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The Role of Sox Transcription Factors in Brain Tumourigenesis

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1. Introduction

1.1 Brain tumours/ glioma and medulloblastoma

The total amount of brain tumours that effect humans is less than 2%. In children are brain tumours the second most common cancer type after leukaemia. Brain tumours and tumours in CNS (central nervous system) constitute 25% of all childhood tumours and is the most common cause of cancer mortality in children. Medulloblastoma is the most frequent malignant brain tumour type in children, whereas in adult glioblastoma multiforme (GBM) is the most malignant and common form. Although GBM occur in children but the diagnose is more uncommon.

Primary brain tumours are classified according to the World Health Organization (WHO) which means grading (I-IV) of the tumours based on tumour histology and pathology (Louis, et al., 2007). However, other criteria such as the age of the patient, tumour location, radiological features, surgical resection, proliferation index and genetic alterations are important when predicting a response of therapy (Louis, et al., 2007).

1.1.1 Glioma

Gliomas, tumours arise from glial cells, are the most common primary brain tumours of the central nervous system. Gliomas can be divided into astrocytomas, oligodendrogliomas, oligoastrocytomas and ependymomas based on their histological pattern (Louis, et al., 2007). Gliomas are further divided into four clinical grades based on their histology and pathology where GBM is a grade IV glioma. High grade gliomas are often biphasic tumours composed of distinct histological parts and they contain a very heterogeneous cell population (Kattar, et al., 1997). GBM develops either de novo (primary GBM), or through progression of lower grade glioma (secondary GBM). The number of genes and chromosomal changes are often correlated to glioma grade. For patients diagnosed with GBM, the mean survival time is less than 1 year. Most gliomas diffusely infiltrate the surrounding brain tissue which makes it very difficult to completely eliminate the tumour and which later makes the tumour relapse after treatment (Louis, et al., 2007). The cell-of-origin for gliomas is still not known but the origin is suggested to be a glial stem-like cell or progenitor cell.

Recently GBM is proposed to be subdivided in to four groups, classical, mesenchymal, proneural and neural, based on their specific gene-signature. The classical subgroup is

primarily characterized by EGFR (Epithelial growth factor receptor) amplification and expression of stem cell and neural progenitor markers. The mesenchymal group is distinguished with deletions in *NF1* gene which results in low expression of NF1 (Neurofibromatosis type 1) and expression of mesenchymal markers such as CHI3L1 and MET. GBM of proneural origin are characterized by *PDGFR* alterations and mutations in the *IDH1* gene (isocitrate dehydrogenase 1). Further the proneural group express markers for oligodendrocytes as well as *SOX* genes. This group of GBM has somewhat longer survival. The features of the neural subgroup are expression of neural markers for instance *NEFL*, *GABRA1*, *SYT1* and *SLC12A5* (Phillips, et al., 2006; Verhaak, et al., 2010).

1.1.2 Medulloblastoma

Medulloblastoma is a highly invasive tumour located in the cerebellum, and belongs to the group of primitive neuroectodermal tumours (PNET), and generally affects children between three and nine years. Medulloblastoma is a grade IV tumour and the cell-of-origin is thought to be a pluripotent neural stem cells. Several chromosomal and genetical changes are identified in medulloblastoma. The most frequent change is isochromosome 17q. Other frequent genetical changes are affecting the Sonic hedgehog (Shh) signalling pathway, which are found in approximately 25% of medulloblastomas (Ellison, et al., 2003). Medulloblastoma is mainly divided into two subgroups, classical and desmoplastic medulloblastoma, and the tumour types differ in histology as well as in genetics (Ellison, et al., 2003). Recently medulloblastomas were subdivided into 5 different subtypes based on their characteristic gene-signature caused by genetic aberrations and mutations in specific signalling pathways as well as on their clinicopathological features (Kool, et al., 2008). The five subgroups are characterized by WNT-signalling (medulloblastoma type A), Shh-signalling (type B), neuronal differentiation (type C and D) and phosphoreceptor differentiation (type D and E) (Kool, et al., 2008).

A better insight and understanding of the molecular mechanisms behind infiltrative brain tumours and discovery of the cell-of-origin may help to generate novel ideas for treatment. Today treatment of brain tumours includes surgery if possible, radiation and chemotherapy but despite that tumours often recur and 50% of the GBM patients die within the first year (Holland, 2001). There have been many attempts to treat human gliomas but the success on the prognosis is still absent and this is mainly due to the diffuse infiltration of tumour cells into the normal brain tissue and unsuspected cell proliferation. Medulloblastomas are more sensitive to radiation and chemotherapy and about 60% are cured but many children suffer from severe side effects as motorical difficulties, learning problems and signs of fatigue (Ellison, et al., 2003).

1.2 Cancer stem cells/ progenitor cells

Current data suggest that initiation and progression of brain tumours are driven by cancer stem-like cells/progenitor cells. Cancer stem-like cells are rare tumour cells defined as cells which have the ability of unlimited self-renewal, the capacity to initiate and force tumour progression, and to differentiate into different cell lineages (Galderisi, et al., 2006). The cancer stem-like/progenitor cell has been identified in a number of studies of brain tumours (Galli, et al., 2004; Singh, et al., 2003; Yuan, et al., 2004) but exactly which cell that initially is transformed into the tumour initiating cell is still not clarified. Tumour progenitor cells have a slower division rate which could make them more resistant to treatment than the bulk tumour and which later can re-generate the tumour (Hirschmann-Jax, et al., 2004; G. Liu, et

al., 2006). Cancer stem-like cells are believed to be responsible for tumour initiation, progression and for tumour relapse, which make the cancer stem-like cell become a recent and very interesting target for novel and more effective therapies. There are many mechanisms involved in regulating neural stem cells and several of these seems to be involved in brain tumour development. To identify potential tumour stem-like cells in brain tumours, different neuronal precursor markers are used and further markers are used to study their differentiation capacity. In this chapter I will discuss certain transcription factors belonging to the Sox super-family. For example Sox1-4 are involved in regulating neural precursor cells as well as the developing CNS, these transcription factors have also recently been shown to be involved in the regulation of the brain tumour stem-like cell (Gangemi, et al., 2009; Ghods, et al., 2007; Ikushima, et al., 2009). In addition, other members of the Sox super-family are suggested to be involved in the differentiation process and several of the Sox protein family members are proposed to be used as markers for different types of brain tumours.

I will discuss the new findings concerning the role of the Sox super-family in brain tumours and in brain tumour stem-like cells, as potential differentiation factors or as potential diagnostic markers of glioma but first there will be an overview of the Sox super-family and the normal expression of Sox proteins in the brain.

2. The Sox super-family

2.1 Sox structure and classification

The first identified *Sox* gene was *Sry*, the mammalian sex-determining Y-linked gene. *Sry* contains a DNA-binding motiv known as the HMG domain (high mobility group domain) (Gubbay, et al., 1992; Sinclair, et al., 1990). The HMG domain is present in a number of genes which belongs to the HMG box super-family. The HMG domain consists of 79 amino acids and some of these amino acids are conserved within the HMG box super-family, although the HMG domains can alter to a large extent. One difference with HMG domains compare to other DNA-binding domains is that the HMG domains interact with the minor groove on the DNA helix and this binding bends the DNA drastically (for review (Wegner, 1999). The Sox protein family is a group of transcription factors which all contain a highly conserved HMG domain, the domain has more than 60% similarity to the Sry HMG domain (Sox - Sry related HMG box) (Laudet, et al., 1993). To date 20 different *Sox* genes are identified in humans and mice and they are divided into eight different subgroups, A-H (Table 1). Proteins in the same subgroup share >80% of the amino acids within the HMG domain (for review (Wegner, 1999). The binding properties of the HMG domains to the DNA are similar between the Sox proteins and the DNA sequence of recognition for binding is only 6-7 base pair (for review (Kamachi, et al., 2000). Except for the HMG domain, Sox proteins contain activating and/or repressing domains, which play a part in there transcription activity (Pusch, et al., 1998; van de Wetering, et al., 1993). In addition there is evidence that Sox proteins perform their function by a complex interplay with specific partner factors to regulate gene transcription. The partner factors can be different depending on cell type, promoter and developmental stage. This enhances the specificity of the transcriptional regulation by a particular Sox protein to a large extent (for review (Kamachi, et al., 2000).

2.2 The function of Sox proteins during development and in adult

Sox proteins are involved in several developmental and adult processes in a cell specific manner. A number of Sox proteins have partial overlapping expression patterns and others

not. Further, several of the Sox proteins have similar effects like Sox1, Sox2 and Sox3 are all expressed in progenitor cells during CNS development (Bylund, et al., 2003). Reduction in expression of one of Sox1-3 does not result in significant loss of function, e.g. deletion of Sox1 in mouse results in spontaneous seizures which give rise to a relatively mild CNS phenotype (Nishiguchi, et al., 1998) indicating that the similarities between Sox1-3 makes it possible for the proteins to at least some extent compensate for each other. In other cell types this may not be the case; for example Ferri et al show that neural precursors with deficient Sox2 expression in adult are dependent of correct Sox2 expression levels to generate new precursor cells and neurons (Ferri, et al., 2004). Sox2 is also essential in early embryonic development. Ablation of Sox2 in homozygous mouse case death at implantation and it is not even possible to generate Sox2 homozygous ES cells (Avilion, et al., 2003). Group C, containing Sox4, Sox11 and Sox12/22 is another group which often shows overlapping protein expression in both CNS and PNS (peripheral nervous system) (Cheung, et al., 2000; Hoser, et al., 2008).

On the other hand the same cell type can express more than one Sox protein although the proteins can have counteracting effects. One example of that is the Group B of *Sox* genes, where Sox1-3, which belong to the B1 subgroup, contains an activating domain and on the other hand Sox14 and Sox21, subgroup B2, includes a repressive domain (Uchikawa, et al., 1999). During embryogenesis and neurogenesis of the neural tube of chicken are genes of Group B1 and B2 expressed in an overlapping manner (Sandberg, et al., 2005; Uchikawa, et al., 1999). It is suggested that a proper balance between Group B1 and B2 proteins determine whether the cell stays in a progenitor/proliferating state or if the cells starts to differentiate (Sandberg, et al., 2005; Uchikawa, et al., 1999). It is shown that induced expression of Sox21 in neural cells promote differentiation by disturbing the balance between Sox1-3 and Sox21 (Sandberg, et al., 2005). Further, we have shown that an overexpression of Sox21 in glioma cells reduces glioma cell proliferation by inhibition of Sox2 (Ferletta, et al., 2011).

2.3 Expression pattern of Sox proteins in the normal CNS

The expression patterns of the different Sox proteins in brain and CNS are summarized in Table 1. Several of the Sox proteins are expressed during embryogenesis, one of the first is Sox2. Sox2 RNA is detected already at day 2.5 postcoitum (dpc) at the morula stage and Sox2 is shown to be important in the epiblast and the extra embryonic ectoderm as well as in pluripotent precursors of all embryonic and trophoblast cell types. Targed disruption of the *Sox2* gene is embryonic lethal around implantation (Avilion, et al., 2003).

Sox2 is important in early stages of the embryonic nervous system. In adult nervous system, Sox2 is mainly found in neuronal stem cells and in undifferentiated precursors (Wegner & Stolt, 2005) even though Sox2 is expressed in some differentiated neurons (Cavallaro, et al., 2008). In adult is the expression of Sox2 found in the subventricular zone (SVZ) and in the hippocampus dentate gyrus (DG) and in these regions Sox2 is found to be co-expressed with GFAP and nestin and further these cells are thought to be the adult neural stem cells (Ellis, et al., 2004; Ferri, et al., 2004; Suh, et al., 2007). All proteins of the SoxB group (Sox1-3, Sox14 and Sox21) are expressed in the developing brain to different extent during the development and many of the Sox proteins coexist throughout the CNS (Uchikawa, et al., 1999). When SoxB1 genes (*Sox1*, *Sox2* or *Sox3*) are overexpressed in chicken neural progenitor cells, the cells remain in their neural progenitor state (Bylund, et al., 2003; Graham, et al., 2003). On the other hand inhibition of SoxB1 proteins force cell-cycle exit and neuronal differentiation

(Bylund, et al., 2003). As mentioned Sox21 is able to counteract the activity of SoxB1 proteins and overexpression of Sox21 in chick embryos drives the neural progenitor cells to neuronal differentiation (Sandberg, et al., 2005). Even though all the members of the SoxB1 genes are expressed in neuronal stem cells neither the Sox1 nor the Sox3 deficient mice suffer from sever CNS defects (Nishiguchi, et al., 1998; Weiss, et al., 2003).

Sox subgroup	**Sox transcription factor**	**Expression in CNS**	**References:**
A	SRY	Midbrain and hypothalamus in adult male brain.	(Lahr, et al., 1995).
B1	SOX1	Developing CNS. Neural stem cells. Adult cerebellum: Purkinje cells, Bergman glia.	(Alcock, et al., 2009; Alcock & Sottile, 2009; Bylund, et al., 2003; Pevny, et al., 1998; Uchikawa, et al., 1999).
B1	SOX2	Developing CNS. Embryonic stem cells, neural stem cells. Adult: Neural stem cells, postmitotic neurons, pyramidal cells, Purkinje cells, Bergman glia	(Alcock, et al., 2009; Alcock & Sottile, 2009; Avilion, et al., 2003; Bylund, et al., 2003; Ferri, et al., 2004; Uchikawa, et al., 1999; Zappone, et al., 2000).
B1	SOX3	Developing CNS. Neural stem cells, mature neurons of the ventral hypothalamus	(Bylund, et al., 2003; Rizzoti, et al., 2004; Uchikawa, et al., 1999).
B2	SOX14/SOX28	Developing CNS.	(Uchikawa, et al., 1999).
B2	SOX21/SOX25	Developing CNS.	(Uchikawa, et al., 1999).
C	SOX4	Developing CNS. Oligodendrocyte precursors, neural precursors. Early differentiating cells in the CNS, neurons.	(Cheung, et al., 2000; Kuhlbrodt, Herbarth, Sock, Enderich, et al., 1998).
C	SOX11	Developing CNS. Oligodendrocyte precursors, neural precursors, mature neurons and later in differentiating brain areas as cortical plate and inferior colliculus.	(Kuhlbrodt, Herbarth, Sock, Enderich, et al., 1998; Uwanogho, et al., 1995).
C	SOX12; SOX22	Developing CNS	(Jay, et al., 1997).
D	SOX5	Developing CNS, oligodendrocyte progenitors, oligodendrocytes and neuronal subpopulations (as dorsal horn neurons). Adult: oligodendrocyte progenitors	(Stolt, et al., 2006).
D	SOX6	Developing CNS, oligodendrocyte progenitors, oligodendrocytes and neuronal subpopulations. Adult: oligodendrocyte progenitors	(Connor, et al., 1995; Stolt, et al., 2006).
D	SOX13	Developing CNS, neural progenitors and in differentiating neuronal cells.	(Y. Wang, et al., 2005).

Sox subgroup	Sox transcription factor	Expression in CNS	References:
E	SOX8	During development of CNS in neurons. Oligodendrocyte precursors, astrocytes and oligodendrocytes. Immature Bergman glia and EGL cells (external granule layer), and macroglia.	(Cheng, et al., 2001; Sock, et al., 2001; Stolt, et al., 2004).
E	SOX9	Neural stem cells, astrocytes, oligodendrocytes, Radial glia in developing CNS. Adult: neural stem cells, astrocytes and Bergman glia. Adult cerebellum: Purkinje cells	(Alcock & Sottile, 2009; Scott, et al., 2010; Stolt, et al., 2003) (Alcock, et al., 2009).
E	SOX10	Precursor and mature oligodendrocytes during development and in adult	(Kuhlbrodt, Herbarth, Sock, Hermans-Borgmeyer, et al., 1998; Stolt, et al., 2002).
F	SOX7	Abundant expressed in the brain	(Takash, et al., 2001).
F	SOX17	No expression reported.	
F	SOX18	Weak expression in brain.	(Azuma, et al., 2000).
G	SOX15/SOX20 / SOX26/SOX27	Embryonic stem cells	(H. J. Lee, et al., 2004; Maruyama, et al., 2005).
H	SOX30	Developing CNS, midbrain-hindbrain boundary (zebrafish)	(De Martino, et al., 1999).

Table 1. Sox expression in CNS.

Sox5 and Sox6, which belong to the SoxD group, are also expressed in the developing CNS and are mainly found in oligodendrocyte precursors, oligodendrocytes and different types of neurons (Stolt, et al., 2006). Sox5 and Sox6 are primarily co-expressed, as in the subventricular zone, but they can be differentially expressed as in dorsal–horn neurons where only Sox5 is found to be expressed (Stolt, et al., 2006). Further, Stolt et al showed that Sox5 and Sox6 are involved in the regulation of oligodendrocyte differentiation; the oligodendrocytes start the terminal differentiation when Sox5 and Sox6 are downregulated. Mice deficient in Sox5 and Sox6 have a higher number of oligodendrocyte precursors and the precursors are found earlier. This is the opposite to when SoxE proteins are absent (Sox8-10), which results in a reduced number or lack of oligodendrocytes (Stolt, et al., 2003; Stolt, et al., 2005). As Sox21 can counteract the function of Sox1-3 in neural stem cells, SoxD proteins are suggested to counteract the function of Sox10 in oligodendrocytes (Sandberg, et al., 2005; Stolt, et al., 2006). Sox13, also belonging to the SoxD proteins, is likewise found during the development of CNS and especially during active neurogenesis. Sox13 is primarily suggested to participate in specification and/or differentiation of neurons and Sox13 is mainly found in differentiated areas and missed in the dividing ventricular zone (Wang, et al., 2005). Sox13 starts to be expressed in neural progenitors when the differentiation program is initiated (Wang, et al., 2005). Moreover, in the developing neocortex the expression of Sox13 is very similar to the expression of Sox4 and Sox11 in the primordial plexiform layer. However later during the development only Sox13 and Sox4 are

found in more differentiated neurons of the cortical plate and the expression of Sox11 is instead found in differentiating neurons of the subventricular zone (Cheung, et al., 2000; Uwanogho, et al., 1995; Wang, et al., 2005).

Sox4 and Sox11, belonging to the group of SoxC proteins, are shown to have an overlapping expression pattern during early development of the CNS particularly in differentiating areas, later the expression patterns differ to a higher extent (Cheung, et al., 2000). Both Sox4 and Sox11 are found in neural progenitors which have exited mitosis and started to differentiate even though expression are lost when the cells are full differentiated (Cheung, et al., 2000). Further, Sox4 and Sox11 are found to have comparable expression profiles in oligodendrocyte precursor cells and in neurons, both proteins are reduced during oligodendrocyte differentiation (Kuhlbrodt, Herbarth, Sock, Enderich, et al., 1998). In *Sox4*- and *Sox11*-null mice there were no signs of severe CNS defects even though they died during embryogenesis or at birth (Schilham, et al., 1996; Sock, et al., 2004). The *Sox11*-null mice die from heart defects and mutations in the *Sox11* gene are suggested to be important in human malformation syndromes (Sock, et al., 2004). Sox12 is widely expressed both during embryogenesis and adulthood, and consequently expressed in the developing CNS with sustained expression in adult (Jay, et al., 1997). Even though Sox12 has a broad expression pattern is the *Sox12*-null mice viable and fertile and since Sox12 is expressed in lower levels is the overlapping expression of Sox4 and Sox11 suggested to compensate for the loss of Sox12 (Hoser, et al., 2008).

In addition to the SoxC group, the SoxE group is expressed during the development of CNS but the expression starts just before gliogenesis. The earliest oligodendrocyte precursors in the CNS are developed from neuronal stem cells in the ventral ventricular zone and are spread from there (Pringle & Richardson, 1993). In mice, *Sox9* was deleted from neural stem cells, which resulted in defects in the specification of oligodendrocytes and astrocytes, oligodendrocyte progenitors were still detected but to a much lesser extent (Stolt, et al., 2003). Mice deficient in both *Sox8* and *Sox9* failed to generate oligodendrocytes almost completely (Stolt, et al., 2005). In the absence of only Sox8 oligodendrocytes are generated normally (Stolt, et al., 2004) suggesting that lack of Sox8 can be compensated by Sox9 and Sox10 as well as Sox8 can compensate to same extent for the lack of Sox9 and that is why there still are some oligodendrocytes generated. After specification Sox10 starts to be expressed in the developing CNS shortly after Sox8 and Sox9 in oligodendrocyte precursors but in contrast to Sox8 and Sox9, is the expression of Sox10 sustained in oligodendrocytes in adult (Kuhlbrodt, Herbarth, Sock, Hermans-Borgmeyer, et al., 1998; Stolt, et al., 2004; Stolt, et al., 2002). Sox10 is shown to be important for the terminal differentiation of oligodendrocytes (Stolt, et al., 2002) and at this stage Sox9 is downregulated and the expression of Sox8 is low which makes Sox10 crucial for the terminal differentiation and the myelination (Stolt, et al., 2004; Stolt, et al., 2002). Sox8, Sox9 and Sox10 are not essential for the neuronal stem cells but they are suggested to be important in the role of altering the neural stem cell fate to a gliogenic fate.

The only member of the G group is Sox15. In addition to Sox2, Sox15 is expressed in mouse embryonic stem cells but the mRNA is hardly detectable in the brain (Ito, 2010; H. J. Lee, et al., 2004; Maruyama, et al., 2005). In addition, when *Sox15* is targeted disrupted the mouse is viable and fertile and Sox15 is suggested to have an important role in skeletal muscle regeneration.

Sox genes are expressed in different systems and in different stages both during embryonic development and in adult. In addition to neural development and CNS, Sox proteins are

reported do have important roles in lens development and in the developing PNS. Other important areas are cartilage development, chondrocyte development, haemopoiesis and sex determination (review (Wegner, 1999). Further, Sox proteins take part in several different cellular responses such as cell proliferation, survival, and differentiation in diverse cell types and tissues. Sox protein are also involved in different kinds of diseases as well as in cancer. In the next session the role of Sox proteins in brain tumourigenesis and especially the role in glioma development will be discussed.

3. The role and expression pattern of Sox proteins in brain tumourigenesis

Several of the Sox proteins have recently been identified in different kinds of brain tumours. Here I will focus on the Sox proteins which are reported to be expressed and play a role in brain tumourigenesis. I will mainly concentrate on the role in gliomagenesis but medulloblastoma and ependymoma will also be mentioned. Table 2 summaries the expression data reported in the literature and the IST (In Silico Transcriptomics) database is used to evaluate the mRNA expression of the different *Sox* genes in glioma (www.genesapiens.com) (Kilpinen, et al., 2008) and the Human protein atlas (HPA) is used to evaluate the protein expression (www.proteinatlas.org) (Berglund, et al., 2008; Uhlen, et al., 2005). Glioma is the only tumour type that is represented both in the IST and the HPA database.

3.1 The essence of Sox2 and Sox21 in brain tumours

There are surprisingly few reports about the role of Sox2 and Sox21 in brain tumour development and there are no reports about Sox1, Sox3 and Sox14, although the IST database tells us that Sox1 and Sox3 are expressed in glioma (Table 2).

Considering the recent data that the tumour-initiating cell probably is a cell of immature nature makes Sox2 extra interesting since Sox2 is reported to be expressed in ES cells, stem cells and progenitor cells (as described above), both during development and adulthood (Ferri, et al., 2004). Further Sox2 is found in the subventricular zone of the lateral ventricles and in the subgranular layer of the adult hippocampus areas where brain tumours are thought to arise (Phi, et al., 2008; Suh, et al., 2007). All ready at an early stage we showed that Sox2 was expressed in different kinds of mouse glioma induced by retroviruses containing the *PDGFB* (platelet-derived growth factor B) gene (Ferletta, et al., 2007). Further, we and others have reported that Sox2 has a broad expression pattern in human brain tumours. Sox2 is found in all sorts of glioma both high and low grade as well as in ependymoma (Ferletta, et al., 2011; Phi, et al., 2008; Schmitz, Temme, et al., 2007). Sox2 is also reported to be expressed in different kinds of paediatric brain tumours such as PNET, medulloblastoma and glioma as well as in undifferentiated and differentiated neurospheres from these tumours (Ferletta, et al., 2011; Hemmati, et al., 2003; Phi, et al., 2010). The expression data of Sox2 in medulloblastoma is a bit contradictable. In our hands the medulloblastomas are positive for Sox2 expression (Ferletta, et al., 2011) but no expression is reported by Phi et al (Phi, et al., 2010). This discrepancy can be explained if different subgroups of medulloblastoma have been used. Moreover by studying paediatric tumour-derived spheres it turned out that tumour-derived spheres were similar to normal neural stem cells, as they expressed the stem cell markers CD133, Musashi-1, melk, PSP, Bmi-1, nestin and Sox2 and the cells were able to migrate, proliferate and give rise to neurons and glia (Hemmati, et al., 2003), strengthening the idea that the brain tumours arise from a cell type of immature origin.

Up to date there is only one report about Sox21 and brain tumours. We have shown that Sox21 is expressed in gliomas of different grade, ependymoma, PNET and medulloblastoma (Ferletta, et al., 2011) (Ferletta unpublished data). In glioma, Sox2 and Sox21 are found to be co-expressed in the same cell and there is a correlation between the expression of Sox2 and Sox21, high expression of Sox2 is associated with high expression of Sox21 (Ferletta, et al., 2011). During development it is suggested that Sox2 and Sox21 have a counteracting activity (Sandberg, et al., 2005). We suggest that in brain tumour cells this fine tuning effect between Sox2 and Sox21 is disturbed and Sox21 is not able to inhibit the proliferation stimulated by Sox2. Moreover, we suggest that glioma consists of at least two cell populations: in the first population Sox21 is co-expressed with both Sox2 and GFAP and negative for fibronectin, the other cell population is instead negative for the expression of Sox2, Sox21 and GFAP but express fibronectin (Ferletta, et al., 2011). The co-expression of Sox2 and GFAP supports the idea that an adult neural stem cell in the subventricular zone could be the tumour-initiating cell of gliomagenesis. Also Phi et al report that Sox2 and GFAP are co-expressed in glial tumours of astroglial, oligodendroglial and ependymal lineages (Phi, et al., 2008). The $Sox2^-/GFAP^-/Sox21^-/fibronectin^+$ population could be of a more mesenchymal phenotype (Rieske, et al., 2009; Tso, et al., 2006). Further, in a study of isolation and characterization of cancer-stem-like cells from the 9L gliosarcoma cell line, they found that the expression of Sox2 was turned on when the cells were cultured as spheres compared to monolayer cultures. The cancer stem-like cells from the spheres were able to redevelop the tumour *in vivo* with a more aggressive phenotype compared to monolayer cells and sphere forming cells were less susceptible to chemotherapy, this could be a result of a slower division rate (Ghods, et al., 2007). This even more emphasizes the importance of targeting cancer stem-like cells to treat glioma.

There are a few studies where Sox2 is downregulated in glioma cells. In one investigation Sox2 expression is diminished by microRNA in GBM tumour-initiating cells which results in reduced cell proliferation and that tumour cells slowly exited the cell cycle. Reduced levels of Sox2 further result in decreased levels of Olig2 and BF1, which are transcription factors that normally are expressed in neural progenitor cells. Moreover, when tumour-initiating cells with a silenced Sox2 were orthotopically injected into NOD/SCID mice, the cells failed to recapitulate the tumour compared to tumour-initiating cells that still expressed Sox2 (Gangemi, et al., 2009). This is supported by our study showing that siRNA against Sox2 reduces the expression of Sox2 which results in decreased cell proliferation. Reduced expression levels of Sox2 additionally results in decreased expression of GFAP as well as Sox21, further supporting the correlation between Sox2, GFAP and Sox21 (Ferletta, et al., 2011). We have also investigated the correlation of Sox2 and Sox21 by using tetracycline Sox21-inducible glioma cells (by adding tetracycline Sox21 is upregulated in U-343 MGa Cl2.6 cells). The upregulation of Sox21 results in reduced expression of Sox2 and the cell proliferation was apparently decreased and this was partially a consequence of induced apoptosis (Ferletta, et al., 2011). During chicken development it is suggested that Sox2 and Sox21 must be expressed in a proper balance (Sandberg, et al., 2005; Uchikawa, et al., 1999) which supports our finding that when Sox21 is overexpressed are Sox2 and Sox21 able to act in a counteracting manner in glioma cells. From our findings we propose that Sox2 inhibitors or Sox21 activators or proteins downstream or upstream could be potential targets for novel glioma therapy.

There are a few other reports where the expression of Sox2 has been affected. Korur et al show that while Bmi1 is downregulated is the expression of Sox2 and nestin reduced and

the cells become more differentiated. Bmi1 is essential for self-renewal of neural stem cells and is highly expressed in GBM. In addition, while Bmi1 is reduced is the expression of GSK3β (glycogen synthesis kinase 3 beta) also diminished and differentiation is induced while proliferation, survival, migration and clonogenicity decreases (Korur, et al., 2009). From this the authors suggest that specific inhibitors for GSK3β or LiCl could be useful to downregulate Sox2 specifically and reduce the tumourigenic role of Sox2 in glioma. Further, Sox2 is also reported to be connected to the TGF-β (transforming growth factor-β) signalling pathway, in this study Sox2 is regulated by Sox4 (Ikushima, et al., 2009), this will be further mentioned in the discussion of Sox4 below.

Yet another study shows that Sox2 is involved in self-renewal in glioma, by overexpressing Sox2 in glioma cells did the number and size of neurospheres increase. In addition there is a correlation between Sox2 expression and eIF4E (eukaryotic initiation factor 4E) in glioma tissue samples (Ge, et al., 2010). eIF4E is a mRNA 5' cap-binding protein, which takes part in regulation of translational initiation (Richter & Sonenberg, 2005). The expression of eIF4E is upregulated in several kinds of cancer (Bjornsti & Houghton, 2004). In this study the authors suggest that eIF4E is regulating Sox2 on the protein level but not on the mRNA level and that the eIF4E-Sox2 affiliation could be a new potential therapeutic target (Ge, et al., 2010).

An immunotherapy study has been performed by Schmitz et al, who first showed that Sox2 is overexpressed in GBM. Thereafter they identified a Sox2 peptide that binds to immunogenic HLA-A*0201. The immunogenic HLA-A*0201-restricted peptide originated from Sox2 can activate tumour-directed CD8+ cytotoxic T lymphocytes (CTLs). The authors highlight the possible role of this Sox2-peptide in T-cell-based immunotherapy (Schmitz, Temme, et al., 2007).

Moreover, there is one study of the genome-wide binding pattern for Sox2 in GBM, where 4883 binding sites for Sox2 were identified. The expression of Sox2 in GBM was demolished and a microarray was performed which resulted in altered expression of 489 genes. The main groups of genes that were altered due to Sox2 knockdown were genes with signal transducer activity, transmembrane receptor genes and genes with kinase activity (Fang, et al., 2011). This study indicates that Sox2 probably is involved in several signalling pathways and cellular processes and it needs to be further investigated.

Taken together these findings strengthen the feature of Sox2 as being important for the self-renewal capacity and cell proliferation of neural stem cells as well as cancer stem-like cells and tumour cells. Several studies suggest that Sox2 or proteins up- or downstream of Sox2 could be potential targets for brain tumour therapy. The genome-wide binding screen of Sox2 stressed the difficulty of finding one solution for treating glioma or identifying one potential target that will not be involved or be to harmful to the normal adult stem cell population.

3.2 The role of Sox4 and Sox11 in glioma and medulloblastoma

3.2.1 The role of SoxC in gliomagenesis

Both Sox4 and Sox11 are reported to be expressed in glioma even though Sox4 mRNA expression was not found within the IST database (table 2). Sox11 is expressed during the development of CNS but in the adult brain is the expression of Sox11 downregulated. Compared to the adult brain Sox11 seems to be reactivated during gliomagenesis. With quantitative real-time PCR Sox11 is shown to be upregulated 5- to 600-fold in glioma (Weigle, et al., 2005). The same research group identified a ten amino-acid long peptide derived from Sox11 which has the ability to induce CD8+ cytotoxic T cells (CTLs) (Schmitz,

Wehner, et al., 2007). The Sox11 peptide was specifically expressed on glioma cells in large quantities and they suggest that this peptide could be suitable for T cell-based immunotherapy (Schmitz, Wehner, et al., 2007). Another research group confirms that Sox11 is expressed in primary GBM (Hide, et al., 2009). Further, Hide et al establish a mouse glioma cell line by overexpressing HRas in p53-deficient neural stem cells and the cell line contained both glioma-initiating cells (GICs) and non-glioma-initiating cells (non-GICs) (Hide, et al., 2009). The GICs were transformed into the mouse brain and formed glioblastoma-like tumours. They found that the GIC did not express Sox11 compared to the non-GICs which still expressed Sox11. The loss of Sox11 in GICs was also confirmed in human GIC lines. When Sox11 was overexpressed in GICs the cells lost there tumourigenic ability and the cells started to differentiate towards the direction of neurons. In addition, when Sox11 was downregulated with short hairpin RNA in non-GICs they became tumourigenic (Hide, et al., 2009). Hide et al suggest that true GICs with neural stem cell characteristics should be negative for Sox11. Sox11 is primarily found in oligodendrocytes and neuronal precursors during development which fits with the finding that the GICs are negative for Sox11 if the tumour cell-of-origin is a neural stem cell (Kuhlbrodt, Herbarth, Sock, Enderich, et al., 1998; Uwanogho, et al., 1995).

Taken together, since the expression of Sox11 seems to be high at least in primary glioma, Sox11 might be a target for T cell-based immunotherapy but if the GICs are negative for Sox11 they will escape the therapy with the risk that the relapsed tumour will be of an even more aggressive phenotype.

Sox4 has in a few reports been connected to the TGF-β cell signalling pathway in glioma. TGF-β has been shown to play several roles in glioma promoting activities such as proliferation, invasion, metastasis and angiogenesis (review (Golestaneh & Mishra, 2005). The expression of Sox2 in GICs is induced by TGF-β and while the TFG-β signalling pathway is inhibited is Sox2 downregulated and the self-renewal capacity of GICs is lost (Ikushima, et al., 2009). In this study they propose that TGF-β is not directly regulating Sox2, instead they found that Sox4 is a direct target of TGF-β signalling. Further, Sox4 overexpression is able to induce Sox2 expression and reduced expression of Sox4 in GICs results in a diminished self-renewal capacity, which suggests that Sox4 is important for maintaining the GICs (Ikushima, et al., 2009). On the contrary to Sox2, Sox4 is shown to be expressed in progenitor cells rather than in neuronal stem cells (Bylund, et al., 2003; Cheung, et al., 2000; Kuhlbrodt, Herbarth, Sock, Enderich, et al., 1998). The co-expression of Sox2 and Sox4 in glioma is supported in a DNA microarray analysis of 101 gliomas, where both Sox2 and Sox4 are identified at high levels as well as Sox11 (Tso, et al., 2006) even though there is no evidence that they are expressed in the same cell. That the TGF-β signalling pathway is mediated through Sox4 is supported by a study where the MPSS technology (massively parallel signature sequencing) was used on a pool of glioma tissue. Sox4 as well as TGFBI (transforming growth factor beta induced) were identified as alternative TGF-β mediators in addition to SMAD mediated TGF-β signalling (Lin, et al., 2010).

3.2.2 The role of Sox4 and Sox11 in medulloblastoma

The classical way to classify medulloblastomas are to divide them in to classical medulloblastoma and desmoplastic medulloblastoma (Rubinstein & Northfield, 1964). Both Sox4 and Sox11 are shown to be expressed in medulloblastoma and the expression pattern differ in the classical and the desmoplastic variants (C. J. Lee, et al., 2002). Sox4 has a strong

expression in all most all classical medulloblastomas and the expression is mainly found in undifferentiated or poorly differentiated cells. In desmoplastic medulloblastoma Sox4 expression is weak and located to more differentiated cells (C. J. Lee, et al., 2002). In normal cerebellum the expression of Sox4 and Sox11 is upgregulated in granule cells that have stopped the proliferation and Sox4 and Sox11 are continued to be expressed in the deep external granular layer (EGL). As the differentiation process continues the expression of Sox11 is lost but the expression of Sox4 is sustained for some time (Cheung, et al., 2000). The expression of Sox4 in normal cerebellum fits with the expression pattern shown in medulloblastoma and since Sox4 is not expressed in more mature cells of the medulloblastoma, Sox4 is suggested to be a marker for how differentiated the tumour cells are (C. J. Lee, et al., 2002). Further, Sox4 and Sox11 are differentially expressed in medulloblastoma using microarray analysis. Sox4 was identified as a prognostic marker towards slightly better survival, in this study the medulloblastomas were not grouped in classical respectively desmoplastic medulloblastomas (de Bont, et al., 2008).
In other tissues Sox4 is suggested to take part in apoptosis, Sox4 is reported to both induce apoptosis as well as stimulate anti-apoptotic activities, which effect Sox4 has is probably cell and tissue dependent as well as depending on which extracellular signals is reaching the cell (Hur, et al., 2004; P. Liu, et al., 2006). The prognosis of a desmoplastic medulloblastoma is somewhat better compared to classical medulloblastoma (Ellison, et al., 2003).
To correctly classify the different medulloblastomas are important in the view of prognosis and better treatment. Sox4 might be a potential prognostic marker for this together with other cell specific markers. On the other hand Sox11 might be a prognostic marker in glioma connected to better survival (Hide, et al., 2009).

3.3 The feature of SoxD proteins in glioma and medulloblastoma

3.3.1 The role of Sox5 in gliomagenesis

Sox5 was first reported to be involved in gliomagenesis in our retroviral insertional mutagenesis study in mouse. We used a retrovirus containing the *PDGFB* gene to tag genes involved in the development of malignant glioma, these brain tumour lucis can mark both novel or known genes (Johansson, et al., 2004). One of the tagged genes was *Sox5*, three independent proviral insertions were found in three independent tumours. The integration sites suggest that Sox5 expression can be upregulated or truncated which can result in a truncated protein or no product at all (Johansson, et al., 2004). In the follow-up study by Tchougonova et al, *Sox5* is suggested to be a suppressor gene in PDGFB-induced gliomas predominantly in the *Ink4a*-deficient mouse background (Tchougounova, et al., 2009). In human glioma cell lines the expression of Sox5 was low and overexpression of Sox5 reduced the clone formation and the cell proliferation was inhibited. The mechanism by which Sox5 suppresses PDGFB-induced gliomas is suggested to be due to immediate cellular senescence through regulation of $p27^{Kip}$ and Akt (Tchougounova, et al., 2009). Another report confirms that Sox5 expression is lower in oligodendroglial and astrocytic tumours compared to the already low expression in normal adult brain (Schlierf, et al., 2007). Further, it is shown that *Sox5* contains a putative binding site for miR-21, which is a microRNA that functions as an anti-apoptotic factor in GBM (Chen, et al., 2008). On the contrary, another study shows that Sox5 has a higher expression in gliomas compared to normal brain and that about 25% of the glioma patients have IgG antibodies against Sox5 in there sera (Ueda, et al., 2007). The expression of IgG against Sox5 is preferably found in younger patients and the authors suggest

that the presence of IgG against Sox5 is correlated to better prognosis i.e. the survival is prolonged (Ueda, et al., 2007). Taken together these data propose that Sox5 expression in glioma could have a suppressing role in gliomagenesis and the expression of Sox5 might indicate a better prognosis and in that case Sox5 could be useful as a prognostic marker.

Sox transcription factor	**Expression in brain tumour**	**Reported expression of Sox mRNA in glioma by IST database**	**Sox protein expression reported in glioma by the human protein atlas (HPA)**	**References: IST: (Kilpinen, et al., 2008) HPA: (Berglund, et al., 2008; Uhlen, et al., 2005)**
SRY	No data.	No expression.	No expression.	
SOX1	No data.	Expressed in glioma.	No data.	
SOX2	Glioma, medulloblastoma, PNET, ependymoma.	Expressed in glioma.	Expressed in all cases. Strong expression in 75% of the cases.	(Ferletta, et al., 2010; Phi, et al., 2008)
SOX3	No data.	Expressed in glioma.	No data.	
SOX14/SOX 28	No data.	No expression.	No data.	
SOX21/SOX 25	Glioma, medulloblastoma, PNET, ependymoma.	Expressed in glioma.	No data.	(Ferletta, et al., 2010)
SOX4	Glioma, medulloblastoma.	No expression.	Expressed in all cases.	(de Bont, et al., 2008; Ikushima, et al., 2009; C. J. Lee, et al., 2002; Lin, et al., 2010).
SOX11	Glioma, medulloblastoma.	Expressed in glioma.	Expressed with various intensity.	(de Bont, et al., 2008; C. J. Lee, et al., 2002; Weigle, et al., 2005).
SOX12; SOX22	No data.	No expression.	No data.	
SOX5	Glioma.	Expressed in glioma.	No data.	(Schlierf, et al., 2007).
SOX6	Glioma, central neurocytoma, medulloblastoma.	Expressed in glioma.	Expressed in 90% of the cases from high to low levels.	(Schlierf, et al., 2007; Ueda, Yoshida, et al., 2004a, 2004b).

Sox transcription factor	Expression in brain tumour	Reported expression of Sox mRNA in glioma by IST database	Sox protein expression reported in glioma by the human protein atlas (HPA)	References: IST: (Kilpinen, et al., 2008) HPA: (Berglund, et al., 2008; Uhlen, et al., 2005)
SOX13	Glioma.	No expression.	No data.	(Schlierf, et al., 2007).
SOX8	Glioma, medulloblastoma.	Expressed in glioma.	No data.	(Cheng, et al., 2001; Schlierf, et al., 2007).
SOX9	Glioma, medulloblastoma, ependymoma.	Expressed in glioma.	Expressed in all cases to varying extent.	(de Bont, et al., 2008; Kordes & Hagel, 2006; Sutter, et al., 2010)
SOX10	Glioma, ependymoma.	Expressed in glioma.	Expressed in 80% of the cases with varying intensity.	(Bannykh, et al., 2006; Ferletta, et al., 2007),
SOX7	No data.	No expression.	Expressed but with different results.	
SOX17	No data.	No expression.	Expressed in all cases, high expression in 20% of the cases.	
SOX18	No data.	No expression.	No data.	
SOX15/SOX 20/ SOX26/SOX 27	No data.	Expressed in glioma.	No data.	
SOX30	No data.	No expression.	Weak cytoplastic expression in 10% of the cases.	

Table 2. Reported expression of Sox proteins in different kinds of brain tumours, expression of Sox mRNA reported in the IST database and Sox protein expression reported in the HPA database.

3.3.2 Sox6 is expressed in both medulloblastoma and glioma

In addition to Sox5, Sox6 is reported to be expressed in glioma as well as in medulloblastoma and neurocytoma (Schlierf, et al., 2007; Ueda, Yoshida, et al., 2004a, 2004b) and the expression of Sox6 in gliomas is confirmed by the IST and HPA databases (Table 2). The presence of Sox6 in different kinds of glioma is slightly varying. Sox6 is reported to have higher mRNA expression levels in oligodendroglioma compared to astrocytomas. In GBM the expression levels are downregulated compared to normal adult brain and in

astrocytomas grade II and III are the levels slightly up- or downregulated (Schlierf, et al., 2007). Another study showed that the Sox6 protein is expressed in GBM but not all cells are positive in the GBMs (Ueda, Iizuka, et al., 2004). As for Sox5 Ueda et al report that Sox6 has a higher expression in gliomas compared to normal brain and that one third of the patients develop IgG antibodies against Sox6 which is not found in the patients with other brain diseases or healthy persons (Ueda, Iizuka, et al., 2004). The same research group has continued to elucidate the possibility to vaccinate with Sox6 DNA. Glioma-bearing mice were vaccinated with a plasmid encoding the full-length Sox6 protein. The vaccinated mice developed CTLs specific for Sox6 expressing cells which resulted in a tendency of longer survival time compared to control mice (Ueda, et al., 2008). All though vaccination with Sox6 suggests an anti-tumourigenic effect, there is always a risk that the cells receiving the DNA transform (Munger, et al., 1989).

3.3.3 The expression profile of Sox13 in glioma

It is not very much known about the role of Sox13 in gliomagenesis or brain tumourigenesis. All though there is one report showing that the mRNA expression of Sox13 increased in oligodendroglioma, in astrocytomas can the expression levels be either up- or downregulated but in grade IV GBM is the expression mainly downregulated, all tumours are compared to Sox13 expression in adult brain (Schlierf, et al., 2007).

3.4 The role of SoxE proteins in tumourigenesis

3.4.1 The expression pattern of Sox8 in brain tumours

Very little is known about the role of Sox8 in brain tumourigenesis. The expression of Sox8 in gliomas is investigated by real-time RT-PCR and the expressed of Sox8 is significantly upregulated in most oligodendroglial tumours. The expression of Sox8 is increased in low-grade astrocytomas, in grade III astrocytomas the expression is more heterogeneous and in GBM is the expression of Sox8 lower than in normal brain (Schlierf, et al., 2007). The IST database supports the expression of Sox8 in glioma (table 2). Moreover Sox8 is reported to be expressed in medulloblastoma and within medulloblastoma Sox8 is found in more immature cells and not in differentiated cells which fits with the normal expression of Sox8 in microglia, oligodendrocyte progenitors as well as in EGL cells (Cheng, et al., 2001). The EGL cells have been suggested in several reports to be the cell-of-origin of medulloblastoma (Eberhart, 2007).

3.4.2 The function of Sox9 in glioma and medulloblastoma

Sox9 is found in both paediatric brain tumours as well as in adult brain tumours. In paediatric ependymoma Sox9 is predominantly overexpressed but in medulloblastoma the expression is reported to be low. Survival analysis showed that expression of Sox9 in ependymoma was associated with better overall survival (de Bont, et al., 2008). However there is another report indicating that Sox9 is expressed to a higher level in medulloblastoma (Kordes & Hagel, 2006). When studying different cell-of-origin of medulloblastoma in mice, Sox9 was identified as a stem cell marker on medulloblastomas arising from neural stem cells together with Sox2 and nestin, the expression of Sox9 or Sox2 and nestin were not found in medulloblastoma tumour cells originating from EGL cells. In human samples, a Sox2+ and nestin+ profile was identified on a subset of medulloblastoma which were more common in adult patients compared to

children and the profile was associated with poorer prognosis (Sutter, et al., 2010). In human samples the presence of Sox9 was not investigated.The conflicting data on whether Sox9 is expressed to a higher extent in medulloblastoma or not could be due to the fact that different subgroups of medulloblastoma has been studied and not mentioned and if the different medulloblastomas are raised from different cancer initiating cells as Sutter et al show then the tumours will develop in different directions. Five subgroups of medulloblastomas has been identified on the bases of their characteristic gene expressing profile (Kool, et al., 2008) maybe it is possible/necessary to subdivide them into additional and more narrowed subgroups.
The mRNA level of Sox9 in oligodendroglial tumours is lower compared to adult brain and in astrocytic tumours the expression is more varying (Schlierf, et al., 2007). On the protein level Sox9 is found in all grades of glioma with somewhat lower expression in pilocytic astrocytomas (grad I) (Kordes & Hagel, 2006). The reported expression data on Sox9 match nicely the expression data from the IST database as well as the data from the HPA database (Table 2). Moreover, we have investigated the effect of overexpressing cGKII (cyclic guanosine monophosphate (cGMP)-dependent protein kinase II) which results in reduced expression of Sox9 and PDGFRα and this is followed by dephosphorylation of Akt, suggesting a connection between Sox9, PDGFRα and the Akt signalling pathway in glioma (Swartling, et al., 2009). The Akt signalling pathway is often activated in gliomas and the PDGFRα is frequently constitutively activated (Nister, et al., 1988; Phillips, et al., 2006). Further, reduced expression of Sox9 by siRNA is decreasing the cell proliferation rate in glioma cells (Swartling, et al., 2009). In addition to gliomas, Sox9 is expressed in prostate cancers and Sox9 suppression in prostate cancer cause a downregulation of cell growth (Wang, et al., 2007) which support our findings in glioma. Further, overexpression of Sox9 in prostate cancer cells caused enhanced cell proliferation and invasion (Wang, et al., 2008). In prostate cancer Sox9 is suggested to be regulated by the Wnt/β-catenin pathway (Wang, et al., 2007). The Wnt/β-catenin signalling pathway is one of the characteristics of subgroup type A of medulloblastoma which has activated Wnt-signalling (Kool, et al., 2008). In prostate cancer the expression of Sox9 is higher in recurrent tumours suggesting that Sox9 is partially expressed by the cancer initiating cells which manage to escape the treatment (Wang, et al., 2007). Sox9 is expressed in neural stem cells and in progenitor cells in adult as well as in the embryonic CNS (Scott, et al., 2010; Stolt, et al., 2003) indicating that Sox9 could be important also for the brain tumour initiating cell, even though the type A subgroup (Wnt-signalling) of medulloblastoma has a slightly better survival rate (Kool, et al., 2008). It is also shown that Shh induces Sox9 during early generation of neural stem cells and that the expression of Sox9 is essential to keep the multipotency of the neural stem cells (Scott, et al., 2010), the Shh-signalling pathway is one of the activated pathways in subset B of medulloblastoma and is mutated in about 25% of the cases (Ellison, et al., 2003; Kool, et al., 2008). Recurrent gliomas are often of an even more aggressive and invasive phenotype compared to the primary tumour supporting the finding that Sox9 could be important for tumour cell invasion (Wang, et al., 2008).

3.4.3 The presence of Sox10 in glioma may indicate better prognosis

Sox10 was first reported to be involved in gliomagenesis in our retroviral insertional mutagenesis study as Sox5 (Johansson, et al., 2004). Five proviral integration sites were identified upstream of the transcriptional start site of *Sox10* and the positions of the proviral insertions suggests improved expression of Sox10 (Ferletta, et al., 2007; Johansson, et al., 2004).

Consistently with several other studies we have reported that Sox10 is expressed in both paediatric and adult gliomas and ependymomas with a higher expression in low grade tumours compared to high grade tumours (Addo-Yobo, et al., 2006; Bannykh, et al., 2006; Colin, et al., 2007; Ferletta, et al., 2007). On the contrary Schlierf et al found that when investigating the mRNA levels of Sox10 in glioma the expression levels were lower compared to adult brain (Schlierf, et al., 2007). The authors suggest that this could be due to the high expression of Sox10 in differentiated oligodendrocytes (Stolt, et al., 2002), meanwhile the expression in more immature oligodendrocytes are lower which is reflected in the tumour cells (Schlierf, et al., 2007). Further, Etcheverry et al has performed a whole-genome integrative analysis of methylation and gene expression profiles on GBM samples and found that the Sox10 promoter contains two hypermethylated CpG sites which are related to shorter survival. However, shorter survival time is correlated with low-expression of Sox10 in the GBM samples (Etcheverry, et al., 2010), which fits with the expression data that Sox10 is expressed to a higher extent in low grade brain tumours. We and others have not found any expression of Sox10 in medulloblastoma (Ferletta, et al., 2007; Gershon, et al., 2005). The lack of Sox10 in medulloblastomas may be explained by the theory that gliomas and medulloblastomas probably originate from different tumour-initiating cells (Marino, et al., 2000).

The expression of Sox10 by itself is not enough to characterize a subgroup of gliomas as pilocytic astrocytomas, but together with other markers it may be possible (Colin, et al., 2007; Rousseau, et al., 2006). Some researchers have tried to subgroup well-characterized gliomas depending on their expression of GFAP, vimentin, Olig2, Nkx2.2, Sox10 and nestin. They suggest that gliomas with strong expression of GFAP, vimentin, Olig2, Nkx2.2 and Sox10 can be identified as pilocytic astrocytomas, further robust expression of GFAP, vimentin and nestin can categorize GBM and oligodendrogliomas can be recognized by Olig2 expression in almost all tumour cells while Sox10 and Nkx2.2 was found in subpopulations of tumour cells, these findings are not definite but may to some degree extend the diagnostic possibilities (Colin, et al., 2007). Moreover the study indicate how heterogeneous the gliomas are and emphasize the difficulties in finding treatment that will target all different tumour cells from the bulk cells to the tumor-initiating cells.

There are very few reports about how Sox10 regulates/is regulated in brain tumours. Sox10 has in pilocytic astrocytomas been correlated with high expression of ErbB3 suggesting that Sox10 is driving the overexpression of ErbB3 which may result in induced cell proliferation (Addo-Yobo, et al., 2006). This finding is supported by the knowledge that Sox10 is regulating ErbB3 in neural crest cells during development (Britsch, et al., 2001). Further we have investigated the role of Sox10 in gliomagenesis by using the RCAS/tv-a mouse model where a gene(s) of interest can be expressed in a specific cell type as glial progenitor cells (Ntv-a mice). In this study we overexpressed *Sox10* alone or together with the oncogene *PDGFB* in the RCAS system. We found that Sox10 overexpression alone was not enough to induce any tumour formation neither in the Ntv-a wild type mice nor in the *Arf-/-* transgenic mice (Ferletta, et al., 2007). The combination of the RCAS-*Sox10* virus with the RCAS-*PDGFB* virus induced glioma and the induction was four times higher with the combination compared to RCAS-*PDGFB* alone in the *Arf-/-* null mice. Therefore we suggest that *Sox10* is not a potent oncogene by itself but in combination with other oncogenes as *PDGFB Sox10* is able to increase the gliomagenicity at least in mouse (Ferletta, et al., 2007). Autocrine stimulation of growth factors such as PDGFA are common event in human brain tumours (Nistér & Westermark, 1998). Moreover, in oligodendrocyte precursors is the expression of

Sox10 presiding the expression of PDGFRα and as soon as the expression of PDGFRα is turned on, they are co-expressed (Stolt, et al., 2002). This supports the data that a combined overexpression of Sox10 and PDGFB gives raise to glioma-like tumours and that Sox10 can increase tumour incidence. In addition, the tumours induced with RCAS-*PDGFB* alone or together with RCAS-*Sox10* both had a high expression of Sox10 suggesting that the tumour-initiating cell is of immature origin as the oligodendrocyte precursor (Ferletta, et al., 2007) and this was further supported by the expression of markers for oligodendrocyte precursors as NG2 and PDGFRα (Stallcup & Beasley, 1987) in the tumours, as well as Sox2 and nestin, markers for neural stem cells (Avilion, et al., 2003; Wiese, et al., 2004).
The wide expression pattern of Sox10 in different types of human gliomas indicates that oligodendroglioma and astrocytoma may arise from a common tumour-initiating cell. Sox10 does not appear to be an oncogene alone but when combined with other mutations Sox10 is able to increase the tumour incidence. Further, Sox10 may be used as a prognostic marker the presence of Sox10 is connected to better prognosis.

4. Conclusion

Lately there are a lot of new reports coming up about the Sox super-family and their roles in brain tumourigenesis, even though it is still a lot more to explore. Ten out of the 20 known Sox proteins are reported to be expressed in brain tumors.
There are several discussions going on in the research field as the difference between cancer stem-like cells and normal neural stem cells. Sox2, Sox9 and to some extent Sox4 are shown to be involved in the regulation of cancer stem-like cells and the presence of these proteins seems to be important for the self-renewal capacity and the cell proliferation of cancer stem-like cells. There are indications that cancer stem-like cells can escape the radiation better compared to the tumour bulk, this make the tumour able to relapse and often is the relapsed tumour even more aggressive and invasive. Specific inhibitors against Sox2, Sox9 and Sox4 or up- or downstream targets could be of therapeutic interest if it is possible to avoid too much harm on the normal stem cells and the neural progenitor cells. We also show that it is possible to inhibit the cell proliferation induced by Sox2 with Sox21.
In different studies specific peptides for T-cell-based immunotherapy have been made available for; Sox2, Sox4, Sox11, and Sox6. This needs to be further investigated, the risk with immunotherapy is that the cells receiving the DNA can transform and become tumourigenic itself. Other Sox proteins are suggested to be used as prognostic markers, as the expression of Sox5, Sox6, Sox4, Sox11 and Sox10 is associated with better survival. Unfortunately in most cases it is probably not enough with just one marker, it is a need of a combination of markers to get a prognostic overview of the tumours.
Gliomas and medulloblastomas are very heterogeneous tumour types and lately they have been divided into different subgroups depending on their genetic background, which signalling pathways are activated and common genetic mutations all this to make it a little bit easier to find a potential target for therapy.
Many of the Sox proteins are co-expressed in the same cell, some with interacting activity others with counteracting activity, but this has not been taken in to account in many of the reports about Sox proteins during brain tumourigenesis. Further, today there are several different brain tumour models in mice, both viral-induced models and transgenic models which can be used when studying the role of different Sox proteins during brain tumourigenesis to get new functional and new therapeutic ideas.

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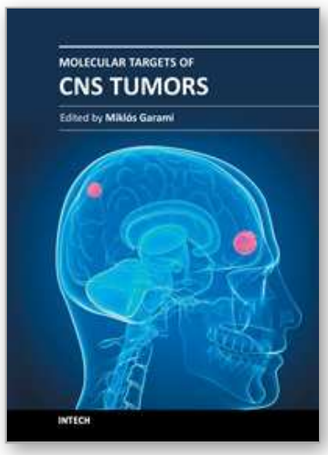

Molecular Targets of CNS Tumors

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