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The role of extracellular matrix in spinal cord development

Stefan Wiese [a], Andreas Faissner [b,*]

[a] Faculty for Biology and Biotechnology, Group for Molecular Cell Biology, Universitaetsstr. 150, Ruhr University Bochum, Germany
[b] Faculty for Biology and Biotechnology, Department for Cell Morphology and Molecular Neurobiology, Universitaetsstr. 150, Ruhr University Bochum, Germany

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ABSTRACT

The development of the spinal cord represents one of the most complex structure developments of the central nervous system (CNS) as it has to unfold along the longitudinal axis and within segmental cues. There it has to cope with on the one hand connection to the periphery (skeletal muscle, dermomyotome, smooth muscles) and connect it to the higher midbrain and cortical regions of the CNS. Major studies have been performed to analyze the specific subset of transcription factors of the different types of cells within the different segments of the spinal cord. But transcription factor expression is always a result of cellular positioning as the environment defines the intracellular changes during differentiation and in adulthood. The surrounding composed of mainly extracellular matrix does not only provide a "glue" to attach cells to each other but also provides signals with special domains docking to cell surface receptors and presents soluble molecules such as basic fibroblast growth factors (bFGFs) or Wnt-proteins. The availability of these molecules depends on the matrix composition and influences the transcription factor code of each cell. Recent research has also provided strong evidence that depletion of single matrix molecules like Tenascin C (TnC) can lead to developmental changes within the progenitor pools. Therefore beyond the transcription factor code that defines cellular properties we want to focus on the role of the extracellular matrix in the development of the spinal cord.

1. Spinal cord development

The spinal cord in the adult is a specific structure that builds up a connection between the central nervous system and the periphery of the body. The function of the spinal cord is quite diverging. It integrates signals coming from different brain regions to generate a movement signal. It also coordinates muscle movement for more autonomous functions like breathing and sets rhythmic activities of muscle cells with a constant feed back to the higher brain regions. The importance and diversity of functions arising from this structure get clearer when looking at some of the motoneuron-based disorders. Patients with Amyotrophic lateral sclerosis or Spinal muscular atrophy are characterized by the progressive inability not only to walk and move but rather suffer from the increasing inability to breathe and speak. This article therefore takes a look at the starting point of spinal cord development including the transcription factor code of the most prominent cells, the motoneurons, with final focus on the role of extracellular matrix (ECM) molecules and components as the past years of research has shifted the focus also on the role of these proteins and molecules during development. The further elucidation of ECM and ECM component function might lead not only to a better understanding of pathological processes but also to new ways towards development of cures for such disastrous diseases.

1.1. Initial specification steps for the spinal cord in development

At the neural tube stage the CNS epithelial cells are pseudo stratified and perform symmetric cell divisions. This leads to an increased cell number in the initial pool of neural precursor cells (NPC). These neuroepithelial cells are generated along the entire anterior–posterior axis while different regional signals through different molecules along this axis already start to instruct the positional identity of the cells. Therefore, the different regions of the central nervous system (forebrain, midbrain, hindbrain, and spinal cord) become evident at this very early stage. Determination of the caudal identity is induced by retinoic acid (RA), a derivative of the vitamin A, and subsequent expression of Pax3 for the neuroepithelial cells (Maden, 2007) (Fig. 1A) and mutant mice deficient for the retinoic acid producing enzyme, the retinaldehyde dehydrogenase 2 (Raldh2), show severe alterations in hindbrain and spinal cord patterning (Chambers et al., 2007; Molotkova et al., 2005; Ribes et al., 2009). Besides RA signaling, fibroblast growth factor (FGF) signaling appears to be of critical importance for the specification of the spinal cord (Bertrand et al., 2000; Diez del Corral et al., 2002). Both RA and FGF molecules form antagonizing gradients to determine the anterior hindbrain and the posterior spinal cord. The specific regionalization within the caudal CNS is specified by

* Corresponding author.
E-mail address: andreas.faissner@rub.de (A. Faissner).

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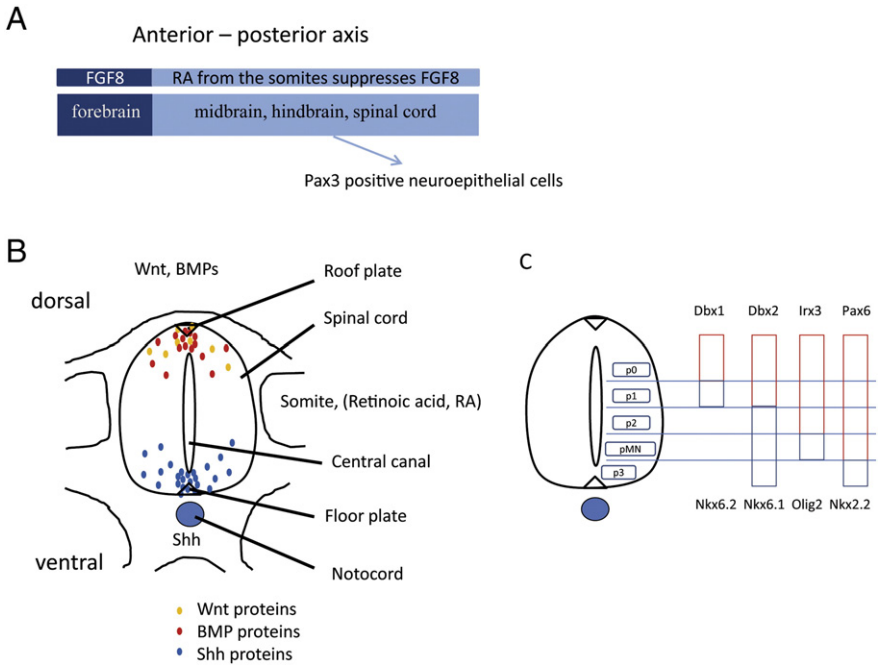

Fig. 1. Generation of different cell types during spinal cord development. (A) Midbrain, Hindbrain and spinal cord are defined by morphogenetic signaling molecules such as retinoic acid (RA) and FGF8 and subsequently express the neuroepithelial cell marker Pax3. RA provided by the somites promotes neuronal differentiation and ventral patterning genes by suppressing FGF-signaling by the neuroepithelium and the mesoderm (Diez del Corral et al., 2003). (B) The dorso-ventral axis is defined by the roof plate cells secreting Wnt and BMPs to provide a dorsalizing signal and by sonic hedgehog from the notocord and later on from the floor plate cells to release a ventralizing signal. Retinoic acid from the somite cells defines the neurogenic precursor cells (C). The regional identity is given by a specific transcription factor code spanning the p0, p1, p2, pMN and p3 regions of the spinal cord. The different progenitor pools can switch to generate different differentiated cell types, e.g. the pMN pool first gives rise to motoneurons and later in development generates oligodendrocyte precursor cells. The transcription factors Dbx1, Dbx2, Irx3 and Pax6 define the dorsal part and the transcription factors Nkx6.2, Nkx6.1, Olig2 and Nkx2.2 define the more ventral part of the spinal cord progenitor pools.

expression of various homeobox domain transcription factors (Hox genes) (Diez del Corral et al., 2003). These Hox transcription factors in turn are responsible for a neuronal subtype identity of the embryonic hindbrain and for the spinal cord (Wu et al., 2008).

1.2. Dorso-ventral pattering and generation of different cell types in the spinal cord

RA and FGFs define the cellular identity for the rostro-caudal axis. In contrast, other molecules regulate the cellular identities along the dorso-ventral axis of the developing hindbrain and spinal cord. Members of the bone morphogenetic protein (BMP) and of the wingless/Int-1 (Wnt) family are secreted from the roof plate cells. They are necessary for patterning of the dorsal part of the spinal cord (Caspary and Anderson, 2003; Chizhikov and Millen, 2004). The floor plate derived Sonic hedgehog (Shh) in turn is an essential morphogen for ventralization of the spinal cord cells (Dessaud et al., 2008; Jessell, 2000; Tanabe et al., 1995) (Fig. 1.B). Therefore both gradients antagonize each other. The graded Shh signal forms different neural progenitor regions characterized by a specific expression patterning of homeodomain transcription factors. The combination of homeodomain transcription factors expressed by the cells defines the neuronal subtypes within the spinal cord. Subsequently, mutations in Patched 1 or Smoothened, which are both receptor elements of the Shh pathway result in severe patterning defects during embryogenesis (Briscoe et al., 2001; Wijgerde et al., 2002). Shh-signaling is at least partly regulated by heparansulfate proteoglycans (see below) which link morphogenic gradients, ECM composition and transcription factor codes to a functional complex of interacting entities (Chang et al., 2011; Ramsbottom et al., 2014; Whalen et al., 2013; Witt et al., 2013).

The homeodomain transcription factor concept has been considered as the essential mechanism for specification of neuronal and the latter glial subtype identities. Interestingly, the pMN motoneuron pool switches to generate oligodendrocyte precursor cells and therefore the same pool of precursor cells is used for both latter cell types. The exact mechanism by which this switch occurs is still yet unknown and fate map analysis using Olig2-CreER mice even could show that the switched latter Olig2-positive progenitors can give rise to some white matter astrocytes in development (Masahira et al., 2006). Other transcription factors have been shown to be critically involved and expressed during astrocyte development. The basic Helix–Loop–Helix (bHLH) transcription factor Stem cell leukemia (Scl) is expressed in the V2 domain during spinal cord development. Mutants lacking Scl exhibit an increased number of oligodendrocytes and lack many of the astrocytes normally initiated from here (Muroyama et al., 2005). Apart from these regionally acting factors there are more generalized acting factors like the paired box homeodomain transcription factor 6 (Pax6). Pax6 is expressed in the astroglial lineage both during development and adulthood and when absent the astroglial lineage appears delayed in the spinal cord (Sakurai and Osumi, 2008). Pax6 and the NK6 homeobox 1 (Nkx6.1) together define distinct astrocyte progenitor domains in the ventral white matter of the spinal cord (Hochstim et al., 2008) (Fig. 1C). Therefore, the same homeodomain code that defines neuronal subtypes also induces glial subtype identities in the developing spinal cord. The transcription factor combination regulating subtype specification and regional identity of the cells might be used as marker for such cells but in general does not finally clarify why first this switch occurs and second what the signal is that makes the cells express these transcription factors and factor combinations leading to the different cellular identities.

1.3. Motoneuron subtypes and their functional columns

Motoneuron subtypes are generated during embryonic development to serve the needs for adulthood. These subtypes are well organized along the rostro-caudal and dorso-ventral axis in the spinal cord sorted by function and innervation targets. So neurons innervating the