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Nanog, Gli, and p53: a new network of stemness in development and cancer

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Nanog and Hedgehog (HH) are both essential regulators of stemness by promoting self-renewal in embryonic stem cells, during early embryonal development (Mitsui *et al*, 2003) and in cancer cells (Jeter *et al*, 2009). Two groups have now shown that HH signalling regulates Nanog expression in neural stem cells in the adult brain and in brain tumours. In this issue of *The EMBO Journal*, Po *et al* (2010) and Zbinden *et al* (2010) demonstrate that downstream effectors in the HH pathway, Gli1 and Gli2 directly bind to the Nanog promoter and thus activate Nanog expression (Figure 1A). Po *et al* (2010) use the cerebellum as experimental paradigm (Figure 1C) and show that Nanog is highly expressed in stem cells derived from the postnatal cerebellum and in medulloblastoma, a malignant brain tumour arising from the cerebellum in children. This work is complemented by a study by Zbinden *et al* (2010), who use glial tumours and tumour spheres to demonstrate that the Gli–Nanog axis promotes stemness and growth in gliomas (Figure 1B).

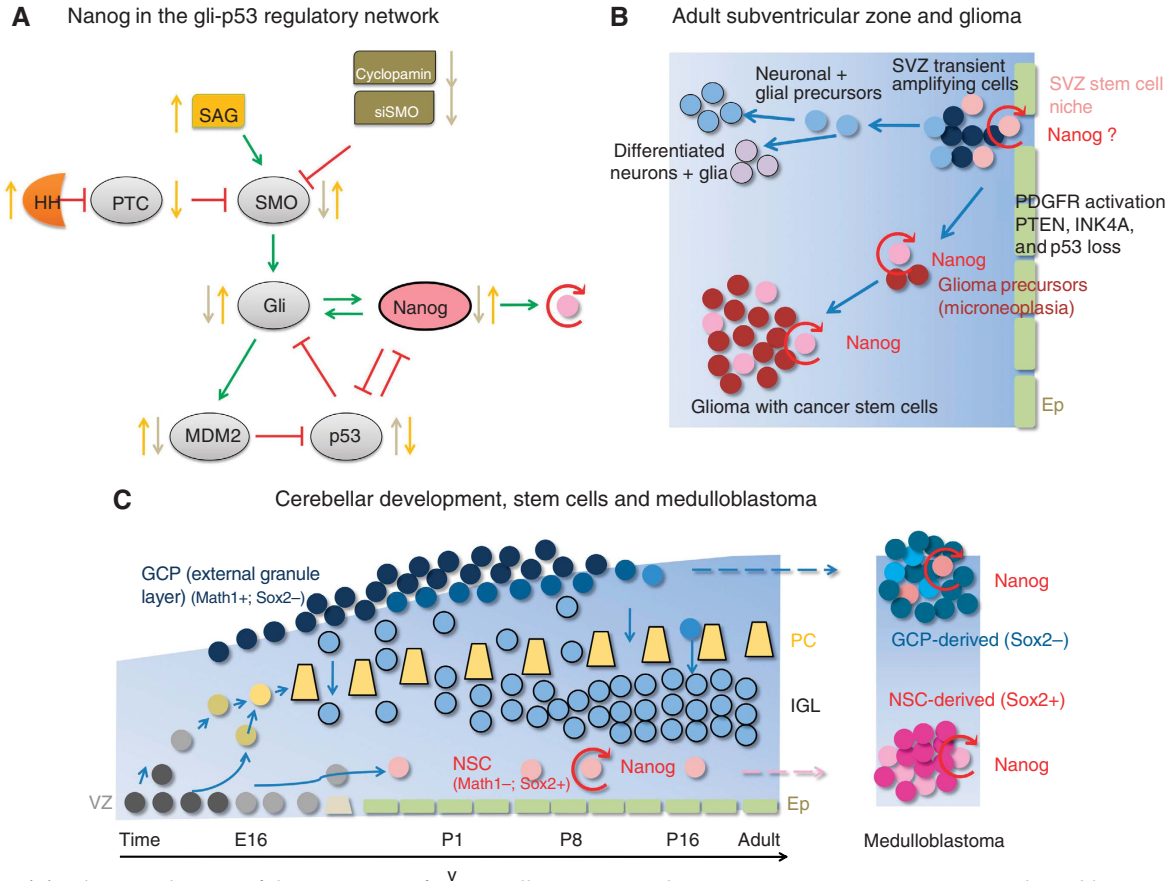

Figure 1 (**A**) Schematic diagram of the interaction of HH signalling on p53 and Nanog. Activating interactions are indicated by green arrows and inhibition is indicated by red symbols. The effect of HH or the HH agonist SAG are indicated by yellow arrows next to the molecules, whereas the effect of HH pathway inhibitors (Cyclopamine, siSMO) is symbolized with grey arrows. (**B**) Nanog promotes clonogenicity and proliferation of gliomas, and probably also has a function in the maintenance of stemness in the stem cell niche of the subventricular zone. (**C**) Nanog controls stemness in cerebellar stem cells and in medulloblastoma cancer (stem) cells. The developing cerebellum is illustrated on a time axis relevant for the mouse brain. Darker colours indicate higher proliferation, and circles symbolize postmitotic cells in panels (**B**, **C**). VZ, ventricular zone; Ep, ependymal layer; GCP, granule cell precursor; IGL, internal granule layer; NSC, neural stem cell; PC, Purkinje cells.

Two cell populations of stem/progenitor cells are involved in cerebellar morphogenesis and in medulloblastoma pathogenesis (Figure 1C). A population of transient amplifying progenitor cells originates from the rhombic lip and migrates along the outer surface of the developing cerebellum to form the external granular layer. This cell population (termed granule cell precursors, GCPs) is only transiently present during cerebellar development: GCP divide, and during their migration towards and ultimately past the Purkinje cells they differentiate and form the definitive layer of internal granule neurones. This process is dependent on the mitogen sonic HH (Shh), secreted by Purkinje cells, whereas GCP express the Shh receptor PTCH. Binding of Shh to PTCH leads to disinhibition of smoothened (SMO), which activates its downstream targets Gli1 and Gli2, promoting growth and counteracting differentiation (Figure 1A). It is well established that aberrant activation of the HH pathway in EGL progenitor cells either by PTCH loss of function or SMO gain of function mutations causes their sustained, uncontrolled proliferation and initiates medulloblastomas originating from the EGL (Goodrich *et al*, 1997). A well-established characteristic of these GCP as well as medulloblastomas derived thereof is expression of Math1 and lack of the stemness marker Sox2 (Figure 1C).

The second cell population that contributes to cerebellar morphogenesis and also to pathogenesis of a subtype of medulloblastomas arises from the ventricular plate. These cells give rise to neurons that migrate outwards to form the Purkinje cell layer, interneurons, Bergmann glia and to cells that persist as stem cell population in the white matter during adulthood. This stem cell population is negative for Math1, but expresses Sox2 and CD133, though controversy remains whether this population is HH responsive (Yang *et al*, 2008; Po *et al*, 2010; Lee *et al*, 2005). In keeping with the origin from Sox2-positive stem cells, medulloblastoma arising from this population are Sox2-positive (Sutter *et al*, 2010) (Figure 1C).

Another population of stem and progenitor cells in the adult brain resides beneath the lateral ventricles, the subventricular zone. These cells are responsive to HH signalling (Palma *et al*, 2005), and they are thought to be the origin of gliomas (Zheng *et al*, 2008; Alcantara Llaguno *et al*, 2009; Jacques *et al*, 2010). In young or middle-aged adults, gliomas present as low-grade astrocytomas or as anaplastic (high grade) astrocytomas, both of which ultimately progress to glioblastomas, whereas *de novo* (primary) glioblastomas more commonly occur in the elderly. Although HH is not involved in glioma initiation (Yang *et al*, 2008), it does promote and maintain glioma growth by maintaining their stemness (Clement *et al*, 2007). Data presented by Zbinden *et al* (2010) take these findings further, demonstrating that HH responsive glioma stem cells show a cross-activation of Nanog and Gli (Figure 1A and B). This provides an attractive novel scenario for the concept of cancer stem cells in the growth of gliomas.

A compelling further addition to this regulatory network is p53, which directly suppresses Nanog by binding to its promoter. Loss of p53 promotes stemness and self-renewal and in keeping, both studies demonstrate an activation of Gli and Nanog upon knockdown of p53, while intact p53 suppresses Nanog function.

This newly established network of Nanog, Gli, and p53 opens an exciting new playground for future studies of stemness in health and disease, and will allow further illumination of the cancer stem cell concept.

Conflict of interest

The author declares that he has no conflict of interest.

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