



Oncogenic insult to the brain: sox proteins rise to the occasion

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The concept of cancer stem or stem-like cells has changed thinking and approaches in oncology just as much as the discovery of stem cells did in developmental biology and regenerative medicine before. Glioblastoma multiforme (GBM) as the most frequent and malignant primary brain tumor with an extremely poor prognosis is a case in point (1). So-called glioma stem-like cells (GSCs) are thought to originate from neural stem cells (NSCs) and play an important role in GBM initiation (2). The transcriptional network of GSCs still bears resemblance to the one of normal NSCs. However, during malignant transformation changes occur that deregulate expression of neural stem cell traits (3) and factors such as complexes consisting of cyclins and cyclin-dependent kinases (CDK), CDK inhibitors (CDKi) and p53 (4,5), which in turn influence proliferation, cell cycle, mode of division and decisions to self-renew or differentiate. Levels of CDKi and p53 are, for instance, usually low in GSCs and GBM. Their increase in normal NSCs counteracts and prevents malignant cell transformation upon oncogene-based cellular stress (6,7).

In a recent publication, Kurtsdotter and colleagues identified a surprising mechanism that prevents oncogene-driven transformation of NSCs in the adult brain by raising CDKi and p53 levels. This mechanism involves the Sox family of high-mobility-group (HMG) domain transcription factors, in particular Sox5, Sox6 and Sox21 (Sox5/6/21). The SoxD proteins Sox5 and Sox6 are important transcriptional modulators of cell fate choices and regulators of differentiation processes, including chondrogenesis, neurogenesis and gliogenesis, erythropoiesis, neural crest

and (heart) muscle development [for review see (8)]. In line with the important developmental functions of Sox5 and Sox6, Sox5-deficient mice die during late embryogenesis, while Sox6-deficient mice usually do not survive beyond the third postnatal week. Sox5 and Sox6 have both redundant as well as unique functions. They interact in several cell types including chondrocytes and glia with Sox9 and Sox10 to boost or antagonize the function of these distantly related SoxE proteins (9,10). However, functions in other cell types are independent of Sox9 or Sox10 (8).

Sox21 belongs to a different group of Sox proteins, the SoxB2 class. It was shown to impact neuronal fate decisions and trophoblast stem cell differentiation and placentation (11-13). Deletion of Sox21, however, results in viable mice that only exhibit a mild phenotype of alopecia (11).

Previous *in vivo* and *in vitro* studies indicated that these transcription factors may have a role in counteracting glioma progression (14,15). In their current study, Kurtsdotter and colleagues focused on the role of Sox5/6/21 in NSCs of the adult mouse subventricular zone (SVZ) and provide evidence for a new role of these Sox proteins in preventing transformation of NSCs upon oncogenic insult.

Sox5/6/21 are already expressed in the vast majority of NSCs in the SVZ of the brain. Upon targeted expression of the well-known oncogenes AKT and H-RAS (referred to as oncogenic insult), Sox5/6/21 expression levels increased dramatically in NSCs and were found to promote cell cycle exit in agreement with previous findings (16,17). This suggested that Sox5/6/21 are part of the cellular response to counteract oncogenic transformation. In line

with such an assumption, loss of Sox5/6/21 in the mouse SVZ greatly enhanced the incidence of glioma-like tumors as well as their size upon oncogenic insult. Additionally, genes affecting tumor progression, cell cycle regulation and proliferation were deregulated under Sox5/6/21 deficiency. Cyclin levels were dramatically increased and the physiological upregulation of CDKi and p53 levels was prevented. While high levels of cyclins D2 and E1 were predominantly associated with loss of Sox21, the most significant increase in Sox5/6-deficient cells was found in cyclin A1, indicating that Sox21 regulates a different phase of the cell cycle than the structurally different Sox5 and Sox6 proteins (8,12,18).

These data provide convincing evidence for the essential role of the three Sox proteins in mounting an anti-proliferative response and in activating important tumor suppressors under oncogenic stress. The importance of Sox5/6/21 was supported by the fact that high levels restored an anti-tumorigenic expression profile and tumor suppressor responses in human primary GBM cells such that Sox5/6/21-transduced GBM cells failed to form secondary tumors upon striatal transplantation in NOD-SCID mice. Previous publications also support such a role. Sox5 had been shown to promote senescence in glioma with loss of the tumor suppressor gene *Ink4a* (15), while Sox21 had been found to inhibit glioma progression and induce apoptosis of glioma cells (14). Intriguingly, loss of Sox5/6/21 did not cause excessive proliferation in NSCs of the adult SVZ in the absence of an oncogenic insult, arguing that their function in NSCs is oncogene-induced.

Kurtsdotter and colleagues also addressed the underlying mechanism. By performing p53 knockdown experiments the authors found that p53 is essential for the capacity of Sox21 to restore a tumor suppressor response in human primary GBM cells. Strikingly, misexpression of Sox21 did not increase *p53* gene expression, but p53 protein levels. This in turn upregulated p21 and p57 as CDKi, both transcriptionally and on protein level. Furthermore, protein, but not transcript levels of Mdm2 as the major negative regulator of p53 were reduced. Thus, Sox21 partly restores the tumor suppressor response by counteracting p53 protein turnover, most likely by controlling Mdm2 protein levels. Although being a transcription factor, Sox21 appears to exert its regulatory function predominantly on the posttranscriptional level. Interestingly, this is not unheard of for Sox proteins and fits well to other studies that attribute the tumor suppressor role of Sox6 in hepatocellular carcinoma to stabilization of p53 protein and

upregulation of p21 protein levels (19,20).

Overall, the work of Kurtsdotter *et al.* provides exciting novel insights into the roles of Sox5, Sox6 and Sox21 in glioma formation. Frequently, the function of a particular protein in tumors can be deduced from its developmental or physiological function. Strikingly, this is not the case for the three Sox proteins whose ability to elicit an anti-proliferative and anti-tumorigenic response in NSCs becomes evident only upon oncogenic insult and does not correlate with any comparable function in NSCs during ontogenetic development or in the unchallenged brain. Physiologically, Sox5 and Sox6 are instead prominently involved in cell fate decisions and differentiation processes (8). Sox21 even appears to be mostly dispensable during normogenesis (11). This argues that the three Sox proteins may have a tumor-specific function.

Despite their similar role in preventing oncogenic transformation, Sox21 is structurally quite different from Sox5 and Sox6. They belong to different subgroups of the Sox family and share little similarity outside the DNA-binding HMG-domain (18). Even their interaction with DNA is quite different. Whereas Sox21 usually binds as a monomer, Sox5 and Sox6 constitutively act as homo- or heterodimers. A transcriptional mechanism for a common function is thus not obvious. In fact, there is evidence from the work by Kurtsdotter and colleagues that there are differences in the exact function of the three Sox proteins as indicated by their ability to target different cyclins and function additively.

However, in this context, it is also noteworthy that Kurtsdotter and colleagues could not find evidence that the three Sox proteins work on the transcriptional level. This may also explain why their differences as transcription factors do not show so much. Instead, the three Sox proteins seem to function predominantly on the posttranslational level by influencing protein levels of p53, Mdm2 and CDKi. How they exactly do this, still remains to be established. Thanks to Kurtsdotter *et al.*, Sox5, Sox6 and Sox21 have been added to the list of important factors for GSC and glioma formation. The study also argues that there may be ways to boost the anti-tumorigenic response in GSCs as an alternative therapeutic strategy for glioma.

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Footnote

Conflicts of Interest: Wüst HM is a graduate student of RTG2162 “Neurodevelopment and Vulnerability of the Central Nervous System”. The other author has no conflicts of interest to declare.

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