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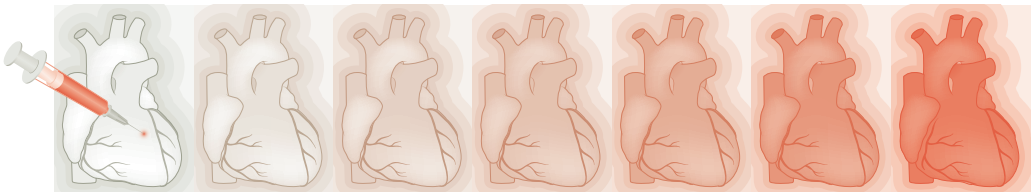

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REGENERATIVE MEDICINE

New targets for enhancing cardiac regeneration

The capacity of the adult mammalian heart to regenerate after injury is limited and is insufficient for repairing tissue damage after injury. Strikingly, the neonatal mammalian heart has regenerative potential, but this capacity is lost shortly after birth. Understanding the mechanisms that lead to the loss of cardiac regenerative potential could help to identify potential therapeutic targets to promote regeneration in adults. Two studies published in *Nature* unravel some of these mechanisms.

Bassat and colleagues set out to identify extracellular matrix (ECM) factors that affect cardiomyocyte growth and differentiation by comparing ECM fragments extracted from postnatal day 1 mouse hearts, and from day 7 hearts, when the cardiac regenerative capacity is lost. They identified a large extracellular heparan sulfate proteoglycan, agrin, that was enriched in day 1 ECM compared with day 7 ECM. *In vitro*, recombinant agrin induced proliferation of mouse cardiomyocytes, and also promoted proliferation and attenuated the maturation of human induced pluripotent stem cell-derived cardiomyocytes. To assess whether agrin had a role in neonatal cardiac regeneration, Bassat *et al.* generated a conditional *Agrn* knockout mouse model and found that agrin was necessary for the full regenerative capacity of the neonatal mouse heart.

The research team next investigated whether agrin could promote regeneration in the juvenile and adult heart. Indeed, a single intramyocardial injection of recombinant agrin promoted cardiac regeneration after myocardial infarction in mice. Given the degree of regenerative response achieved with a single administration of agrin, the investigators argue that additional therapeutic mechanisms must be involved beyond induction of cardiomyocyte proliferation, such as inhibition of fibrosis or modification of the immune response. "Collectively, we uncover a new inducer of mammalian heart regeneration, highlighting fundamental roles of the ECM in cardiac repair," conclude the investigators.

Agrin-induced cardiomyocyte proliferation involved binding of agrin to dystroglycan 1 (DAG1), which led to a partial dissasembly of the dystrophin–glycoprotein complex (DGC) and activation of downstream signalling, including the Hippo pathway effector Yap. This finding is in line with previous studies linking the DGC — a multicomponent complex connecting the ECM with the inner contractile machinery — and Hippo signalling, but the connection was poorly understood. A new study now provides further insights into this interaction.

James Martin and colleagues demonstrate that the DGC component DAG1 binds to and sequesters Yap to inhibit cardiomyocyte proliferation, and that this interaction was enhanced by Hippo-induced Yap phosphorylation. "It was known that the Hippo pathway represses Yap activity," explains Martin, corresponding author of the study, "and we have found a parallel pathway that also represses Yap activity."

Using loss-of-function mouse models and gene therapy approaches, the investigators showed that in the adult mouse heart the DGC and Hippo pathway cooperatively inhibit cardiomyocyte proliferation and limit tissue growth after injury through inhibition of Yap nuclear translocation, thereby preventing Yap transcriptional activity. Martin's research group previously showed that both the DGC and the Hippo pathway are involved in mammalian heart regeneration. Hippo deficiency resulted in heart repair with correct organ dimensions after ischaemic damage in both postnatal and adult mice. By contrast, deficiency in both the Hippo pathway and the DGC component dystrophin resulted in heart regeneration with excessive cardiomyocyte proliferation at the injury site in postnatal mice. Further investigations indicated that Hippo deficiency protected against overload-induced heart failure in a mouse model of Duchenne muscular dystrophy, suggesting that Hippo signalling can be a therapeutic target in this condition.

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ORIGINAL ARTICLES Bassat, E. *et al.* The extracellular matrix protein Agrin promotes heart regeneration in mice. *Nature* http://dx.doi.org/10.1038/nature22978 (2017) | Morikawa, Y. *et al.* Dystrophin glycoprotein complex sequesters Yap to inhibit cardiomyocyte proliferation. *Nature* http://dx.doi.org/10.1038/nature22979 (2017)

FURTHER READING Behfar, A. *et al.* Cell therapy for cardiac repair —lessons from clinical trials. *Nat. Rev. Cardiol.* **11**, 232–246 (2014)

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