Chapter 3

The Role of Smad Proteins for Development, Differentiation and Dedifferentiation of Neurons

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1. Introduction

The development of the nervous system, neuralization of ectodermal cells, specification of cell types as well as generation of neurological diseases are closely linked to Smad proteins, which play a central role by integrating TGFβ and BMP signalling with other essential pathways. Due to new findings on Smad activity in neurons and the nervous system, which comprises new roles for brain plasticity and functions, independent of the canonical signalling pathways, we reconsider their relevance for neuronal differentiation and dedifferentiation processes and as therapeutic targets for treatment of neurological diseases. In this chapter we develop a view at Smad molecules, which attributes them a basic significance and allow proving their specific contextual molecular, cellular and tissue relationships. In order to facilitate the understanding of the complex Smad network in the nervous system an overview of the canonical Smad signalling pathway is briefly summarized in the following paragraph.

Smads are phylogenetic old proteins, which are mediating intracellular signalling of the large group of solube TGFβ ligands (Figure 1), containing transforming growth factor βs (TGFβs), bone morphogentic proteins (BMPs), growth and differentiation factors (GDFs), Müllerian inhibitory factors (MISs), activins and inhibins [4]. Ligand binding to activated heteromeric receptor complexes, recruited from seven type I and five type II serine/threonine receptors, results in the specific phosphorylation of receptor-associated Smads (R-Smads) at two C-terminal serine residues.

Activin, nodal and TGFβ activate R-Smad2 and 3, while BMP acts by R-Smad1,5 and 8 phosphorylation. In the cytoplasm non-phosphorylated R-Smads are sequestrated by interacting with specific retention proteins e.g. SARA (Smad anchor for receptor activation) [5], endofin [8], tubulin [3], actin, myosin [11] or filamin [12]. Inhibitory Smad(I-Smad)6 and 7 negatively regulate R-Smad signalling by competing for binding to activated type I receptor and inhibiting R-Smad phosphorylation. I-Smads can also prevent R-Smad complexing to the co-operating Smad(Co-Smad)4, which is required for the nuclear translocation of activated R-Smads to subsequently control Smad sensitive promoter activity. Moreover, I-Smads support recruitment of HECT-type E3-ubiquitin ligases Smurf1/2, which allow type I receptor ubiquitination and its degradation. Members of HECT-type and RING-type E3 ubiquitin ligases have also been implicated in Smad degradation [13]. Regulating Smad activity allows the control of highly complex developmental networks, e.g. the patterning of ventro-lateral mesoderm, the decisive development of epidermal/neural cell lineages including the induction and establishment of neural plate border, the dorso-ventral patterning of the neural tube, or the migration of neural crest cells [18-21].

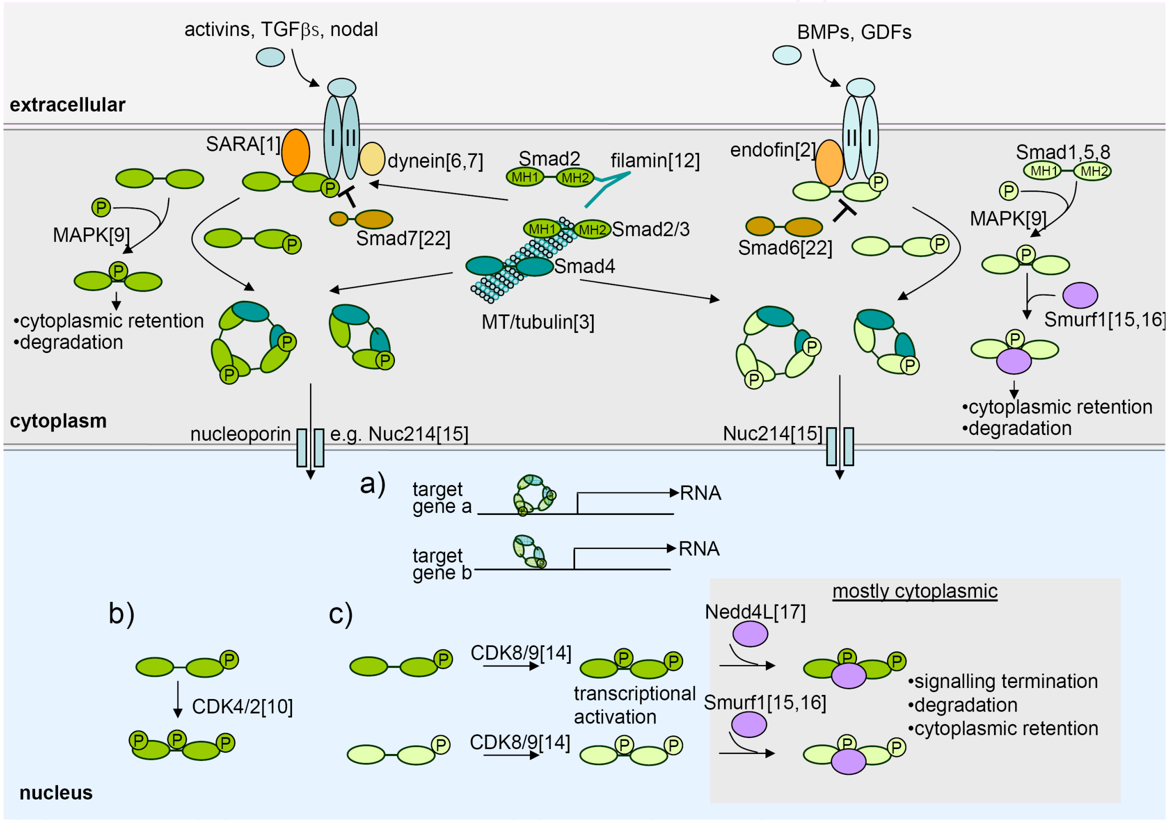

Figure 1. Synopsis of canonical Smad signalling. The upper panel shows the binding of ligands belonging to the TGFβ superfamily to their serine/threonine kinase receptors types I and II, leading to intracellular activation of R-Smads by receptor type I induced phosphorylation of the C-terminal Smad motif SSXS. The left and right receptor complexes represent the TGFβ/activin/nodal linked Smad2/3 signalling and the BMP/GDF linked Smad1/5/8 signalling, respectiviely. The middle panel also displays a set of relevant binding partners of Smad proteins and shows the generation of heterotrimer or heterodimer Smad complexes consisting of C-terminally phosphorylated R-Smads and Co-Smad4, which are transported into the nucleus to excert their transcriptional activity by binding to susceptible promoter sequences (a). In (b) and (c) examples of the agonist-induced Smad linker phosphorylation mediated by cyclin-dependent kinases are shown, which increases Smad transcriptional activity prior to signal termination and Smad degradation [14, 17]. In contrast, the MAPK triggered linker phosphorylation of Smads in cytoplasm diminishes the receptor type I responsible Smad phosphorylation and favours the cytoplasmic retention and degradation of Smad. More information is provided in the main text.*Note*: Numbers in square brackets indicate relevant references included in the reference list provided at the chapters end.*Abbreviations*: CDK, cyclin-dependent kinase; dynein, dynein light chain km23-1 or km23-2; MAPK, mitogen activated protein kinase; MT, microtubuli; Nedd4L, neuronal precursor cell expressed developmentally down-regulated 4-like ubiquitin ligase; Nuc214, nucleoporin 214; SARA, Smad achor for receptor activation; Smurf1, HECT-domain ubiquitin ligase Smurf1.

In R-Smads a linker region, located between the highly conserved N-terminal MH1- and the C-terminal MH2 region (MH represents Mad homology), is rich in potential serine/threonine phosphorylation sites. Several kinases (e.g. MAPK, GSK, CDKs, CamKII, SGK1) can phosphorylate the linker region and determine cellular distribution or protein stability of Smads [14,23-26]. Linker phosphorylation by mitogen-activated protein kinases (MAPKs) restricts Smad1 activity by enabling Smurf1 binding, causing polyubiquitination and inhibiting interaction of Smad1 with nuclear transclocation factor Nup214, thus leading to Smad1 degradation or cytoplasmic retention [15].

A similar mechanism acts on Smad2 and 3, where ubiquitination is controlled by ubiquitin ligase Nedd4L [17]. A sustained MAPK activation, as reported from dissociated embryonic ectodermal cells, phosphorylates Smad linker and interrupt a continuing BMP mediated Smad1 signalling finally resulting in neuralisation of dissociated Xenopus [27]. Remarably, if linker phosphorylation is performed by extracellular signal regulated kinase (Erk) at nuclearly localized phosphorylated Smad, the duration of Smad targeted gene transcription can be increased [28]. Linker phosphorylation by CDK8 and CDK9 promotes both, the Smad transcriptional action, and the cooperation with YAP, an effector of the Hippo organ size control pathway, to finally suppress neural differentiation of stem cells [14]. The data demonstrate the particular role of the linker region for distinct Smad functions.

Numerous Smad binding proteins (e.g. Ski, SnoN) effectively influence essential steps during neural development mostly by repression of Smad activity [29-33]. The group of Smad interacting proteins (SIP), containing several zinc finger proteins, complex to Smad and can directly or indirectly regulate its transcription efficiency [34]. For example, the induction of neuroectoderm is dependent on SIP1 [35-37], which is also involved in the myelination process and the oligodendrocyte maturation [38].

2. The role of Smads during neural/non-neuronal development

2.1. Already early development requires Smad expression

During early ontogenesis, development and aging as well as prior to individual cell death Smad proteins differentially affect cellular function, depending on time and local partners. Already at very early stages of postnatal rat development Smads1-7 were detectable in the ovary [39]. At all stages of follicular development (e.g. in primordial, primary and secondary follicles) Smad proteins are present in oocytes as well as in granulosa cells and theca cells, though with different concentrations [39-41]. While Smad3,6 and 8 content did not change, the expression of Smad1,2,4,5,6 and 7 seems to be regulated in ovary [39]. In mice oocytes a clear and persistent nuclear localization of phosphorylated Smad1,5,9 and Smad2,3 demonstrates activated activin/GDF9/nodal/TGFβ and BMP/MIS pathways, respectively, and confirms oocytes as a major target for Smad signalling pathways [42]. Smad proteins play also important roles already during maturation of human oocytes [43]. In unfertilized oocytes, Smad2 and 3 and TGFβ receptors I and II are present [44]. After fertilization at the 4-cell and 8-cell stages Smad2 and 3 are also present, while neither of the TGFβ receptors is detectable. Later on in the blastocyte stage Smad2 and 3 kept present and TGFβ receptor I again appears [44]. Human granulosa cells express Smad1-7 and 9, but Smad2,3, and 4 with the highest expression levels [45]. A mutual interaction between oocytes and granulosa cells is necessary for normal folliculogenesis. However, if Smad4 is deleted in granulosa cells infertility results, while deletion of Smad4 in oocytes only marginally effects the primordial follicle stage [46]. However, Smad2 reduction in zebrafish oocytes completely blocks activin A-induced oocyte maturation and a Smad2 knockdown decreases basal and hCG-induced oocyte maturation demonstrating a key role of Smads during oocyte maturation [47].

2.2. Gastrulation and neurulation

2.2.1. Suppression of Smad signalling specifies neuroectoderm generation

Initially, the ectoderm cells in Xenopus are pluripotent until gastrulation [48]. Early gastrulation steps are characterized by the formation of mesenchymal cells and the induction of mesoderm in the marginal-zone by an epithelial-to-mesenchymal transition (EMT) process, which involves activation of Smad2,3,4 signalling by TGFβ/nodal ligands after binding to corresponding receptors [49-53].

Mesoderm induction requires a subtle coordination of the canonical TGFβ/nodal signalling, with Smad4 as a key player. However, initially it was shown, that a simple ectopic Smad4 expression in the Xenopus animal cap was inefficient to induce mesoderm [54], due to its binding to ectodermin, a RING-type ubiquitin ligase, which is highly expressed in the animal cap [53]. Ectodermin limits Smad4 function via antagonizing nuclear accumulation of Smad4 and supporting Smad4 degradation by ubiquitin-proteosome pathway [53]. By this, ectodermin ensures that ectoderm cells do only develop to a mesodermal lineage, but also supports neural differentiation of ectoderm towards neuroectodermal fates by interfering with BMP signalling via limiting Smad4 function [53]. However, the stable presence of soluble BMP which prevents the execution of an intrinsic program of ectodermal cells to form neural tissue can also be undermined by the release of BMP antagonists as noggin, chordin, follistatin or cerberus, which however, allows creation and development of neural cells. This interrelation is basically reflected in the ´default model´ of neural induction [55,56]. Confirming this model it was shown, that the simultaneous depletion of BMP2, BMP4 and BMP7 induces massive brain formation [57]. Accordingly, during early gastrulation-stage of chick embryo Smad1,5,8 signalling is undetectable [21] but is activated at neurula stage. So, phosphorylated Smad1 becomes detectable only at late gastrulation stages in the posterior territory of the embryo [21].

The default model has been further modified due to experiments showing that inhibition of BMP/Smad1 signalling, e.g. by Smad6, was insufficient to induce neural markers efficiently [58], while the additional suppression of Smad2 was sufficient [59]. Moreover, stimulation of Smad2 signalling blocks neural induction even at gastrula stages and indicate prospective neural cells to further undergo mesodermal and non-neural fates [59]. These data are supported by experiments in sea urchin embryos showing that Smad2 and 3 suppress neural differentiation in the oral ectoderm [60].

Remarkably, conversely, it has also been suggested from very early studies on Smad2$^{+/-}$; Smad3$^{-/-}$ mutants in zebrafish showing anterior truncations [49], that Smad2 and Smad3, which are mainly effectors of TGFβ/nodal pathways, are also positively involved in neural development [61]. Dominant negative Smad3 mutants inhibit the expression of early neural markers sox2 and sox3 at the onset of gastrulation and lead to reduction of anterior and posterior neuroectodermal markers otx2 and hoxb1b, respectively, during late gastrulation. Accordingly, elevated Smad2 and Smad3 activities increased sox2 and sox3 expression, probably at least partly due to its positive impact on chordin expression, which is a BMP antagonist [61]. In mouse embryo BMP signalling also inhibits premature neural differentiation, but in contrast to Xenopus [62] and chick [63,64] FGF signalling seems additionally required to induce neural differentiation [65].

In summary, the data indicate that simultaneous suppression of both Smad1,5,8 and Smad2,3 pathways, e.g. suppression of mesoderm- and ectoderm-inducing Smad signals, respectively, are required for neural induction. In principle, the `dual Smad inhibition` method is adopted for induction of efficient neuralization of human (-induced) pluripotent stem cells (hiPSCs, hPSCs) [66,67].

2.2.2. Neural tube closure

To establish a precise borderline between neuroectoderm (containing low BMP2/4 levels) and non-neuroectoderm (containing high BMP2/4 levels) regions during early neurulation, specific strategies are required and examined in urchin embryos, where Fez, a zinc finger protein, drops down the BMP controlled pSmad1,5,8 levels [68]. It is probable that Fez acts as a transcriptional repressor of Smad or interferes with genes attenuating intracellular BMP signalling e.g. SIP1, Smurf1, Ski or SnoN.

Once the neuroectoderm forming is initiated a flat neural plate rolls up, the process of neural plate folding proceeds and is finished by neural tube closure [69]. The closure of neural tube is a complex process involving hinge points (HP), representing specialized neural plate cells. The cells of ventral midline/median hinge point (MHP) as well as both dorso-lateral hinge points (DLHPs) are affected by dynamic BMP signalling [70-73]. Folding of neural plate is connected with a two-dimentionally spatiotemporal gradient of phosphorylated Smad1,5,8 (pSmad1,5,8) [71,73]. While initially a mosaic labelling of pSmad1,5,8 was observed at the apical surface of the presumptive neuroectoderm later two intersecting Smad gradients were exerted: a lateromedial gradient with the lowest pSmad1,5,8 expression at the MHP and a second gradient along the apicobasal axis of the presumptive midbrain plate with mosaic expression in apical nuclei [71]. Some of the apical pSmad1,5,8 positive cells proliferate and thus support the neural fold elevation [71]. Disturbances of the phosphorylation state of Smad1,5,8 alter midbrain shape by multiple hinge-like invaginations but do not affect the ventral cell-fate specification [71]. However, the extent of Smad1,5,8 phosphorylation seems to control MHP formation during neurulation in vertebrates. The correct MHF formation is obviously directly linked to the pSmad1,5,8 controlled regulation of apicobasal polarity of neural plates cells. After phosphorylation, Smad1,5,8 interact with the PAR3-PAR6-aPKC complex and stabilizes linked tight junctions, while inversely low pSmad1,5,8 phosphorylation supports re-arrangement of neural plate cells, a prerequisite for MHP formation and neural fold elevation [72].

2.2.3. Patterning and developing of the spinal cord

After closure, the neural tube starts to develop the spinal cord pattern along its dorso-ventral axis which is essentially established by the expression of Wnt and BMPs, the main roof plate morphogens, and sonic hedgehog (SHH) and TGFβs, the morphogens released from the floor plate [74-76]. On the basis of provided intricated morphogenic gradients functionally distinct neurons are generated.

Both roof plate derived BMP6 and BMP7 are evoking Smad1,5,8 phosphorylation and subsequent induction of distinct dorsal interneurons (dI) via BMP receptor I activation [77-79]. While the BMP7/pSmad1,5 activated induction of dI1, dI3 and dI5 is independent of the patterned expression of progenitor proteins, e.g. Pax7, Gsh1/2 or Olig3, a Smad regulated expression of specific proneural proteins, e.g. cAth, and cAscl1, is required [79]. The patterning of dorsal progenitor proteins could be associated with other BMPs, e.g. BMP4 [80]. Smad1 and Smad5 activity seems to be important for the maintenance of neural cells as committed progenitors, because the loss of Smad1,5 reduced the total number of newly generated neurons and forces cell cycle exit and premature neurogenesis of neural progenitors [79]. The inhibitory Smad6 also promotes the neuronal differentiation in the spinal cord by interfering with Wnt-signalling [81]. Hazen and colleagues demonstrated, that the inhibitory Smad6 and Smad7 function to restrict the action of roof plate released BMPs to distinct dorsal interneurons and participate in the determination of dI4-dI6 spinal neuron number [82].

However, the subsequent orientation of spinal neurons is also controlled by BMP7 but not via activation of Smad signalling instead using phosphoinosite-3-kinase (PI3K) activation by the BMP receptor type II [77]. Nevertheless, Smad6 most potently allows blocking dI1 axon outgrowth [82].

While Smad3 was also expressed in the developing spinal cord, Smad2 was not detected [83]. Contrasting to Smad1,5,8, the expression of Smad3 in the developing spinal cord depends on progenitor proteins, e.g. Nkx6.1, Olig2, Nkx2.2, which directs the Smad3 expression mainly to discrete ventral progenitor domains [83]. Smad3 activity in turn reduces expression of progenitor proteins and promotes activation of neuronal differentiation, e.g. by supporting cell cycle exit via activating of $p27^{Kip1}$ expression [83]. The Smad3 expression is sufficient to promote differentiation of ventral and various dorsal interneurons, while differentiation of motor neurons is impaired. Therefore Smad3 expression is excluded in the prospective motor neuron progenitor cells [83].

2.2.4. Induction of neural crest (NC)

Multipotent embryonic cells of the dorsal region of the neural tube, an area existing immediately before forming the neural plate border (NPB), are the origin of neural crest cells (NC) that migrate to initiate a panel of diverse derivatives including various non-neural but also neural cells e.g. sensory neurons of the peripheral nervous system. The combination of several signalling pathways is required [84] for a timely and locally well tuned progression. Besides Wnt signalling a major role in NC induction plays canonical BMP signalling [85-90] combined with FGF signalling [21,91]. The inductive step of NPB development during gastrulation requires a concerted action of activated Wnt signals and inhibition of BMP signalling represented by low Smad1,5,8 activity. Later, when neurulation proceeds and NC develops from NPB, activated Wnt signals cooperate with a robust Smad1,5,8 activation in NPB. While during the inductive step of NC gastrulation FGF downregulates Smad1,5,8 activity by triggering MAPK, the catalysed phosphorylation of Smad1,5,8 linker region is nearly completely absent in NPB during neurulation. In consequence, a strongly elevated Smad1,5,8 signalling is observed suggesting a ´two step model of NC development´ with respect to activated Smad1,5,8 signalling [21].

2.3. Peripheral nervous system (PNS)

The further outcome of NC cells including the generation of the PNS also strongly depends on Smad signalling. Interestingly, Smad expression regulates both the formation of neurons of PNS as well as early stages of peripheral glial development.

Precursors that emigrate from the neural crest to the bowel generates the enteric nervous system (ENS) belonging to PNS. If fetal enteral neural crest-derived cells (ENCDC) of gut are exposed to BMP2 or BMP4 phosphorylated Smad1 translocates to the nucleus and the cells develop processes, indicating an essential role of Smad phosphorylation for neuron induction in the gut [92]. However, Smad phosphorylation alone is not sufficient to direct development of ENCDC towards ENS neurons or glial cells but requires further factors e.g. glial growth factor 2 (GGF2) [93]. Moreover, besides generation, also maturation of enteric neurons (as well as regulation of gliogenesis) during postnatal development is Smad-dependent. This function was identified because mice lacking in the homeodomain interacting protein kinase 2 (HIPK2), which can interact with Smad1, Smad2 and Smad3 [94] and therefore control transcription of subsequent Smad-dependent promoters, are characterized by a progressive loss of enteric neurons and an arrest in synaptic maturation postnatally. Additionally, in the HIPK2$^{-/-}$ mice the remaining enteric neurons exhibit an increased number of cells with nuclear Smad1,5,8 phosphorylation [95]. Interestingly, both in the enteric nervous system and in the midbrain [96], HIPK2 reduction severely reduces survival of dopaminergic neurons through interference with Smad signalling pathways, regulated by BMP2/4 or TGFβ, respectively. Whether altered Smad signalling, affected by HIPK2, is also responsible for Parkinson´s disease and would allow to develop a therapeutic intervention has to be investigated in the future.

Recent data demonstrate, that Smad1 signalling by BMP2 induction is implicated in differentiation of primary enteric neurons to catecholaminergic (TH expression) but not to cholinergic (ChAT expression) neuronal subtypes [97].

Peripheral glia precursors derived from neural-crest and exhibiting characteristic expression of immature glia markers e.g. nestin, are critically influenced by BMP2/Smad signalling. Using Smad1 activation, neural-crest precursor cells, that begin to develop along glial pathway are kept in an undifferentiated immature multipotent state, thus allowing migration to their postmigratory locations [98] where they later acquire myelinating properties. Smad-linked activation of GFAP promoter is part of this process [99]. Generally, oligodendroglial differentiation of precursor cells is actively suppressed by BMPs concomitant with the stimulation of astrocytic differentiation [100]. Accordingly, BMP4-activation directs progenitor cells in vivo to commit to the astrocytic rather than the oligodendroglial lineage [101].

3. Specific cell types and the role of Smad expression for their induction and maintenance

3.1. Cell type decision, maturation and differentiation

Both generation and differentiation of neurons in the brain (CNS) comprises several different and complex principles. The initial proliferation of neural precursor cells is followed by the decision to specify neuronal or glial outcome. Afterwards, the primary neurogenesis of neuronal progenitors involves migration, settlement and stopping proliferation by cell cycle exit to enter a terminal differentiation pathway. Many of these basic biological routes as well as further differentiation steps, e.g. dendritic and axonal growth and orientating, synapse formation and myelination depend on Smad proteins. The parallel occurrence of long term and acute Smad-dependent processes require a distinct contextual organisation. For example, in the developing brain an important neural stem cell is provided by radial glia cells which can generate both glial cells and neurons. While TGFβ promoted differentiation of radial glia into astrocytes is mainly regulated by activation of MAPK signalling, neurogenesis is controlled by the interplay of Smad2,3 activity and PI3K activity [102].

3.1.1. Glial cells

Radial glial cells can function as neuronal precursors and also control migration of neurons during cerebral cortex development [103]. Developing neurons are also actively implicated in the radial glial cell fate commitment [104]. Using TGFβ release, neurons can activate Smad signalling in radial glia cells and support their transformation to astrocytes [105] and also induces astrocytic differentiation and GFAP expression [106-109].

Moreover, endothelial cells also promote astrocytic differentiation by BMP-induced Smad signalling, but inhibit oligodendrocyte differentiation of postnatal cortical progenitors [110], and therefore participate in the sequential order of the two macroglial cell gliogenesis. The function of BMP/Smad signalling to drive precursors to astrocytic fate seems a common feature [111,112] which is also involved in CNS injury processes where oligodendrocyte precursors are driven towards type II astrocytes [113]. Accordingly, inhibition of BMP induced nuclear translocation of phospho-Smad1 by FGF2 activated MAPK activity is linked to Smad4 dissociation from Olig2 promoter and results in upregulation of oligodendrogenesis [114]. The very importance of a spatially and temporally regulated BMP induced Smad activation for the fate of neurogenic precursor cells was shown in chick spinal cord. At embryonic day 5, in neuroepithelial progenitors, astrocyte marker expression was inhibited and at embryonic day 6 it was promoted initiating a gliogenic period [115].

3.1.2. Neurons

The commitment of cell fates in the nervous system is strongly dependent on Smad2,3 signalling cascade. However, there have been contradictory results on the role of Smad3 for neuronal precursor proliferation and their differentiation, indicating a complex Smad signalling network dependent on local, temporal and contextual characteristics.

Some reports show, that TGFβ, which activates Smad3 signalling, diminishes neurogenesis in hippocampus after its chronical increase [116], and in SVZ and DG after intracerebroventricular TGFβ1 infusion [117] and promotes neuronal differentiation from hippocampal and cortical progenitors [118]. An clear inhibitory function of Smad3 on neural precursor proliferation was shown in the developing spinal cord [119], where Smad3 also promotes differentiation and influences the fate of selected neurons. The antiproliferative role of Smad3 and Smad4 plays a role during early-postnatal differentiation of cerebellar neurons into postmitotic neurons, where TGFβ stimulation induces nuclear translocation of phosphorylated Smads and induction of cyclin-dependent kinase inhibitors p21, p27 and markers of neuronal maturity [120].

However, other reports show that TGFβ increased neurogenesis in DG after adrenalectomy [121] or in SVZ after stroke [122].

To clarify the relevance of Smad3 for adult neurogenesis Smad3 null mice were studied [123,124]. These mice show decreased neurogenesis in the DG and the SVZ and exhibit a thinner and more disorganized rostral migratory stream (RMS) of neuronal precursor cells (NPC). Using RMS NPCs migrate from SVZ to reach the olfactory bulb, where they differentiate into granular and periglomerular neurons. Though a decreased number of proliferating cells demonstrates the requirement of Smad3 for maintaining a proper cell division rate in SVZ, the neuronal fate is not altered by Smad3 deficiency [123].

For differentiation of mesencephalic progenitors into dopaminergic (DA) neurons a concerted interaction of Smad2,3 signalling and p38 MAPK-pathways by TGFβ receptor stimulation is necessary. Accordingly, treatment of ventral mesencephalic neural progenitors with TGFβ increased the number of tyrosine-hydroxylase (TH)-positive cells [125]. Though not required for the neurogenesis, the survival of midbrain dopaminergic neurons depends on function of the homeodomain interacting protein kinase 2 (HIPK2), which interacts with R-Smads to activate TGFβ responsive genes [96]. Loss of HIPK2 increases apoptosis in DA neurons during development. Nevertheless, apoptosis of specific neural progenitors during neural differentiation also involves Smad phosphorylation as shown for Smad1,5,8 [126,127].

In vitro, treatment of ventral mesencephalic cells with BMP5,6 and 7 also significantly increased the number of TH-positive neurons via Smad phosphorylation and nuclear translocation [128], while the neurotrophin growth/differentiation factor 5 (GDF5) induced Smad pathway promotes neuronal but not dopaminergic differentiation [129]. Remarkably, the in vitro generation of functional dopaminergic substantia nigra neurons for transplantation requires a protocol which uses the temporarily and contextually distinct roles of Smad proteins: Firstly, the dual inhibition of Smad signalling in embryonic stem cells is required to allow induction of floor plate cell state which then passes over to midbrain floor plate cell state.

Secondly, an activation of Smad signalling using TGFβ pathway is necessary to finally obtain dopaminergic neurons suitable to threat Parkinson´s like symptoms [130].

In the developing cerebellum, Smad1 is expressed in the external germinal layer and Smad5 is synthesized in newly differentiated granule neurons. In the granule precursor cells, Smad5 overexpression is sufficient to initiate differentiation [131]. In mice lacking Smad4, a decreased number of cerebellar Purkinje cells and parvalbumin-positive interneurons [132] is found while no alterations of proliferation of neuronal precursor cells were detectable. Loss of Smad4 also reduces differentiation of noradrenergic neurons [133].

Basal forebrain cholinergic neurons are essentially involved in the organisation of cortical brain structures, learning and memory. Smad1-5 are expressed in basal forebrain from embryonic day 14 to the adult age [134]. An intact canonical TGFβ/Smad2,3 cascade is important for the function of cholinergic neurons. Smad signalling mediates rapid inhibition of calcium influx in cholinergic basal forebrain neurons [135]. The sleep/wake circadian rhythm controlled by cholinergic neurons of the pedunculopontine nucleus (PPT) is also dependent on phosphorylation levels of Smad2 and Smad3. Overactivation of Smad2,3 signalling resulting in increased nuclear translocation is linked to sleep/wake circadian rhythm amplitude deficits [136]. BMP9 driven Smad1,5 phosphorylation and their formation of complexes with Smad4 are involved in the induction of the cholinergic phenotype in the basal forebrain [134,137]. Moreover, only in postmitotic cholinergic neurons, this pathway induces NGF expression, an autocrine/paracrine cholinergic trophic factor, which stimulates ACh production [138]. Accordingly, it is of therapeutic relevance for treatment of Alzheimer´s disease, that BMP9/Smad1,5 signalling can prevent lesion-evoked impairment of the cholinergic septo-hippocampal neurons in adult mice [139]. The basal forebrain cholinergic neuron specific gene expression pattern is also basically linked to an interaction of Smad and Sizn1 (Smad-interacting zinc finger protein), a factor which causes mental retardation if mutated [140,141].

3.2. Axon and synapse formation

Induction of axons and orienting of axon responses are controlled by several Smad molecules of both the BMP and the TGFβ/activin pathways in a timely and spatially organized manner. Several different neuronal/neural cell types use individual aspects of the Smad machinery.

3.2.1. Basic role of Smads for neuritic outgrowth

In PC12 cells, which are initially derived from neural crest cells and are used as model system for neuronal differentiation, BMP2 induces neurite outgrowth [142] by activation of TAK1/p38 kinase signalling pathway [143,144], which is in turn tightly controlled by the simultaneous, also BMP2-induced expression of the inhibitory Smad6 and Smad7 [142] performed via activation of Smad1,5,8 pathway. The inhibitory Smads are considered to inversely inhibit BMP signalling in a concerted action by repressing Smad1,5,8, mediating BMP receptor degradation by Smurf1 [16,145], and by physical interaction with TAK1-binding protein, which finally reduces the p38-mediated neuritic outgrowth [143,144]. Neurotrophin 3 induced neuritic outgrowth is potentiated by BMP4/6 induced phosphorylation of Smad1,5,8 and their subsequent inhibition of MEK in chicken neurons [146].

Otherwise, BMP2 inhibits neuritic outgrowth and differentiation of motor neuron-like NSC-34 cells by activation of Smad1,5,8-dependent signalling and subsequent Id genes activation, which are main targets of Smad signalling and which negatively regulate differentiation of various cells including neurogenic precursors and motor-neuron precursors [147].

3.2.2. *Subtle control of axonal morphogenesis*

The axonal morphogenesis is strongly influenced by the TGFβ-regulated signalling protein Smad2. Endogenous Smad2 is constitutively activated and its phosphorylated form is nuclearly localized in human and mouse hippocampal and cortical neurons [148,149] and in primary granule neurons of rat cerebellum [150]. In granule neurons Smad2 can form a physical complex with the endogenous transcriptional modulator SnoN, which is also nuclearly localized and strongly enhances axonal growth [151] and neuronal branching [152] by regulating a large number of neuronal genes [153]. SnoN ubiquitination and degradation is controlled by the nuclear ubiquitin ligase Cdh1-anaphase-promoting complex (Cdh1-APC), which physically interact with nuclear SnoN thus suppressing axonal growth. [151,154]. Obviously Smad2 binding to SnoN facilitates the ability of Cdh1-APC to control SnoN degradation. Consequently, if phosphorylation levels of Smad2 are reduced, SnoN levels increased and axonal growth is stimulated which allow therapeutic potential after brain injury [150]. The constitutive neuronal expression of axonal growth inhibitors e.g. Smad2, Smad3 [148] and Cdh1 [155] and the reduced expression of axon growth promoters (SnoN) in terminally differentiated neurons [150] generate an intrinsic axon growth inhibition control, allowing a balance between steady state and neuronal plasticity.

3.2.3. *Axonal regeneration*

Axonal regeneration requires the reversal of an age-dependent loss of intrinsic axonal growth capability [156,157]. In dorsal root ganglion cells (DRG), which possess two branches of a initially unipolar axon, (a) a central branch containing in the spinal cord and (b) a peripheral branch innervating sensory targets, the axotomy of the peripheral branch requires function of transcription factor Smad1 for successful regeneration [158]. While in embryonic DRG neurons during the phase of active axon growth Smad1 RNA and protein were strongly expressed and found abundantly C-terminally phosphorylated in the nuclei (while Smad8 expression was low and Smad5 expression was concentrated to the periventricular zone), in adult DRG neurons Smad1 phosphorylation was diminished [159]. However, after axotomy, the induction and nuclear translocation of Smad1 precedes the onset of axonal extension and are maintained over longer time, demonstrating the importance of Smad1 for the perpetuation of the activated axonal growth program [158]. Interestingly, Smad1-dependent axonal growth program is an intrinsic feature of DRG neurons which functions independently of extracellular BMP. Until now, the detailed underlying mechanism for BMP-independent Smad1 phosphorylation is not completely elucidated. It is possible, that endogenous cytoplasmic kinases or intracellularly available BMP/BMP-receptor complexes might be involved. The ligand-independent C-terminal phosphorylation of the SSXS domain of Smad2 and Smad3 was already reported [160] suggesting a possible extracellular ligand-independent universal strategy. Probably, Smad1 signalling is also involved in the axonogenesis of many other classes of neurons, e.g. Purkinje cells, retinal ganglionic, olfactory and motor neurons which were already found positively labelled for pSmad1 immunoreactivity [159]. Due to the possible linker phosphorylation of Smad1 by several kinases (e.g. MAPK, GSK, CDK), the molecule might serve as an integrator of various pathways relevant for axon growth and regeneration [14,23-26]. However, for clinical and therapeutic relevance, the transduction of adeno-associated vector encoded BMP4 allows stimulation of Smad1 phosphorylation and activation of axonal growth independent of axotomy and also promotes sensory axon regeneration after axotomy [159]. At least partly BMP effects are dependent on its binding to repulsive guidance molecules [161].

While Smad1 positively supports axonal growth, the inhibitory Smad6 can block axon outgrowth, as shown for post-mitotic dI1 axons of the spinal cord [82] and therefore exert roles in spatially limiting the influence of BMP signalling on neurons.

In Drosophila, Smad2 is involved in motor neuron axon guidance, as null mutants of Smad2 exhibit axon guidance defects [162]. It is suggested, that a chemoattractant signal of TGFβ superfamily members provided by muscle cells might guide motor axons to their appropriate innervation sites.

3.2.4. R-Smads and Co-Smads exert neuronal plasticity

The development of peripheral tissues is connected to axonal growth of peripheral nerves, linking sensory information to the spinal cord via neuronal cell bodies localized in ganglia. After initial axon extension for trigeminal sensory neurons in mice, a Smad4-dependent retrograde signalling from developing face to the neuronal nuclei was found, which control the expression of genes in neurons of the trigeminal ganglion in dependence on their position. Extrinsic signals released from developing craniofacial tissue, e.g. BMP4, activate phosphorylation of Smad1,5,8 at the axon terminals and selectively retrogradely signals this information to selected trigeminal neuronal cell bodies thus inducing spacially patterned expression of further transcription factors along the dorso-ventral axis of the trigeminal ganglion [163]. A comparable retrograde mechanism based on dSmad2 was found in R7 axons in the Drosophila visual system, where activin, secreted from the R7 cells growth cone in an autocrine manner, activates its receptor and initiates intracellular Smad2 phosphorylation. The pSmad2 complexes to the nuclear import adaptor Importin-$\alpha 3$, shuttles to the nucleus and reduces growth cone motility and synaptogenesis via transcriptional regulation of several target genes [164]. Already in Drosophila, a retrograde Smad-based signalling of the BMP homolog Gbb regulates synaptic growth in presynaptic motor neurons [165]. The underlying mechanism for the retrograde Smad-based signalling was recently examined for the BMP4 signalling system. Ji and colleagues (2012) discovered that endosomes carrying the BMP-signalling complex containing phosphorylated Smad1,5,8, are essentially linked to a BDNF-induced axonal or growth cone translation of Smad proteins to retrogradely control transcription in trigeminal neurons [166,167]. This `two-target-derived signalling´ integrates neurotrophin and BMP signals on the level of Smad proteins, which are axonally translated on demand. This process is involved in the acquisition of positional identity markers during trigeminal ganglia development and selectively works in ophthalmic and maxillary but not in mandibular axons obviously due to the failure of BDNF in the mandibular target field [166]. The underlying mechanism suggests to re-evaluate the role and extent of Smad based transcriptional regulation. (1) Nearly all cellular surfaces/membranes, including dendrites, axons, growth cones and spines might receive information which could be integrated by Smad signalling. (2) The retrograde transport of other ligands of the TGFβ group was already reported, e.g. TGFβ2 in normal and injured motor neurons [168], implicating the question whether axonal Smad signalling is involved in injury-response. (3) The mechanism might work with all those extracellular and also intracellular factors that affect Smad translation, and might at least partly explain neurodegenerative disorders, which are characterized by disturbed axonal transport and/or neurotrophin deficiency at neuronal terminals

The specific structure of axons and the axonal transport of Smad signals [166] as well as simple translocation of receptor phosphorylated Smads from cytoplasmic receptor site into the nucleus require intact microtubule network. Phosphorylated Smad2 is transported using microtubules by support of kinesin-1 and kinesinATPase activity [169] and also requires dynein light chain km23-1 [6], whereas pSmad3 transport was dependent on km23-2 function [170]. Additionally retrograde axonal transport of phosphorylated Smads, which is necessary for transition of axonal synaptic BMP-like ligand mediated phosphorylation of Smads in Drosophila, also depends on an intact function of p150Glued protein. P150Glued is a component of the dynactin complex, which is necessarily involved in synapse assembly and stability [171]. However, a p150Glued knockdown induced disruption of synaptic homeostasis can be rescued by activation of Smad signalling at the soma [172,173], confirming the important role of nuclear phosphorylated Smad to synaptic homeostasis.

3.2.5. Astrocytic and oligodenrocytic Smad signalling influences neuronal axonal growth

Astrocytes surrounding synapses are also target of neuronal activity. Glial metabotropic glutamate 2/3 receptor activation by neuronally released glutamate induces astrocytic TGFβ1 secretion, leading to GFAP gene activation and astrocyte differentiation involving astrocytic Smad signalling pathways [174].

Chondroitin sulphate proteoglycans (CSPG), mainly synthesized by astrocytes, can inhibit axonal growth and regeneration. After traumatic brain injury or disruptions of the blood brain barrier, mature or fibrinogen-coupled latent TGFβ is released into the CNS and increases the CSPG expression by a Smad signalling manner in astrocytes [175,176]. Both astrocytic Smad2 and Smad3 expression and phosphorylation leads to inhibition of neuronal outgrowth and is required for astrocytic neurocan synthesis, whereas phosphacan only requires Smad2 [175,176]. Reduced Smad3 levels selectively reduced induction of chondroitin-4- sulphotransferase 1 and the amount of 4-sulfated CSPGs secreted by astrocytes and also promoted axonal growth of neurons which were fed on these astrocytes [175]. Taxol treatment of astrocytes can reduce CSPG expression by interfering with kinesin-1-dependent pSmad transport into the nucleus [177] and improve axon regeneration after spinal cord injury.

The Smad-interacting-protein 1 (Sip1) is an essential modulator for CNS myelination. In oligodendrocytes, it functions in a dual-mode manner by repressing the differentiation inhibitory signals of the BMP-receptor activated Smad1,5,8 activity [178] and activating oligodendrocytes-promoting factors, thus controlling proper myelination in the CNS [38].

3.3. Smads contribute to synapse formation and synaptic transmission processes

Synapse formation and remodelling are results of intrinsic programs and environmental insults. Synapses are characterized by close cell-to-cell communications, which also include synaptic transmission and signalling processes mediated by growth factors e.g. members of the TGFβ superfamily. In spinster a mutation of the inhibitory Smad Dad (Daughters against dpp) causes synaptic overgrowth [179]. A well investigated synaptic system is the neuromuscular junction (NMJ) of Drosophila, showing the involvement of Smad proteins in synapse function both in pre- and in postsynaptic cells. The release of muscular BMP4-type ligand Gbb, which is required for intact function of a large part of postsynaptic muscles [165], allows its binding to a presynaptic receptor consisting of one type I and one type II receptor, Sax or Tkv and Wit, respectively [180,181], and the subsequent phosphorylation of the R-Smad, Mothers against dpp (Mad) [165]. Activated Mad is responsible for presynaptic nuclear propagation of the postsynaptic muscular BMP signals and finally for regulating synapse growth, morphology and function of motor-neurons at least partly by altering transcription [165,180,182]. The retrograde transport of Mad utilizes microtubule motor proteins, e.g. dynein complexes, and is sensitive to disruption of dynein motor function [165]. The Drosophila Co-Smad/Smad4 homolog Medea (Med) is also necessary for presynaptic BMP signalling cascade and essential for synaptic growth [183]. Both, Med and Mad mutants, exhibit defects in neurotransmitter release and synaptic ultrastructure [165,183]. It is suggested that an equilibrium exist between the binding of presynaptic phosphorylated Mad to Med and the binding of Med to the RING finger E3 ubiquitin ligase Hiw [184], which regulate the synaptic growth in NMJ [183].

Additionally to the retrograde neuronal Mad/Med-mediated Gbb signalling, anterogradely released TGFβ type ligands activate Mad phosphorylation at the postsynaptic density (PSD) zone of postsynaptic muscles and NMJ depolarization supports Mad nuclear transition in the muscles [185]. In summary, a mutual information flow of neuron and muscle on each physiological state and the synaptic cleft situation is essentially controlled by specific R- and Co-Smad signalling in both cellular systems.

Importantly, the activation of Mad phosphorylation and nuclear translocation by the BMP ligand Gbb directs the expression of synaptic homeostasis independently of synaptic growth control in Drosophila [173]. However, retrograde transport of Mad, which was phosphorylated at the periphery of the axon terminal due to synaptic Gbb binding, mediates synaptic homeostasis. Remarkably, Gbb induced phosphorylation of Mad at the soma site of the neuron compensate for a disturbed retrograde axonal pMad transport completely [173]. The release of muscular Gbb into the synaptic cleft at the periphery to activate neuronal retrograde pMad transport, can be regulated by activin, which controls the muscular Gbb synthesis by recruiting the Drosophila dSmad2 [186]. Cdc42-interacting protein 4 (dCIP4) which is also localized postsynaptically at the NMJs co-regulates the phosphorylation of neuronal Mad levels by inhibiting postsynaptic Gbb secretion [187].

These data indicate, that both activin and BMP directed R-Smad signalling controls synaptic function at NMJ and affects the development of synaptic homeostasis.

4. Role of Smads for neurological disorders

Several neurological diseases are characterized by disturbed cellular or subcellular Smad localization and show artificial Smad sequestration or deposition. Especially in neurodegenerative and motor neuron diseases a disruption of Smad controlled transcriptional machinery was reported.

Neurodegenerative diseases are characterised by selective and progressive loss of specific populations of neurones. Four disease-classes are proposed based on four major affected proteins, tau, βA4-amyloid (βA4), α-synuclein and TDP-43, and therefore, neurodegenerative diseases can roughly be classified into four main groups: amyloidosis, tauopathies, synucleinopathies and TDP-43 proteinopathies (for review see [188]). Recent data indicate, that in all four disease groups Smad proteins are essentially involved in the disease progression, finally indicating a remarkable commonness of these diseases.

4.1. Alzheimer´s disease

Alzheimer´s disease (AD), representing a mixture of both amyloidosis and tauopathy, is a severe neurodegenerative disorder and the most common cause of dementia in the elderly. Typical clinical symptoms are memory loss, disturbed activities of daily life and deficiency of social competence. Common morphological correlates to the clinical features are extracellular βA4-plaque depositions, intraneuronal tau pathology, neuronal cell death, and cell cycle activation [189].

In AD, we identified a strong disturbance of the normal constitutive nuclear localization of phosphorylated Smad2 and Smad3 in hippocampal and cortical neurons [148], which subsequently was confirmed by others [190,191]. In AD brain, a strong colocalization of pSmad2,3 with intracellular neurofibrillary tangles (NFTs) in neurons and with βA4-amyloid plaques in addition to a sequestration of pSmad2,3 in cytoplasmic granular vesicles is detectable [148]. Additionally a significant reduction of Smad2,3,4, which are involved in activation of cell cycle proteins was described. Smad4 directly controls cyclin-dependent kinase 4 (CDK4) expression in neuronal cells and is involved in cell cycle activation of neurons in AD brain [192]. It is quite possible, that the recently identified TGFβ1-induced antiapoptotic factor (TIAF1), which can bind and block Smad4-dependent promoter activation [193], participates in the cytoplasmic Smad sequestration in AD neurons and suppresses Smad-regulated promoter activation. Environmental stress or TGFβ1, can induce TIAF aggregation, which in turn removes soluble Smad4, induces apoptosis and activates βA4 generation and its aggregation [193].

A reason for the intraneuronal dislocation of Smads could be due to the disturbed nucleocytoplasmic transport in hippocampal AD neurons [194,195]. The inner nuclear membrane comprises integral proteins, e.g. MAN1, which regulate Smad phosphorylation and nuclear translocation [196], while the outer nuclear membrane is directly continuous with the rough endoplasmic reticulum. Both membranes are separated by nuclear core complexes, which also control nucleocytoplasmic shuttling of Smad2 [197]. Altered nuclear membrane integrity [195] might provoke misrouting of phosphorylated Smads into the associated ER compartment, indicated by the co-localization of phosphorylated Smad2 granules with a luminal marker protein of the ER, protein disulphide isomerase [148,198]. ER containing Smad2 could be secreted and thus explain the extracellular association of pSmad2,3 with amyloid plaques [148,190]. Alternatively, pSmad2 could interact in early endosomes with βA4-peptides which are accumulating in the early stages of AD [199], and there also meet BACE, the β-secretase, generating β-amyloid peptides [200], activated TGFβ receptors type I and II as well as SARA, a Smad anchor for receptor activation [201-203]. It is also possible, that early endosomes can fuse to the ER thus allowing a direct route of Smad proteins to the lumen of the ER [204,205].

However, activation of cell cycle is a hallmark of AD and (1) probably supports hyperphosphorylation of tau protein which leads to generation of neurofibrillary tangles and (2) increases neuronal apoptosis by phosphorylation of retinoblastoma protein and activation of E2F based apoptotic impacts (for review see [206]. Hyperphosphorylation of tau affects the neuronal Smad2,3 localization, diminishes its nuclear concentration and thus impedes with transcriptional Smad functions as shown after βA4 treatment of primary neurons [207]. NFT formation in AD brain disturbs common intra-neuronal transport mechanisms [208]. This disturbance could also interfere with retrograde Smad signalling which could be suggested for hippocampal neurons but so far has only demonstrated for Drosophila motor neurons [173]. Moreover, we also suggest, that the principle of the two-target-derived signalling integrating neurotrophin (BDNF) and Smad pathway found in rat trigeminal neurons [166,167] might also play a role for AD progression, because BDNF is deficient in entorhinal cortex and hippocampus in AD [209,210]. Finally, a disturbed nuclear Smad localization might influence competence of neurons to express synaptic homeostasis and plasticity, both processes are well investigated for Drosophila motor neurons.

Pathogenic reduction of neuronal Smads can also support activation of neuronal cell cycle, resulting in neuronal apoptosis [211] e.g. by repression of cyclin-dependent kinase inhibitors (CDIs) $p15^{Ink4B}$, $p16^{Ink4A}$, or $p21^{Cip}$, which expression is controlled by TGFβ/Smad signalling [212-214]. Though the increased levels of TGFβ1 in AD [215,216] does not seem to be able to compensate for the compromised canonical neuronal Smad pathway [148,190], astrocytes were shown responsive to this growth factor, which induces amyloid precursor protein (APP) expression in cooperation with Sp1 [217] and CTCF [218]. Altered APP cleavage by the concerted action of α-, β- and γ-secretases is a main aspect of AD pathology and results in the generation of the pathogenetic βA4 peptide 1-42, which is neurotoxic and leads to βA4-amyloid plaques. Whether βA4 peptide 1-42 can further suppress neuronal TGFβ1/Smad2,3 signalling by activation of the inhibitory Smad7 in neurons as already shown for human monocytes cannot be excluded [219].

Clearance of βA4 peptide was reported by microglia cells [220]. TGFβ released by neurons or astrocytes stimulates βA4 peptide uptake through Smad3-dependent increased scavenger receptor SR-A expression and increased phagocytosis [221]. Though the microglial capacity to remove βA4-plaques is limited [222], peripheral phagocytes, migrating into the brain if their Smad2,3 signalling is blocked at the expense of Smad1,5,8 phosphorylation, might perform this task successfully [223].

In other tauopathies, e.g. Pick disease, progressive supranuclear palsy, and corticobasal degeneration, cytoplasmic phospho-tau bound pSmad2,3 was also identified, though reduced nuclear pSmad levels were not found [224] suggesting a different impact on Smad signalling in these diseases compared to AD.

4.2. Parkinson´s disease

Parkinson´s disease (PD) is a progressive neurodegenerative disorder which is characterized by dopaminergic neurodegeneration in the substantia nigra (SN) pars compacta. The closely associated loss of dopaminergic inputs into the striatum results in failure of motor programmes (e.g. voluntary movements) and initiates a striatal plastic change [225,226]. The gradual loss of dopaminergic neurons is linked to an increase of dopamine turnover [227,228]. α-synuclein (α-syn) is the major protein component of Lewy bodies, a hallmark of PD. It can aggregate to form toxic oligomers and fibrillar structures [226,229].

It was shown, that the TGFβ3-Smad-HIPK2 pathway is important for the survival of dopaminergic neurons during development [96,230]. However, recently, a very specific and important role of Smad3 for the nigrostriatal system was explored in a Smad3 null mouse model representing an exciting model of PD [231]. These animals show a reduced number of dopaminergic neurons in the rostral SN, resulting from a postnatal neurodegenerative process. The selective pro-survival effect of Smad3 for SN dopaminergic neurons was emphasized by stereological quantifications showing no alterations of the striatal neuronal number. In Smad3 null mice a diminished trophic support provided by Erk1/2 signalling and a reduced astrocytic support to nigral dopaminergic neurons was detected [231]. Though striatal dopamine levels were not changed in Smad3 null mice, a strong increase of DA metabolism, including elevated monoamine-oxidase (MAO) levels were identified, resembling PD findings [232]. Finally, increased expression and aggregation of α-syn in neurites and cell bodies of several telencephalic, mesencephalic and rombencephalic brain regions and in fibres of the primary and secondary motor cortex were found [231]. Two possible functional Smad3-based circuits are suggested. Either Smad3 might directly regulate the α-syn transcription, which further allows modulating DA metabolism, or the Smad3 deficiency caused elevated DA catabolism generates oxidative stress which allow toxic aggregation of α-syn. The data qualify Smad3 as a possible target for PD therapy. Interestingly, the currently pursued target to re-implant dopaminergic neurons is also based on modification of Smad signalling during their in vitro establishment [130,233].

4.3. Motor neuron diseases

As mentioned above, Smads are essentially controlling the plasticity of NMJ, the intra-axonal transport and affect axonal repair processes. Accordingly, selective motor neuron diseases exhibit disturbances of Smad signalling, e.g. spinal muscular atrophy, [234], spinal bulbar muscular atrophy [235] or amyotrophic lateral sclerosis (ALS).

ALS is a progressive neurodegenerative disease, which targets upper and lower motor neurons. In the primary motor cortex and the anterior horn of the spinal cord, motor neurons disappear and the pyramidal tract degenerates [236-238]. The remaining motor neurons exhibit inclusion bodies e.g. Bunina bodies, hyaline and skein-like inclusions. The pathological transactive response DNA-binding protein with a molecular weight of 43 kDa (TDP-43) was shown to be the major disease protein in ALS. Recently, increased nuclear immunoreactivity for pSmad2,3 in motor neurons was reported from sporadic ALS patients in spinal cord [239]. Motor neurons, where a colocalization of TDP-43 and pSmad2,3 in skeine-like and round hyaline inclusions was detected [239], show reduced nuclear pSmad2,3 immunoreactivity [240]. Obviously a disruption of Smad signalling by Smad segregation, comparable to AD or several tauopathies, enhances the loss of motor neuron function. Smad4 seems actively involved in the control of motor function as targeted disruption of Smad4 demonstrates [132]. Probably, increased nuclear pSmad2,3 content in the remaining ALS motor neurons indicates an endogenously initiated approach to a functional improvement. Experiments with an ALS mouse model support this hypothesis, because TGFβ2 administration ameliorated the motor performance of the mice [241]. A reduction of TDP-43 containing aggregates by Smad2 overexpression confirms in vitro a protective role of activated Smad signalling in ALS [242].

In summary, initiation and/or progression of many neurological disorders are directly linked to altered Smad signalling, comprising cytoplasmic Smad aggregation/sequestration, and nuclear reduction, disruption of transcriptional machinery and stimulating proapoptotic signalling, therefore disturbing biological processes, which are essential for all phases of nervous system development and homeostasis.

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