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SIGNALLING

Fill in the blanks...

...or 'join the (molecular) dots' from Wnt to the myogenic determinant genes. The solution comes from Chen, Ginty and Fan, who have found that signalling from protein kinase A (PKA) through cyclic-AMP-response-element-binding protein (CREB) mediates the induction by Wnt of the myogenic determinants *Pax3*, *MyoD* and *Myf5*.

Wnt proteins are expressed in areas close to myogenic precursor cells and, *in vitro*, can induce *Pax3*, *MyoD* and *Myf5*, but apparently not through canonical β -catenin-mediated transcription. As evidence is mounting that Wnt uses G-proteins to signal, the authors investigated a potential role for one of the main G-protein pathways through adenylyl cyclase to the transcription factor CREB in myogenesis. They used CREB phosphorylation as a readout of the activity of PKA, which lies downstream of adenylyl cyclase, and found dynamic patterns of CREB phosphorylation in areas that mirror the patterns of myogenic induction. 10.5-day-old embryos from *Creb*^{-/-} mice showed reduced and restricted gene-expression patterns for *Pax3*, *MyoD* and *Myf5*, which were also mirrored at the protein level. There was a compensatory increase in other CREB-family members, and so, when all family members were inhibited using a dominant-negative approach (adenovirally expressed acidic CREB, Ad-ACREB), the myogenic defects were, as expected, more severe.

To see where CREB fits between Wnt and myogenic induction, Chen, Ginty and Fan used an *in vitro* assay in which embryonic presomitic mesoderm (psm) explants were co-cultured with Wnt1- or Wnt7a-expressing cells to induce myogenic genes. Infecting the explants with Ad-ACREB repressed Wnt1- or Wnt7a-induced myogenesis at the same time as repressing expression of the myogenic genes. Both Wnt1 and Wnt7a induced CREB phosphorylation in psm cells in this system. Co-culture of Wnt1- or Wnt7a-expressing cells with two other cell types could also induce CREB-mediated transcription (measured using a CRE-luciferase reporter). In both cases, Ad-ACREB or an adenylyl-cyclase inhibitor blocked reporter induction. Recombinant Wnt3a induced CREB phosphorylation in psm cells, and this, too, was inhibited by an adenylyl-cyclase inhibitor or by a dominant-negative form of PKA. All of these findings point to CREB being

downstream of adenylyl cyclase and PKA in Wnt signalling.

Consistent with this, artificially increasing or decreasing adenylyl-cyclase activity by modulating G α proteins in psm-Wnt-cell co-cultures enhanced or repressed, respectively, myogenic gene expression. Finally, the authors used the psm explant cultures to show that Wnt proteins require adenylyl cyclase and PKA activity to mediate myogenesis. Although there are core CRE sites in the *Myf5* and *Pax3* promoters, it remains to be seen whether CREB directly activates the myogenic genes. Wnt researchers will also puzzle over a potential involvement of the PKA-CREB pathway in Wnt-induced cell proliferation and survival for stem cells and cancer cells.

Katrin Bussell

References and links

ORIGINAL RESEARCH PAPER Chen, A. E., Ginty, D. D. & Fan, C.-M. Protein kinase A signalling via CREB controls myogenesis induced by Wnt proteins. *Nature* 28 Nov 2004 (doi:10.1038/nature03126)