardiac effects versus cardiomyopathic TOT disease stem from subtle differences in tropomodulin expression and resultant calcineurin activation within the first week after birth.

Neonatal life is a time of rapid cardiac growth and compensation in response to the workload of systemic circulation [21,22]. Disruption of neonatal cardiac development leads to cardiomyopathy by altering the molecular program of growth and hypertrophy. Tropomodulin expression in TOT hearts ‘reprograms’ cardiac development by calcineurin activation, inducing aberrant hypertrophy during a vulnerable period when structure is susceptible to the effects of altered signaling. Pathology results from coincidence of critical postnatal cardiac myofibrillogenesis and accumulation of tropomodulin which impairs myofibril assembly. The heart is especially sensitive to disruption of contractile function during this developmental time window. Compromised heart function during this period causes the myocardium to respond with an intense compensatory reaction which sets the stage for cardiomyopathic disease later in life. If tropomodulin expression levels are attenuated during the first week after birth, then the phenotype of dilation is averted as shown by ATOT mice (Fig. 7) and PTU treatment of TOTs (Fig. 10). Early developmental ‘reprogramming’ does not occur in ATOT because tropomodulin levels are insufficient to induce calcineurin activation during the vulnerable period. Instead, delayed tropomodulin accumulation in ATOT hearts renders them ‘at risk’ for pathological consequences if challenged during neonatal development. When confronted with activated calcineurin from the CAL cross-breeding, CAL–ATOT hearts manifested cardiomyopathy comparable to CAL–TOT hearts. Thus, ATOT hearts are predisposed to dilated cardiomyopathy which, like TOT

4. Discussion

Combinatorial approaches to understand the relative roles of dilation and hypertrophy in disease are now possible using transgenic mice with specific cardiomyopathies induced by activation of known signal transduction pathways. By selective cross-breeding of cardiomyopathic mouse lines, interactions between signal pathways can be assessed for competition, conflict, or mutually exclusive effects. This study used the cross-breeding approach to examine the relationship between Tmod expression and calcineurin activation in the development of cardiomyopathy. Collective results reflecting our current understanding of these relationships are summarized in Fig. 11. Although oversimplified, this hypothetical schematic model accounts for the initiation and progression of cardiomyopathic changes described in this study. Tmod expression in the TOT line leads to elevation of intracellular calcium and activation of calcineurin [16]. However, TOT mice are unable to mount a structural hypertrophic response and proceed to decompensate (Fig. 11, fail). In contrast, the CAL line capable of normal
Fig. 11. Hypothetical flow chart of steps leading to heart failure in TOT, CAL and CAL–ATOT lines. Nontransgenic control and transgenic lines are incorporated along the pathway in positions corresponding to their inherent condition. Calcineurin activation results in a decision process leading to either compensation (adapt) or decompensation (fail). TOT mice proceed directly to decompensation, whereas CAL mice undergo hypertrophy for several weeks prior to transition into failure. If any intermediate steps in the pathway of compensation are impaired, then the heart transitions into decompensation. The ATOT line carries a hidden defect in compensatory ability that, when stimulated by calcineurin activation, results in failure as observed for the CAL–ATOT.

disease, is unmasked by early postnatal calcineurin-driven hypertrophy.

Although hypertrophy and dilation have distinct functional consequences, this study suggests that hypertrophy and dilation are two different endpoints along a shared molecular program of cardiac compensation. Following this rationale, if hypertrophy and dilation share a common molecular origin, then downstream events determine the relative degree of hypertrophy or dilation. For example, activation of a normally hypertrophic pathway (calcineurin) in TOTs leads to dilated cardiomyopathy that is the end result of a failed hypertrophic response. TOTs demonstrate that hypertrophic stimulation superimposed upon impaired contractility causes dilation, thereby accelerating the process of cardiac failure. In this context, end stage dilated heart failure can be thought of as failure to mount or maintain an appropriate hypertrophic response. In fact, the transition from hypertrophy to failure shares important similarities with overt dilation: increased myofibrillar disarray and loss of contractile function. Decompensated hypertrophic heart failure may be the result of ongoing hypertrophic stimulation in a heart which has lost the ability to hypertrophy. Thus, the phenomenon of decompensation could be considered dilation in the absence of concomitant hypertrophy. This is potentially relevant for prophylactic intervention during cardiac hypertrophy with agents to inhibit chronic stimulation which could eventually result in decompensation.

Cardiomyopathies have been defined in functional terms related to systolic or diastolic abnormalities. In addition, cardiomyopathies are classified by specific structural criteria related to ventricular wall thickness and chamber size. Together, functional and structural characteristics describe progression from diastolic abnormalities (hypertrophy) to systolic insufficiency (dilation) in numerous clinical case reports [23–29]. The transition to decompensated heart failure involves a marked shift of cardiac function and structure from hypertrophy toward dilated cardiomyopathy. In general, onset of dilation is associated with poor outcome as systolic function deteriorates [30], particularly in infants and children where developmental processes can exacerbate disease [31,32]. However, when the transition to heart failure is not abrupt, a mixture of hypertrophic and dilated characteristics evolves in which
classical definitions of cardiomyopathy blur together. In this situation, hypertrophic molecular pathways to augment contractility are hampered by structural deficits which impair generation or transmission of force to the myocardium. As a result, progression of cardiomyopathy evolves by integration of molecular cross-talk signals between ongoing hypertrophy and dilation. Balance in the multiplex signaling interactions where dilation and hypertrophic pathways coincide determine the type and intensity of compensation, and these signaling overlaps need to be identified for testing as potential targets for interventional approaches. The findings of this report are consistent with hypertrophy and dilation sharing a common beginning, with the ending determined by the ability of the heart to respond with appropriate reactive structural compensation and remodeling.

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