Lin28a – boost your energy for youthful regeneration

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The regenerative capacity of most tissues declines dramatically after embryonic development and during post-natal life. The underlying mechanisms of this phenomenon are incompletely understood. In a recent issue of *Cell*, Shyh-Chang and colleagues provide experimental evidence that Lin28 prolongs youthful regenerative capacity by increasing oxidative glucose metabolism (Shyh-Chang *et al*, 2013).

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The RNA-binding protein Lin28 is a highly conserved regulator of miRNAs that also represses the biogenesis of let-7 – a group of miRNAs impairing growth and stem cell activity by induction of differentiation and inhibition of IGF signals (reviewed in Thornton & Gregory, 2012; Toledano *et al*, 2012; Nishino *et al*, 2013). Mammals contain two paralogs, Lin28a and Lin28b, which both inhibit let-7. While let-7 expression is upregulated with increasing age, Lin28 is expressed during embryogenesis, but downregulated in postnatal tissues.

Due to the close connection of Lin28a/b to developmental processes, Shyh-Chang *et al* hypothesized that regeneration in post-natal animals might be improved after reprogramming with Lin28. To test this, they utilized a doxycycline-inducible Lin28a transgenic mouse (iLin28a Tg). Slightly elevated Lin28a levels in un-induced mice were sufficient to repress let-7 miRNAs resulting in an enhanced regenerative capacity of multiple tissues including hair, cartilage and skin, mesenchymal connective tissue, and

bone. Of note, overexpression of let-7 inhibited Lin28-induced enhancements in tissue repair, but inhibition of let-7 on its own was not sufficient to boost regeneration. These data indicate that targets downstream of the Lin28-let7 axis contribute to the pro-regenerative switch, but Lin28-dependent/let-7-independent targets are required for the full regenerative effect in the investigated tissues.

Lin28a directly binds numerous mRNAs and influences their translation independently of let-7. Among these targets are factors that regulate metabolic processes and cell growth. Interestingly, these targets have originally been identified in human embryonic stem cells (Peng *et al*, 2011). Lin28a thus directly helps to control the metabolic state of cells important for tissue generation. Shyh-Chang *et al* tested whether this role of Lin28a could explain the regained regenerative capacity of adult tissue in inducible Lin28a transgenic mice. Indeed, Lin28a reactivation elevated mitochondrial oxidative phosphorylation (OxPhos) – the most efficient way of releasing energy from glucose. Of note, repression of let-7 did not mimic the Lin28-induced increase in OxPhos, which the investigators show to be required for improvements in regeneration.

The current study by Shyh-Chang *et al* provides the first experimental evidence that Lin28-mediated increases in OxPhos lead to an elevation of the regenerative capacity of various tissues in young adult mice. Similar pro-regenerative effects were previously reported in mice lacking the expression of p21 – a cyclin-dependent kinase inhibitor limiting cell cycle progression (Bedelbaeva *et al*, 2010). The current study shows that

Lin28-dependent increases in regeneration are independent of defects in p21 expression. While p21 was also shown to improve regeneration and stem cell maintenance in ageing tissues with short telomeres (Choudhury *et al*, 2007), the role of Lin28-mediated increases in oxidative glucose metabolism in ageing associated impair-

Figure 1. The current study by Shyh-Chang *et al* shows that Lin28 promotes tissue regeneration by increasing energy production through activation of oxidative phosphorylation (OxPhos) involving let-7 dependent and let-7 independent regulation of target genes.

ments in regeneration and stem cell function remain to be investigated.

Interestingly, a recent study showed that age-dependent increases in the level of let-7 reduce IGF-II messenger RNA binding protein (IMP), which itself promotes expression of genes required for stem cell maintenance in the *Drosophila* testis (Toledano *et al*, 2012). Similarly, accumulating experimental evidences indicate a role of Lin28, let-7 and IMPs in the maintenance of neuronal stem cells during postnatal life and ageing (Nishino *et al*, 2008, 2013). Whether Lin28/let-7/IMP dependent effects on the maintenance of tissue stem cells depend on switches in glucose metabolism remains to be investigated. Intriguingly, one of the mammalian homologues of IMP (IMP2) promotes the maintenance of cancer stem cells in glioblastoma by activating OxPhos via stimulation of mRNA translation and assembly of subunits of the mitochondrial complex (Janiszewska *et al*, 2012).

Together, Lin28/let-7/IMP mediated regulations of glucose metabolism emerge as a potent regulator controlling stem cell functionality, regeneration and carcinogenesis (Fig 1). Targeting of this molecular circuit for regener-

ative medicine will ultimately depend on the possibility to discriminate pro-regenerative from pro-carcinogenic effects.

Conflict of interest

The authors declare that they have no conflict of interest.

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