Reduce, Reuse, Recycle - Developmental Signals in Spinal Cord Regeneration

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Abstract

Anamniotes, fishes and amphibians, have the capacity to regenerate spinal cord tissue after injury, generating new neurons that mature and integrate into the spinal circuitry. Elucidating the molecular signals that promote this regeneration is a fundamental question in regeneration research. Model systems, such as salamanders and larval and adult zebrafish are used to analyse successful regeneration. This shows that many developmental signals, such as Notch, Hedgehog (Hh), Bone Morphogenetic Protein (BMP), Wnt, Fibroblast Growth Factor (FGF), Retinoic Acid (RA) and neurotransmitters are redeployed during regeneration and activate resident spinal progenitor cells. Here we compare the roles of these signals in spinal cord development and regeneration of the much larger and fully patterned adult spinal cord. Understanding how developmental signalling systems are reactivated in successfully regenerating species may ultimately lead to ways to reactivate similar systems in mammalian progenitor cells, which do not show neurogenesis after spinal injury.

Keywords

neural tube, regeneration, development, signalling pathways, spinal cord injury, CNS

Highlights

Regenerating species upregulate developmental signalling systems during repair.

Spinal progenitor cells integrate a multitude of signals to specific output pathways.

Developmental signals direct regeneration of the fully patterned adult spinal cord.

1. Introduction

How animals are capable of reconstructing a functional tissue after a disruptive injury is a fundamental question in regenerative biology. One principle appears to be that mechanisms that regulate cell proliferation, differentiation or death during development are redeployed after injury.

Mammals can functionally regenerate a few organs, such as the liver, but the central nervous system (CNS) regenerates very poorly [e.g.(Hugnot and Franzen, 2011)]. In contrast, some adult vertebrates can regenerate many organ systems successfully, including heart, limbs and CNS (Gemberling et al., 2013). Teleost fishes, larval *Xenopus* and salamanders are the leading models that can successful regenerate spinal cord after an injury (Diaz Quiroz and Echeverri, 2013; Edwards-Faret et al., 2017). Recently, zebrafish larval models of spinal cord injury (SCI) have been introduced, taking advantage of tissue transparency, and transgenic and mutant lines that allow for time-lapse and drug screening analyses (Briona and Dorsky, 2014; Ohnmacht et al., 2016).

Because regeneration of the spinal cord may recapitulate steps in its the development, we briefly summarise major events in spinal cord development. The construction of the spinal cord during initial development requires specific signalling pathways that regionalize and pattern the whole tissue that then grows and gains complexity. Primary neurulation or neural tube (NT) closure occurs during early development, after the specification of the germinal layers. The flat neural plate undergoes a series of morphogenetic changes that end in a dorsal fusion resulting in a closed NT in amniotes. In amphibians and teleosts this process differs (Araya et al., 2016; Lowery and Sive, 2004). The cells of the neural plate fuse in the midline giving rise to a structure called neural keel, which reorganises in a neural rod, thus giving rise to a NT by a process of cavitation. Independently of this difference in neurulation among species, the molecular instructions used for NT patterning are evolutionarily conserved to a high degree (Araya et al., 2016; Lowery and Sive, 2004).

Wnt, FGF and RA signal gradients establish the antero-posterior axis of the CNS (Kudoh et al., 2002; Storey et al., 1998). These gradients also serve as axon guidance cues during development and lead to axonal regeneration along the antero-posterior axis after SCI (Rasmussen and Sagasti, 2016).

Along the dorso-ventral (DV) axis, the patterning of the NT is mainly controlled by Hh, Wnt and BMP signal gradients (Fig. 2) (Le Dreau and Marti, 2012). These gradients establish specific domains of progenitor cells which express distinct combinations of homeodomain proteins (Briscoe et al., 2000). These activate specific transcriptional programmes in progenitor cells, so that distinct progenitor domains give rise to different population of neurons (Gouti et al., 2015).

Proliferation and differentiation of progenitor cells also requires activity of many of the above signals as well as activity of Notch (Yeo and Chitnis, 2007), RA (Wilson et al., 2004), FGF (Diez

del Corral and Storey, 2004) signalling and the action of different neurotransmitters like dopamine or serotonin (Barreiro-Iglesias et al., 2015; Reimer et al., 2013).

During successful spinal cord regeneration, molecular pathways initially used to build the tissue/organ during development are redeployed. In the CNS, Wnt, BMP or Hh pathways (Fig. 1), which are regulating developmental neurogenesis, are dramatically reactivated after injury (Vergara et al., 2005). During adult regeneration, distances over which signal gradients have to be established are much larger. For example, proliferation of ventricular progenitor cells leads to an expansion of the spinal cord central canal in zebrafish, rats, and newts (Radojicic et al., 2007; Zukor et al., 2011) (Fig. 2). New neurons and their processes also have to cover to re-establish connections can be much greater than in embryos. Moreover, the adult cellular and extracellular matrix environment differs from that during development. After injury, processes, such as such inflammation (Kizil et al., 2015) and scar formation contribute to this different environment (Raposo and Schwartz, 2014).
In this review we compare the involvement of the different signalling pathways in neurogenesis during development and regeneration of the spinal cord after an injury.

2. Pathways

2.1 Notch

Notch signalling is known as a regulator of neural progenitor cell fate, controlling neurogenesis and gliogenesis (Ables et al., 2011). Notch is important in juxtracrine cell-cell communication (Fig. 1). However, Notch signalling can also occur between non-neighbouring cells by transient basal actin-based filopodial contacts (Cohen et al., 2010).

Delta-Notch signalling participates in NT formation from early developmental stages. Disruption of Notch signaling prevents progenitors cells in Hensen's node in the chicken from populating the floor plate (Gray and Dale, 2010). Notch activity is necessary to maintain the identity of the floorplate itself in chick hindbrain and spinal cord (le Roux et al., 2003). Mutant studies in zebrafish show that Delta-Notch signaling is required for lateral floor plate and P3 domain development (Schafer et al., 2007). Conditional knock-out of the gene encoding the E3 ligase Mind Bomb-1, which regulates endocytosis of Notch ligands, shows that Notch controls neurogenesis and gliogenesis during NT development in mice (Fig. 2) (Kang et al., 2013). *notch1* or *notch3* are expressed in precursors and immature neurons of the spinal cord in mammals and are important for neuronal differentiation and maturation of the SC (Yamamoto et al., 2001). Indeed, *notch1* expression is enhanced in the SC after injury in the ependymal and parenchymal cells and is thought to suppress neurogenesis (Fig. 2) (Yamamoto et al., 2001).

In the zebrafish spinal cord, different proliferative progenitors express *notch* receptor genes, whereas precursors and post-mitotic neurons expressed *deltaA* and *jagged2* ligand genes. A disruption of Delta function causes overproduction of early-specified motor neurons (MNs) in zebrafish which leads to a depletion of progenitors in the motor neuron progenitor domain (pMN) over time (Appel and Eisen, 1998). This is also observed in *delta1* and *hes1;hes5* double-mutant mice (Hatakeyama et al., 2004; Marklund et al., 2010). *jagged2,* expressed in the pMN, seems to maintain this cell population in an undifferentiated state. The inhibition of Jagged2-

mediated signalling by morpholinos (MO) in zebrafish or short-hairpin RNA (shRNA) in chick cause variations in the number of MN and GABAergic Kolmer-Agduhr (KA'') cells cells in the ventral spinal cord (Yeo and Chitnis, 2007). This particular activity of Notch signalling seems important for SC regeneration in adult zebrafish, as *notch1a/b, notch2*, *her4.1, her4.5, her9*, *jagged1b* and *deltaC* genes are upregulated after SCI (Fig. 2). Indeed, the transgenic over-activation of Notch signalling in ependymo-radial glial (ERG) cells, the progenitor cells in the zebrafish spinal cord (Reimer et al., 2008), during regeneration reduces proliferation of ERGs and the number of new motor neurons generated. Conversely, the blocking of Notch signalling using the gamma-secretase inhibitor DAPT increases motor neuron generation after SCI. Similarly, Notch activity in progenitor cells in the adult zebrafish telencephalon during constitutive neurogenesis also attenuates neurogenesis (Chapouton et al., 2010). These results highlight the potential of modulating Notch signalling in progenitor cells by drug treatments in order to promote generation of motor neurons (Dias et al., 2012). The expression pattern and relationship among Notch signalling proteins in pMN cells and MNs during development and adulthood and the fact that Notch signalling dynamics control asymmetric cell division in the NT (Das and Storey, 2012) raise the question whether altering the mode of division of progenitor cells could lead to motor neurogenesis after spinal cord injury also in mammals.

Notch interacts with other pathways during development and regeneration. For example, Notch1 inactivation specifically in neural progenitor cells results in an increase in the number of V2 interneurons at the expense of MNs and in a gradual disappearance of the ventral central canal in mice (Peng et al., 2007). This is similar to manipulations of the Hh pathway (below and Fig. 3) (Yang et al., 2006). Indeed, Notch signalling maintains Hh responsiveness in neural progenitors during development of the spinal cord, shown in zebrafish (Huang et al., 2012). Notch is associated with Hh signalling at the level of the primary cilium (Stasiulewicz et al., 2015). This cellular structure plays important roles in Hh, Wnt and Notch signal transduction and pathway activity (Sasai and Briscoe, 2012) (Fig. 3). A relation with BMP signalling has been observed during frog tadpole tail regeneration that includes the SC. In this context, the activation of Notch signalling is sufficient to reactivate regeneration after amputation during a refractive period during which tail regeneration normally does not occur. Conversely, regeneration is abolished if Notch is blocked during the regenerative period. The notch effect is apparently downstream of BMP signalling (Fig. 3) (Beck et al., 2003).

It is still unknown whether Notch participates in the regeneration of interneurons during SC regeneration as well as whether and how Notch activity interacts with that of other signalling pathways that are redeployed during regeneration, such as Hh or BMPs.

2.2 Hedgehog

Signalling mediated by the morphogen gradient set up by the secreted protein hedgehog (Hh) determines the ventral patterning of the CNS and therefore plays pivotal roles in nervous system development. Its activity is crucial for early specification, regionalization and differentiation of the NT and for subsequent axon guidance and connectivity (Briscoe and Therond, 2013) (Fig. 1).

During NT development, Shh, expressed in the notochord, activates the signalling pathway in the NT floor plate (Echelard et al., 1993). The floor plate cells, source of many inductive signals, then start to express Shh themselves. The protein diffuses dorsally, thus signalling in a graded manner from ventral to dorsal. This leads to establishing different progenitor domains (Fig. 2) (Chamberlain et al., 2008). Shh spreading and responsiveness of neural progenitor cells are both critical for patterning (Dessaud et al., 2008). It has been also shown more recently that in addition to diffusion Hh ligand can be transported through filopodia-like structures (Sanders et al., 2013), but it is still unknown if this mode of transport plays a significant role during NT development.

During NT development, the receptor and negative feedback regulator *ptch1/2* is expressed in the domains immediately dorsal to the source of Shh, thus inhibiting / balancing the morphogen activity. Ligand concentration and the exposure time to the ligand affect the final fate of the receiving cells (Dessaud et al., 2007). Failure of Hh signalling strongly affects the ventral and also dorsal patterning of the CNS (Chiang et al., 1996). The Shh source, adjacent to pMN and P3 domains, is critical for a normal balance of generation of MNs, oligodendrocytes and ventral interneurons (Ribes and Briscoe, 2009). Zebrafish floor plate secretes Shha, Shhb and also Ihhb which seems particularly important for oligodendrocyte differentiation in zebrafish (Chung et al., 2013).

During regeneration of the axolotl tail, the activity of Hh proteins as ventral organiser is important. Shh expression in the ventral most cells of the SC is required for the establishment of DV progenitor domains in the newly forming ependymal tube. The proliferation of the blastema and the overall tail regeneration also depends on Hh signalling (Schnapp et al., 2005).

After a transection lesion, as has been done in the lesioned spinal cord of adult zebrafish, the patterning activity of the hedgehog pathway may not be required, as the spinal cord progenitor cells maintain their progenitor domain identity from development. However, during regeneration after SCI, *shha*, *ptch2*, *smo* and Hh target genes, like *olig2,* are upregulated in ependymal cells (Fig. 2) and this is important for injury-induced regeneration of neurons. For example, the generation of new MNs (Reimer et al., 2009) or serotonergic interneurons (Kuscha 2012) after injury is reduced by blocking Hh signalling with cyclopamine. Drug treatment experiments suggest that during MN development and regeneration, the strength of Hh signalling can be modulated by dopamine through the dopamine receptor D4a (Fig. 3) (Reimer et al., 2013). Interestingly, *shh* is also upregulated after SC compression injury in mice; expressing high levels for up to at least 1 month after injury (Fig. 2) (Chen et al., 2005).

Future research is needed to understand how Hh pathway components are configured in adult progenitor cells and how *shh* expression is upregulated and the protein spreads during spinal cord regeneration. In other tissues like the heart the outflow tract (epicardial layers of the atrium and the bulbous arteriosus) works as a signalling centre and source of Hh ligand to promote epicardial regeneration after cardiac damage (Wang et al., 2015).

During spinal cord development, Hh signalling controls regulators of the cell cycle in neural progenitors (Cayuso et al., 2006), the mode of division of the pMN cells (Saade et al., 2013) and the size and proportions of the NT (Uygur et al., 2016). It remains to be fully established

which of the different actions of Hh signalling are recapitulated in the progenitor pool of ependymal cells during SC regeneration.

2.3 BMP

The BMP pathway regulates many fundamental processes during development and adulthood and for that, it was suggested to call it "body" morphogenetic protein pathway, rather than "bone" morphogenetic protein, according to where it had been originally discovered (Reddi, 2005).

The BMP pathway (Fig. 1) is critical for CNS development (Hegarty et al., 2013). During gastrulation, neural induction from the Spemann organizer is promoted by Noggin (Lamb et al., 1993) which binds BMP4 with high affinity blocking BMP signalling activity (Zimmerman et al., 1996). Once the neural tissue is determined, BMP signalling plays important roles during NT development from patterning to generation of post-mitotic neurons, axon guidance, synapse formation and gliogenesis (Le Dreau and Marti, 2013).

BMP gradient formation is crucial for DV body axis patterning, including DV patterning of the NT, and this action is highly conserved among animals (Bier and De Robertis, 2015). The expression of *bmp4* and *bmp7* in the epidermal ectoderm is important for the dorsal fate acquisition of the prospective NT at neural plate stage (Fig. 2) (Liem et al., 1995). Bmp activity is required for the entire patterning along the DV axis affecting generation of neurons (Barth et al., 1999). After SCI in adult rats, *bmp7* expression is upregulated in glial cells and MNs (Setoguchi et al., 2001). *bmp2* is also upregulated after SCI in mouse (Setoguchi et al., 2004). *bmp4* is upregulated 1 month after injury in mouse. *bmp4* appears upregulated in neurons and GFAP-positive astrocytes. High levels of *bmp4* are also found in the ependymal cells, the presumptive spinal progenitor cells, within 1mm of the lesion site (Fig. 2) (Chen et al., 2005). These results suggest an active role of BMPs after injury. Indeed, inhibition of BMP signalling in *Xenopus* tadpoles prevents regeneration of the tail after amputation. Conversely, the activation of the pathway during a naturally occurring refractive period during which the tail can normally not regenerate, restores regenerative capacity (Beck et al., 2003).

During development, the release of BMP inhibitors like Chordin, Flik, Follistatin and Noggin from the notochord is critical for the ventral cell fate regulation of the developing NT. For instance, *noggin* mutant mice are characterized by a lack of floor plate cells and lack or reduced number of MNs in the NT (McMahon et al., 1998). During regeneration of the *Xenopus* tail, Noggin induction reduces the rate of cell division in the SC, suggesting a mitogenic role of BMPs (Beck et al., 2006). Noggin induction by cell transplant experiments in the injured SC of mice promotes the differentiation of ß-tubulin positive neurons, oligodendrocytes and astrocytes in correlation with a partial functional recovery of locomotor activity (Setoguchi et al., 2004). However BMP inhibition also increases the lesion volume and the number of macrophages in the injured SC (Enzmann et al., 2005). Moreover, BMP signalling also participates in gliosis and astrocyte differentiation during SCI (Sahni et al., 2010; Xiao et al., 2010). BMP receptor localizes into lipid rafts when *ß1-integrin* is ablated in the

ependymal stem cells, which is associated with increased astrogliosis after SCI (North et al., 2015). Hence, BMP signalling may have different pro- and anti-regenerative roles after SCI.

Despite the central role of BMPs for nervous system development and regeneration in many species, very little is known about its expression and roles in the zebrafish during SC regeneration. Data from an expression profile indicate that BMP signalling components are differentially expressed after spinal cord crush injury, suggesting specific roles for BMP signalling in regeneration (Hui et al., 2014). Fluorescent fusion proteins could be used in future to visualise BMP transports and gradients of the secreted protein. The genetic toolkits available in zebrafish plus the use of models for neuron ablation using the Nitroreductase/Metronidazole (NTR/Mtz) system (Curado et al., 2007; Ohnmacht et al., 2016) could help to elucidate how this pathway is functionally involved in the regeneration of the spinal cord.

2.4 Wnt

Wnt signalling, a regulator of cell proliferation, growth and fate is critical for development and tissue homeostasis (MacDonald et al., 2009). Its roles during tissue regeneration have been studied in different animal models (Clevers et al., 2014; Wehner and Weidinger, 2015). In the CNS, Wnt signalling components are activated as a response to injury (Lambert et al., 2016), suggesting the importance of Wnt signalling in CNS regeneration.

Wnt signalling (Fig. 1) participates in CNS development from neural induction (Stern, 2001). Once the neural tissue is established, Wnt/β-catenin acts as a morphogen patterning the antero-posterior axis of the CNS (Kiecker and Niehrs, 2001). Wnt signalling induces posterior markers (Kudoh et al., 2002). During subsequent development, Wnt, together with Hh and BMP signalling is responsible for the correct dorso-ventral NT patterning (Fig. 2) (Le Dreau and Marti, 2012). Wnts are expressed dorsally in the NT in an opposing gradient to the Hh ventral signalling (Alvarez-Medina et al., 2008). These opposite gradients are important to pattern the different domains of progenitors along the dorso-ventral axis and also to determine the size of the NT structure by controlling the differentiation rate of the progenitors (Kicheva et al., 2014). Dorsal Wnt is important for proliferation of ventricular progenitor cells and the formation of dorsal neurons (Megason and McMahon, 2002). Indeed β-catenin, which is essential for canonical Wnt signalling, is required for the maintenance and proliferation of the neuronal progenitors in the entire spinal cord (Zechner et al., 2003). A prominent activity of Wnt signalling in neurogenesis is the control of the cell cycle (Niehrs and Acebron, 2012). Mouse models carrying a stabilized β-catenin in neural precursors develop bigger brains, associated with the control of cell cycle exits of the progenitors (Chenn and Walsh, 2002). During corticogenesis, Wnt modulates the spindle-size asymmetry which lead the asymmetric cell division; a necessary step for neurogenesis (Delaunay et al., 2014). In adult animals, Wnt signalling controls self-renewal, proliferation and differentiation of stem cell niches in different organs and tissues (Clevers et al., 2014). In the adult CNS, Wnt signalling is necessary for neurogenesis, differentiation and survival of neurons and for synaptogenesis (Inestrosa and Arenas, 2010).

Studies in tail regeneration in urodele amphibians have shown that *wnt5a*, *wnt5b*, *wnt7a*, and *wnt10a* are expressed in different domains along the anteroposterior axis of the intact adult CNS and after an injury (Caubit et al., 1997a). *wnt10a* is strongly expressed after tail amputation, suggesting its importance for the new tissue proliferation and patterning (Caubit et al., 1997b). In *Xenopus* it has been shown by grafting experiments and the Tet-on conditional transgenic system blocking Wnt-β-catenin in a tissue specific manner, that the Wnt-β-catenin pathway is important for SC regeneration (Lin et al., 2012). In rodents, the expression of Wnt ligands and inhibitory components of the pathway are differently regulated after SCI in comparison to the unlesioned condition (Gonzalez-Fernandez et al., 2014).

During SCI in zebrafish larvae, spinal radial glia exhibit Wnt/ß-catenin signalling, which is important for neurogenesis but may also play an important role for axonal regrowth (Briona et al., 2015). After SCI in adult zebrafish, an increase of Wnt/β-catenin signalling is observed, which is necessary for locomotor recovery (Strand et al., 2016).

Studies in zebrafish using conditional knockouts or inducible systems like TetON (Wehner et al., 2015) could help to elucidate cell types and mechanisms by which Wnt and its regulators affect SC regeneration. The strength of imaging in the zebrafish CNS could be used to visualize Wnt protein transport through filopodial structures (Luz et al., 2014) or axons. These technical possibilities and the regenerative ability of the zebrafish makes it particularly interesting to explore Wnt signalling in zebrafish SCI.

2.5 FGF

FGF signalling (Fig. 1) plays important roles in development from cell fate specification to the determination of axis and morphogenetic processes (Dorey and Amaya, 2010). The formation of an FGF gradient is crucial for its morphogenetic activity (Bokel and Brand, 2013). Whether FGF plays a role early during neural induction is still a controversy (discussed in (Dorey and Amaya, 2010)) During the establishment of the anteroposterior axis of the CNS, FGF acts as a neural morphogen (Kengaku and Okamoto, 1995). High levels of FGF promote expression of posterior markers and conversely, low doses, anterior markers (Storey et al., 1998). Indeed, FGF receptor signalling is required for the elongation of the spinal cord primordium in chick, where FGF works as a posteriorising signal (Fig. 2). FGF signalling maintains the neural progenitor population close to the region of the Hensen´s node (Mathis et al., 2001). Later, FGF is crucial for CNS dorso-ventral patterning, contributing particularly to the specification of the ventral progenitor domains (Lupo et al., 2006) and neurogenesis. FGF promotes proliferation and survival of neuroepithelial cells *in vitro* and their differentiation into mature neurons and glia depending on ligand concentration (Qian et al., 1997). In the mouse SC, MNs express the FGF ligand FGF1 (Elde et al., 1991) while human and rat MNs express FGF9 (Nakamura et al., 1997). Indeed, the treatment of forebrain-derived neural stem cells with FGF2 induces the generation of MNs which express the MN marker HB9 (Jordan et al., 2009). In addition, different FGF proteins can act as potent survival factors for spinal MNs in culture (Ford-Perriss et al., 2001).

The activity of FGF in glial cells seems important during regenerative processes in the CNS. Brain or SC injury in the salamander *Pleurodeles waltl* increase FGF2 expression in reactive astrocytes at the lesion site (Fahmy and Moftah, 2010). Tail amputation experiments in *Pleurodeles*, have shown that during regeneration FGF2 expression is upregulated in the ependymal cells, promoting proliferation and neural differentiation from this progenitor cells (Zaky and Moftah, 2014) In other amphibians like *Ambystoma mexicanum* or *Xenopus* tadpoles, FGF signalling is also important during the regenerative process of the spinal cord (Lin et al., 2012; Makanae et al., 2016). In zebrafish, different FGF signalling pathway components are upregulated in neurons and glia after SCI. This upregulation of the FGF pathway is important for the formation of a glial bridge after SCI, which has been proposed to acts as a scaffold for the axons crossing the lesion site (Goldshmit et al., 2012). Evidence from mammalian models shows that FGF plays important roles in glial cells during brain or SC injury (Kang et al., 2014; Tripathi and McTigue, 2008). In mice, the administration of FGF2 following SCI increases the number of progenitor cells at the lesion site and favours glial bridge formation and axonal regeneration (Goldshmit et al., 2014).

It would be interesting to determine whether cross-regulatory interactions of FGF with other signalling pathways like RA or Shh, which contribute to coordinate transcriptional programs as the spinal cord progressively matures (Briscoe and Novitch, 2008; Diez del Corral and Storey, 2004), are recapitulated during regeneration. For example, FGF signalling promotes spinal cord elongation by controlling cell cycle length through the regulation of cyclins D1 and D2 in concert with Hh signalling (Lobjois et al., 2004). During the coordination of ventral patterning and caudal axis extension, FGF and Hh signalling act in a negative feedback loop by modulating the expression of the Shh receptor Patched2 (Fig. 3) (Morales et al., 2015). In the context of

limb regeneration, it has been observed recently how the crosstalk between FGF and Shh leads regeneration (Nacu et al., 2016).

During neural differentiation, FGF signalling can modulate chromatin organisation (Patel et al., 2013) pointing to another potential mechanism of FGF action in regeneration. During the transition from multi-potent progenitor to neural progenitor cell in the chick spinal cord, different chromatin modifiers are downregulated. Among them is HDAC1, which depends on FGF signalling activity. (Olivera-Martinez et al., 2014). Interestingly, HDAC1 is able to regulate proliferation in radial glial cells in the *Xenopus* optic tectum (Tao et al., 2015), indicating a potential mechanism by which FGF controls cell differentiation in the CNS. The capacities of FGF to control chromatin modulators may have implication for the activation of the regeneration-associated gene expression programme in progenitor cells also during neuronal regeneration.

2.6 Retinoic acid

The RA pathway (Fig. 1) is important for cell communication during development and adulthood. Its functions are crucial for spinal cord development (Lara-Ramirez et al., 2013; Maden, 2006). RA has been proposed as an important signal for regeneration of different organs, such as the lungs, limbs, peripheral nervous system (PNS) and CNS (Maden, 2007) .

During development, RA is known as a posteriorising agent (Maden and Holder, 1992). The treatment of *Xenopus* tadpoles with RA promotes the expression of posterior neural genes, such as *hoxb3, and* suppresses anterior markers, like *Xotx2* (Papalopulu and Kintner, 1996). During NT patterning, the RA receptors (RXRα, RARα and RARβ) are expressed in the NT while Raldh2, the enzyme generating RA, is present in the presomitic mesoderm and somites. The RA signal from the somites is necessary for neural differentiation and ventral patterning (Fig. 2) (Diez del Corral et al., 2003). The RA signalling function during NT patterning is conserved in zebrafish (England et al., 2011; Lara-Ramirez et al., 2013). Indeed, a decrease of RA receptor activity is associated with the activation of neural fate (Blumberg et al., 1997). For this posteriorising activity, RA interacts with Wnt and FGF signalling, which is mediated by the RA hydroxylase Cyp26 in zebrafish. Wnt and FGF signalling inhibit cyp26 expression, which in turn inhibits RA signalling (Kudoh et al., 2002).

The RA pathway is also important for the dorsoventral pattering of the spinal cord (Wilson et al., 2004). In a vitamin A-deficient quail model in which RA is absent, V1 interneuron and MN marker genes are downregulated. RA supports the generation of MNs (Sockanathan and Jessell, 1998) by activating genes necessary for ventral NT patterning and MN specification (Novitch et al., 2003). One retinoid-inducible gene is GDE2 (glycerophosphodiester phosphodiesterase 2) which induces MN differentiation (Rao and Sockanathan, 2005) inhibiting Notch signalling in the pMN cells from the differentiated MNs (Sabharwal et al., 2011). RA also promotes the differentiation of a neuronal fate from different types of stem cell lines *in vitro* and *in vivo* in the spinal cord (Duester, 2013; Janesick et al., 2015).

After SCI in rats, RALDH2 activity was found upregulated in cells around the lesion site (Kern et al., 2007) and RARß agonist treatment reduces the formation of the glial scar and enhances

axonal outgrowth capacity (Goncalves et al., 2015). This suggests potential beneficial effects of RA activity after SCI.

In adult newts, retinoid signalling controls the expression of specific microRNAs, which are expressed in ependymoglial cells during tail and spinal cord regeneration. In turn, these microRNAs control the expression of the RA receptor, RARβ2 (Lepp and Carlone, 2015). These observations are opening new insights into how this pathway is balanced and functions during successful spinal cord regeneration.

Little is known about the effects of RA signalling on neurogenesis during spinal cord regeneration in zebrafish. Expression data indicates that the RA signalling pathway is upregulated after a spinal cord lesion (Reimer et al., 2009). There is no apparent need for a function of RA in patterning of the lesioned adult spinal cord, as this retains its dorso-ventral pattern from development (see above). Further functional experiments, including the visualisation and perturbation of RA gradients (Schilling et al., 2016) will have to clarify the role of RA in spinal cord regeneration. In the developing spinal cord, RA seems to maintain high levels of FGF and Notch signalling in order to drive stem cell differentiation (Paschaki et al., 2012). RA is also necessary for the modulation of components of neurotransmitter pathways like dopamine (Samad et al., 1997) or serotonin, discussed further down (O'Reilly et al., 2007) (Fig. 3). These observations open the question if this crosstalk plays an active role during regeneration.

2.7 Dopamine/Serotonin

Neurotransmitters, in addition to their role in transmitting specific neuronal information, also promote neurogenesis in the CNS during development and adulthood. Acetylcholine, dopamine (DA), GABA, glutamate, nitric oxide, neuropeptide Y, noradrenaline and serotonin (5-HT) influence neural cell proliferation and differentiation (Berg et al., 2013). Neurotransmitters are released from producing cells, acting in target cells through transmembrane G-Protein-Coupled Receptors (GPCRs). These common and diverse receptors control cellular processes like proliferation, differentiation and adult neurogenesis (Doze and Perez, 2012).

Different components of DA signalling are expressed in progenitor cells in the CNS (Diaz et al., 1997; Ohtani et al., 2003). Aminergic (DA, 5-HT, noradrenaline) projections to the spinal cord contribute to the maturation of locomotor networks (Sharples et al., 2014). In zebrafish, dopamine from the dopaminergic diencephalo-spinal tract is able to act directly on the spinal progenitor cells during development by promoting the generation of MNs by augmenting Shh signalling (Reimer et al., 2013). Similarly, the depletion of monoamines *in vivo* affects Hh signalling in the adult rat hippocampus (Rajendran et al., 2009). 5-HT plays a similar role during development; 5-HT depletion in rats delays the differentiation of neurons (Lauder and Krebs, 1978). In zebrafish, 5-HT promotes the embryonic development of MNs by acting on progenitor cell proliferation (Barreiro-Iglesias et al., 2015). The effect and mechanism of action appears to be independent of Shh and therefore different from that of DA.

In the salamander brain, DA controls neurogenesis and regeneration of dopaminergic neurons. DA keeps the stem cells that give rise to DA neurons quiescent in a negative feedback loop (Berg et al., 2011). In the adult spinal cord of zebrafish, dopamine and serotonin augment the number of MNs regenerated after an injury, which is similar to their developmental function (Barreiro-Iglesias et al., 2015; Kuscha et al., 2012; Reimer et al., 2013).

To better understand how neurotransmitters act on neurogenesis, these could be tracked in vivo. Fluorescent false neurotransmitters (FFN), which can be tracked by imaging to study monoamine exocytosis have recently been described (Pereira et al., 2016). For future studies, FFN could be applied in the transparent developing and regenerating zebrafish embryo to understand how neurotransmitters control neurogenesis and modulate regeneration. Also, deciphering the localization and interaction of the different receptors would help to elucidate the molecular code that act in progenitors. The crosstalk with signalling pathways, such as the hedgehog pathway, and changes in gene expression downstream of DA or 5-HT signalling are of interest for future studies (Fig. 3).

3. Discussion/Conclusions

Progenitors in the developing and regenerating spinal cord express a multitude of different receptors and are therefore able to receive a large number of signals. In the regenerating spinal cord, developmental signals derived from neighbouring cells, axons, and the cerebrospinal fluid (CSF) are "reused" and direct the regenerative response of spinal progenitors. While each receptor acts on its own signalling cascade, there is also significant cross-talk between pathways, often integrated onto few effectors (as illustrated for Hh in Fig. 3). It will be interesting to determine how these interactions are altered during regeneration, given that they likely integrate signals unique to regeneration, such as inflammatory mediators from immune cells. The recent progress in genetic and imaging technologies now allows the detailed investigation of these subcellular signalling processes *in vivo* using the larval zebrafish to investigate successful central nervous system repair.

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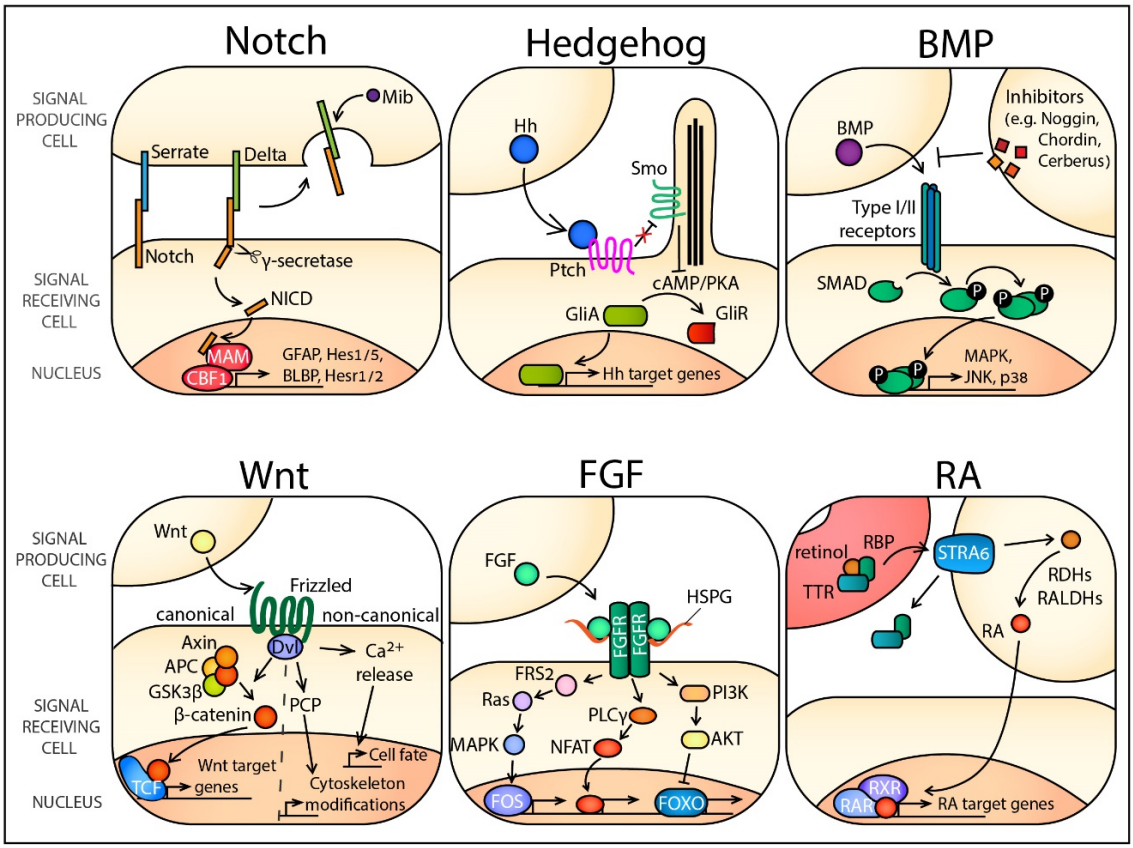

Fig. 1. Molecular basics of signalling pathways. **Notch**: Notch receptor, upon binding to ligands Delta or Serrate, undergoes cleavage by γ-secretase and its intracellular domain (NICD) translocates to the nucleus where it associates with the effectors suppressor of hairless (CBF1/RBPjk) and mastermind (MAM) to activate canonical Notch target genes, which in the nervous system include *hes1/5*, the HES related genes *hesr1/2*, glial fibrillary acidic protein (GFAP) and the brain lipid-binding protein (BLBP). In the signal-producing cell, mindbomb (Mib) promotes ubiquitination and endocytosis of Notch ligand. **Hedgehog (Hh)**: The Hh ligands Sonic Hedgehog (Shh), Desert Hedgehog (Dhh), Indian Hedgehog (Ihh) [in zebrafish there are two more ligands, Shhb and Ihhb], are translated and secreted from producing cells. Hh ligands diffuse or are transported through the tissues over different distances from the source, also through filopodial-like structures, to their receiving cells. In the receiving cells, Hh protein binds to the transmembrane receptor Patched (Ptch), which in turn leads to the disinhibition of Smoothened (Smo) and its translocation to the primary cilium. Smo activates a series of events involving reduction of cAMP/PKA activity, which promotes the accumulation of an activator form of the transcription factor Gli (GliA) over the repressor form (GliR). GliA enters the nucleus and initiates the transcription of Hh target genes. **BMP**: BMP ligands comprise approximately 30 secreted cytokines, which belong to the superfamily of transforming growth factor β (TGF-β). The binding of BMP ligands to the Type I/II receptors in receiving cells, promotes receptor phosphorylation, which in turn leads to the phosphorylation of the Smad proteins. Phosphorylated Smads form a complex that translocates to the nucleus to initiate transcription. The kinase activity of type I receptor requires ligand binding, ligand–receptor oligomerization, and transphosphorylation via the type II receptor. The receptors can activate Smad-dependent or independent pathways like *P38* mitogen-activated protein kinase (p38 MAPK) or c-Jun N-terminal kinases (JNK). Endogenous BMP inhibitors such as Noggin, Chordin

or Cerberus act to diminish the binding of BMP to its receptor and hence the activity of the pathway. **Wnt**: Wnts are secreted Cys-rich proteins, conserved in metazoan animals, encoded by 19 genes in mammals and 25 identified genes in zebrafish. Wnt proteins are secreted from producing cells or transported through filopodial-like structures to target cells. The interaction of Wnt ligands with the receptor Frizzled activates several interconnected downstream pathways, generally known as canonical and non-canonical. In the canonical pathway, Frizzled, through the activation of Dishevelled (Dvl) protein, promotes the dissociation of β-catenin from the Axin/APC/GSK3β complex, leading to the nuclear translocation of β-catenin, where it associates with the T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) proteins to regulate the transcription of Wnt target genes. In the non-canonical Wnt/planar cell polarity (PCP) pathway, the activation of Frizzled and Dvl leads to a signalling cascades resulting in cytoskeleton modifications. The non-canonical Wnt/Ca^{2+} pathway causes an increase in calcium flux across the plasma membrane and/or from the intracellular stores, ultimately leading to the activation of signals affecting cell fate**.** For more details we suggest the "Wnt homepage" (http://web.stanford.edu/group/nusselab/cgi-bin/wnt/). **FGF**: FGF ligands are extracellular proteins, which signal in an autocrine, paracrine or endocrine manner. Secreted FGF ligands bind to their receptors (FGFR), a single-pass transmembrane tyrosine kinase molecule, through the interaction with heparin sulphate proteoglycan (HSPG). FGFRs are encoded by 4 genes (FGFR1-4) which, by being alternatively spliced, confer ligand-receptor binding specificity. They activate FRS2-Ras-MAPK, PLCγ-NFAT and PI3K-AKT signalling pathways to mediate FGF target gene transcription through the activity of the transcription factors FOS, NFAT and FOXO. **Retinoic Acid (RA)**: Retinol, a form of vitamin A, is transported from the bloodstream to the RA-generating cell by retinol binding protein (RBP) and transthyretin (TTR), entering into the cell through STRA6 receptor. Enzymatic processing of retinol by retinaldehyde dehydrogenases (RALDHs) and retinol dehydrogenases (RDHs) results in the formation of RA. This RA-generating cell releases RA to the neighbouring cells, which enters that cell's nucleus and associates with nuclear RA receptor (RAR) and retinoid X receptor (RXR) to initiate gene transcription. For references see text.

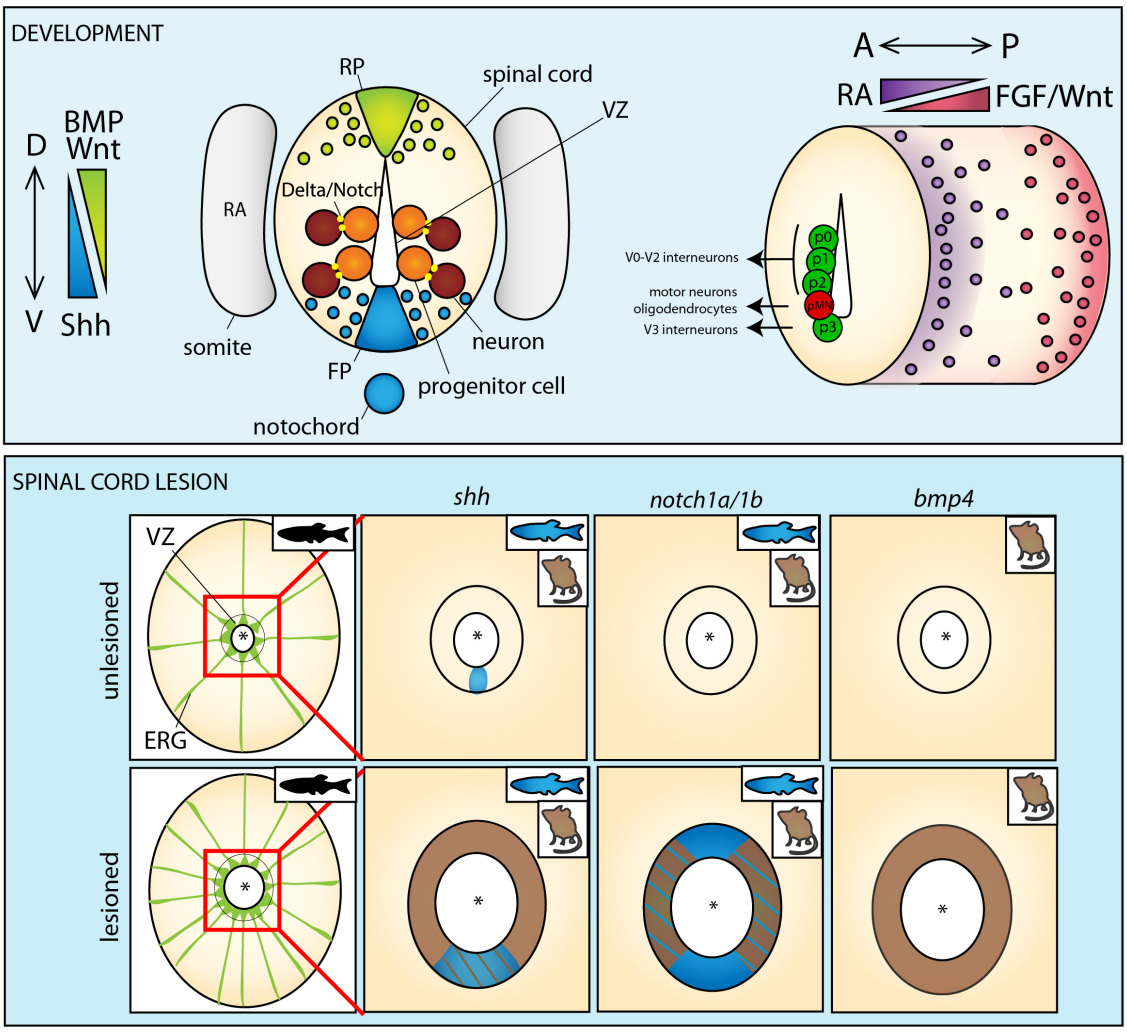

Fig. 2. Signalling pathways during spinal cord development and regeneration. **Development**: During the patterning of the spinal cord, the notochord and the floor plate (FP) are established as a signalling centre for Shh (blue), which diffuses through the tissue in a ventral-high, dorsal-low gradient. In contrast, BMP and Wnt (green) are released from the roof plate (RP) in a dorsal-high, ventral-low gradient. At the ventricular zone (VZ) of the neural tube, the cells that maintain high Notch expression preserve their proliferative state (orange), whereas the cells with higher Delta/Serrate expression differentiate into mature neurons (brown). Distinct ventral progenitor zones (p0-p3 (green) and pMN (red)) are set up by the morphogens diffusing from FP and RP. Along the anterio-posterior axis, the spinal cord is patterned by anterior-high expression of RA (purple) released from the somites which forms an opposing gradient to the posterior-high expression of FGF and Wnt (pink). **Regeneration**: In the unlesioned adult spinal cord, the VZ around the narrow central canal (*) is lined with ependymo-radial glia (ERGs), which show little or no activity of the developmental signalling pathways. After a lesion, the ERGs proliferate, which expands the diameter of the central canal in zebrafish, rats and newts, and ERGs upregulate the expression of genes present during spinal cord development, such as *shh*, *notch1a/1b* and *bmp4*. The inserts in the top right corners of each expression pattern indicate the model organism (zebrafish (blue)/mouse (brown)) used to obtain the data. For references see text.

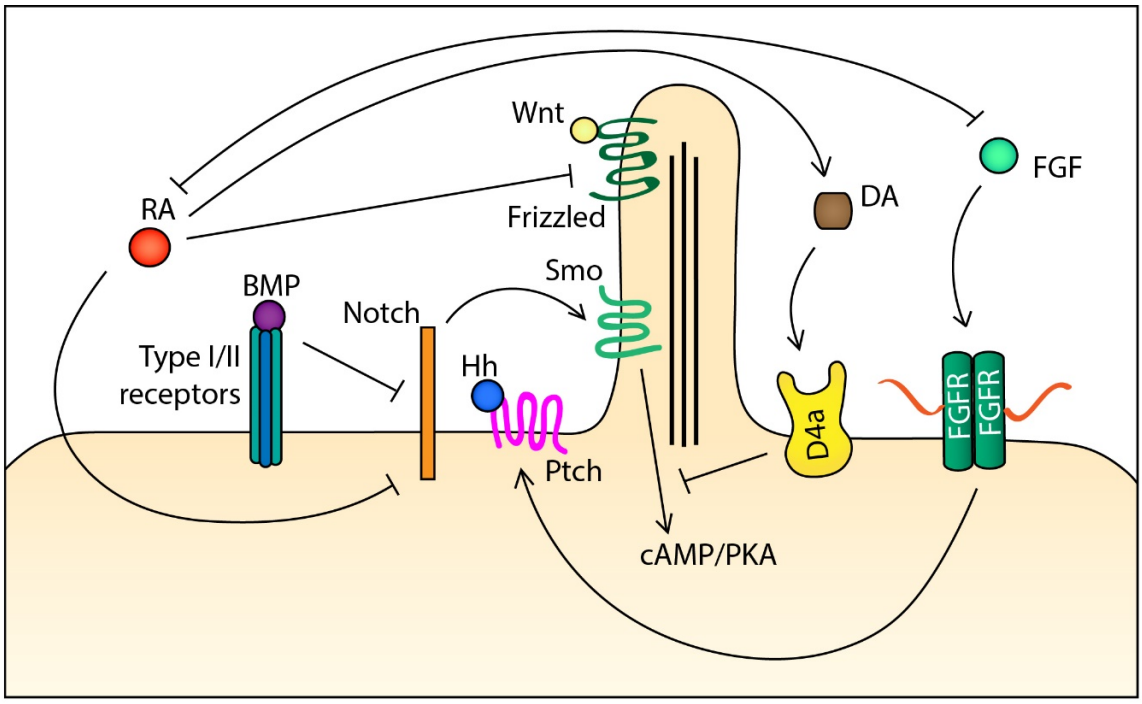

Fig. 3. Example of the convergence of signalling pathways in the neural progenitor cells related to Hh - cAMP/PKA modulation. During spinal cord development, Notch augments Shh signalling by increasing the accumulation of Smo in the primary cilium. Notch signalling is inhibited, if the receptor is blocked downstream of BMP signalling. During the coordination of ventral patterning and caudal axis extension, FGF and Hh signalling act in a negative feedback loop by modulating the expression of Shh receptor Patched2. RA downstream pathways inhibit Notch signalling in the pMN cells to induce MN specification. The cross-regulation between RA, FGF and Wnt acts to determine the anterio-posterior identity of the progenitors and coordinate the transcriptional programs as the spinal cord matures. In addition, RA is necessary for the modulation of components of neurotransmitter pathways like dopamine or serotonin. Dopamine signalling alters the sensitivity of progenitors to Hh signalling during spinal neurogenesis though the dopamine receptor 4a (D4a) during development and regeneration of the spinal cord. For references see text.

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