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News & views

Developmental biology

Nursing heart muscle cells to maturity

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A fatty acid in the milk of nursing mice has been found to trigger a transformation in the metabolic pathways that are active in pups' heart muscle cells, enabling the cells to rapidly mature after birth.

Birth greatly changes an infant's environment. Cardiomyocytes, the heart's contractile cells, undergo a profound set of changes in newborn mice, maturing so that they can efficiently contract to produce heartbeats for an entire lifetime[1]. The mechanisms that trigger and coordinate this maturation process are incompletely understood. Writing in *Nature*, Paredes *et al.*[2] report that a fatty acid in the milk of mother mice, γ-linolenic acid, binds to proteins called retinoid X receptors (RXRs) in newborn cardiomyocytes to drive a switch to their mature metabolic state. This unexpected finding reveals a role for a mother's milk in promoting the maturation of her offspring's heart.

Maturation of cardiomyocytes involves diverse changes in physiology. The cells grow in size, for instance, and acquire structural adaptations that optimize their ability to contract forcefully and synchronously[1]. They also take advantage of greater oxygen availability outside the womb to switch to a more fuel-efficient metabolism, based on oxidation of fatty acids in mitochondria (the cell's energy-generating organelles).

Paredes *et al.* started by investigating the function of RXRs in developing cardiomyocytes. RXRs have been proposed to have diverse functions in cardiovascular development and disease[3], but redundancy between RXR isoforms has complicated their study using gene-inactivation approaches. Paredes and colleagues overcame this barrier by inactivating RXRα and RXRβ, the major RXR isoforms, specifically in fetal cardiomyocytes. The mutant embryos survived normally to birth, but 80% died in the following 24 hours. Cardiac structure was normal, excluding an essential role for cardiomyocyte RXRs in heart morphogenesis, but heart contraction was severely depressed compared with that in normal newborn mice. Gene-expression analysis demonstrated that RXRs are required for activation of genes involved in fatty-acid oxidation (FAO) and mitochondrial function. These results are in keeping with previously reported roles of RXR in promoting cardiomyocyte FAO and energy metabolism[3].

Next, the researchers asked what activates RXR in the neonatal heart. The molecule 9-*cis*-retinoic acid was identified three decades ago as a potent RXR activator *in vitro*, but its level is too low *in vivo* to activate RXR in mice[4]. Paredes *et al.* painstakingly modulated the diet of nursing mothers or the composition of milk ingested by newborns. These experiments revealed that normal neonatal activation of mitochondrial and FAO genes requires the presence of γ-linolenic acid in maternal milk. This fatty-acid derivative cannot be synthesized by mice (or humans) and must be ingested[5].

The need for γ-linolenic acid was most strikingly demonstrated by the finding that wild-type newborns fed milk from mothers that were on a fat-free diet did not survive beyond two days, but supplementing the mothers' diet with γ-linolenic acid restored normal survival. By contrast, supplementing the maternal diet with γ-linolenic acid did not improve the survival rate of RXRα–RXRβ mutant neonates. This indicates that γ-linolenic acid acts through RXRs. Finally, Paredes and colleagues showed that γ-linolenic acid binds physically to RXR , enabling RXR to activate expression of mitochondrial and FAO genes in cardiomyocytes (Fig. 1).

Together, these results reveal a molecular signalling pathway whereby nutrients in the milk of female mice activate a gene-expression program that triggers maturation of cardiomyocytes and prepares them for postnatal function. It is worth noting that this study focused on mice only, and there is no information about whether γ-linolenic acid in human

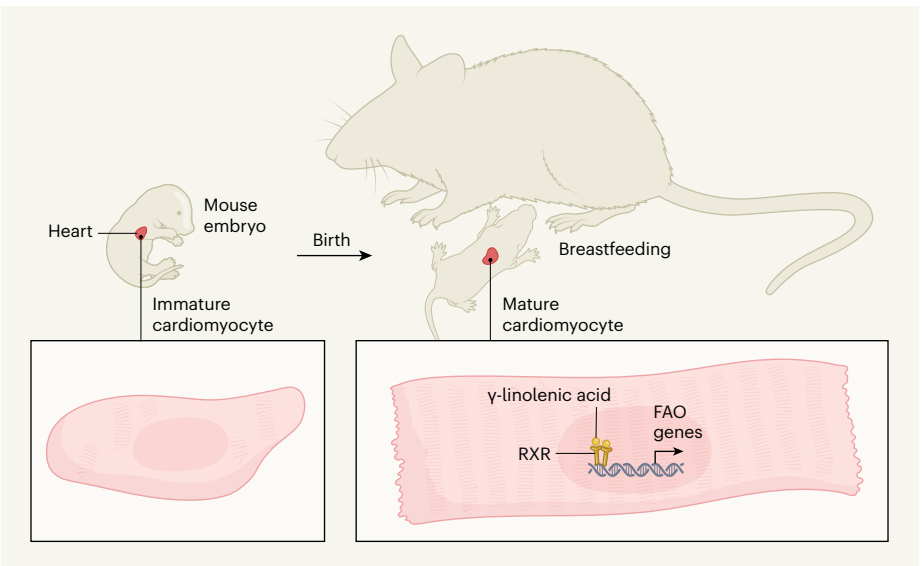

Figure 1 | Trigger for a metabolic switch in cardiomyocytes. Paredes *et al.*[2] demonstrate that the breast milk of female mice contains a fatty acid called γ-linolenic acid that triggers a transformation in cardiomyocytes (the heart's contractile cells). In the embryo, immature cardiomyocytes mainly metabolize glucose to generate energy (not shown). After birth, γ-linolenic acid binds to retinoic acid receptor (RXR) proteins in the nucleus of cardiomyocytes to promote transcription of target genes involved in a different pathway for energy metabolism — fatty-acid oxidation (FAO). Transcription of FAO genes triggers a switch in how the cells produce energy that enables efficient contraction of the mature cardiomyocytes.

and formula milk is similarly essential for newborn heart function or metabolic maturation. Nonetheless, this is a remarkable example of mother–infant interaction that points to many exciting avenues for further study.

For instance, the possibility that neonatal activation of RXR by γ-linolenic acid affects the development and function of other organs could be assessed by specifically inactivating RXR in other tissues. Researchers might investigate whether other components of milk also signal to the infant to trigger different postnatal maturational programs — for example, in the gut and the nervous system. Other nuclear receptors that bind to RXR to form heterodimers and have established roles in promoting cardiomyocyte maturation[6–8] should be analysed, to determine whether γ-linolenic acid modulates signalling through heterodimers or exclusively through RXR homodimers.

In heart failure, energy metabolism in heart cells shifts away from FAO and towards metabolism of glucose[9]. It will be interesting to determine whether altered γ-linolenic acid signalling through RXR contributes to this shift, and if it can be mitigated by administration of γ-linolenic acid. Human stem-cell-derived cardiomyocytes have promising uses in disease modelling and heart regeneration, but these cells fail to mature in culture and resemble neonatal or fetal cardiomyocytes[10]. Treating these cultured cells with a combination of fatty acids enhances their ability to generate force and their oxidative capacity[11]. Could augmentation of RXR signalling, by addition of γ-linolenic acid, further improve the maturity of these cells?

Paredes and colleagues have identified an environmental cue that triggers metabolic maturation of cardiomyocytes. The mechanism they have uncovered adds to a growing body of evidence for the role of the mother–infant relationship in postnatal development. Further investigation of this interplay could help researchers to better understand how the mammalian body is remodelled in the hours and days that follow birth.

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