MicroRNA control of cardiac regeneration

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The inability of the adult mammalian heart to regenerate following injury represents a substantial barrier in cardiovascular medicine. In contrast, we recently identified a brief window during neonatal development when the mammalian heart retains a robust capacity for regeneration following injury. Cardiac regeneration following either apical resection or myocardial infarction in neonatal mice involves proliferation of pre-existing cardiomyocytes, in the absence of any appreciable fibrotic scarring (Porrello *et al.*, 2011a; Porrello *et al.* ,2013). Cardiac regenerative capacity is progressively lost during the first two weeks of postnatal life, although the molecular mechanisms that govern this developmental transition are poorly understood.

Given the potential of microRNAs to regulate complex developmental and disease processes, as well as their emerging attractiveness for therapeutic application, we recently undertook studies to identify microRNAs involved in neonatal heart development and regeneration. These studies have revealed that microRNAs belonging to the miR-15 family are required for postnatal mitotic arrest of cardiomyocytes, which contributes to the loss of cardiac regenerative capacity during the neonatal period (Porrello *et al.*, 2011b; Porrello *et al.*, 2013). Transgenic over-expression of miR-195, a member of the miR-15 family, was sufficient to impair the neonatal cardiac regenerative response and was associated with increased fibrosis and reduced cardiomyocyte proliferation. Conversely, pharmacological inhibition of the miR-15 family by administration of antimiRs from an early postnatal age until adulthood induced myocyte proliferation in the adult heart and improved left ventricular systolic function following ischaemia-reperfusion injury (Porrello *et al.*, 2013).

Recent transcriptional profiling has provided further insight into the role of microRNAs during neonatal heart regeneration. By comparing the microRNA expression profiles of 1-day-old (P1) and 14-day-old (P14) mice following myocardial infarction using microarrays, a unique microRNA expression signature that defines the neonatal cardiac regenerative response was identified. For example, miR-29, which has been previously implicated as a potent repressor of fibrosis in multiple tissues, was found to be up-regulated 2-fold following infarction at P1 (regenerative heart), whereas the same microRNA was down-regulated 2-fold following infarction at P14 (non-regenerative heart).

These findings indicate that microRNAs play an important role in regulating cardiac regenerative capacity during neonatal life and could represent important future drug targets for ischaemic heart disease.

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