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Key molecules in axon regeneration

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Development of adult mammal central nervous system (CNS) is closely related to loosing the ability spontaneously regenerate after injuries. On the other hand, peripheral nervous system (PNS) maintains its capability to regenerate after injuries entire lifespan. Ability to regenerate successfully is mainly determined by the balance of growth promoting and growth inhibiting factors, expressed by both neuronal and non-neuronal cells found in the injury site. Some of signaling cues involved in regeneration are expressed in adult CNS constantly, although expression of other factors occurs only in the injury site of adult mammal. Ephrins, Semaphorins, Slits and Netrins are among most important molecules involved in lack of success in regeneration of CNS. PNS neurons initiate reparation mechanisms right after development of injury, and are capable to recover functional activity even if an area of injury is more than several centimeters wide. Understanding of differences between CNS and PNS regeneration and factors involved in functional nervous system recovery are crucial for both in depth analysis of plasticity of adult mammal neural system, and for developing new treatment strategies.

Key words: spinal cord injuries, nerve regeneration, spinal cord regeneration, spinal nerves

INTRODUCTION

Understanding of nervous system development and regeneration is crucial not only for scientific fundamental understanding, but even more for practical reasons. It is estimated, that average number of new cases of spinal cord injuries (SCI) resulting in incomplete or complete paraplegia or tetraplegia in the United States is 15–40 cases per million people (Bernhard et al., 2005; Burke et al., 2001; Sekhon, Fehlings, 2001). The highest per capita rate of injury occurs between ages 16–30 (Bernhard et al., 2005). SCI has a dramatic personal and economic impact on society. Moreover, diseases like multiple sclerosis, Alzheimer's disease, Parkison's disease and other neurodegenera-

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tive conditions are related to regenerative capabilities of CNS. Despite currently available therapies they provide only modest improvement in neurological and functional recovery (Tator, 2006; Wang et al., 2009; Jablonska et al., 2010). *In vivo* and *in vitro* animal studies mimicking various conditions of CNS dysfunction is a very handy tool to improve the quality of treatment and understanding recovery mechanisms in pathological conditions (Blakemore, Franklin, 2008; Crawford et al., 2009). As in contrast to CNS lesions, PNS injuries are associated with only temporary loss of function and usually are followed by a full recovery (Chew et al., 2012; Bradke et al., 2012). Difference in regeneration mechanisms of nervous system was shown to be mainly due to signaling molecules and factors expressed in close vicinity of the injury site (Chew et al., 2012; Zou, Lyuksyutova, 2007). Moreover, neurons interconnecting CNS and PNS particularly residing in dorsal root ganglions (DRGs) are of exceptional importance for understanding in what way regeneration of axons occurs, leading to full recovery of affected functions (Liu, Snider, 2001; Zhou et al., 2006; Zou et al., 2009).

The aim of the current review is to analyse what are the main reasons that account for tremendous differences in efficiency of regeneration of CNS and PNS and to give some cues on possible treatment strategies for recovery after CNS injuries.

PNS regeneration

Injuries of PNS depending on injury site lead to temporary or permanent paralysis or anesthesia of affected body areas (Allodi et al., 2012). In adult mammals with mild or middling sensory and motoneuron axon injury, in most cases regeneration ends with a full functional recovery (De Winter et al., 2002a; Skene, Virag, 1989). Rupture or severe injury of peripheral axons is followed by decomposition of the base of axon and myelin cover as well as removal of remaining parts of the axon by macrophages and Schwann cells (Stoll, Muller, 1999; Deumens et al., 2010a). Full obviation of remaining axon is an indispensable condition for correct proceeding of regeneration (Stoll, Muller, 1999; Fu, Gordon, 1997; Giger et al., 2010). Consequently, Schwann cells proliferate expressing adhesion molecules such as N-CAM, N-cadherins and P75 as well as trophic factors like NGF and BDNF (Gorio et al., 1996; Gai et al., 1996; Meyer et al., 1992; Fischer, Leibinger, 2012). Successful regeneration of PNS strongly relies on basal lamina of the axon (De Winter et al., 2002a; Loy et al., 2002; Su, He, 2010). In unaltered conditions this tube like structure surrounds groups of axons along with Schwann cells. In severe PNS injuries involving complete disruption of basal lamina fibroblast scar is formed, preventing successful regeneration of axons (Fig. 1).

Contrariwise to CNS lesions, injuries of PNS do not lead to apoptosis of neurons involved. PNS neurons maintain the capacity to renew gene expression programs important for induction of axon regeneration. Expression of genes and transcription factors linked with growth of neurites, such as tubulin, actin, c-fos, c-jun, KROX, increase instantly after injury, and are linked to regenerative capacity of PNS neurons (Robinson, 1994; Herdegen et al., 1997; Marmigere, Ernfors, 2007; Rishal, Fainzilber, 2010).

CNS regeneration

Injury of CNS axon leads to degradation of the neurite detached from the body following obliteration of it by macrophages and activated microglia cells. Neuron body itself can survive, or undergo atrophy if the site of injury is far from soma. If the site of injury is in the vicinity of cell body neurons usually do not survive (De Winter et al., 2002a). Following the injury a glia cell scar is formed in lesion site. The central part of the scar is mainly formed of macrophages and blood vessel endothelial cells, the periphery of the scar surrounding the central part mainly consists of oligodendrocite precursors, astrocytes and microglia cells (Fawcett, Asher, 1999; Sharma et al., 2012; Stocum, 2012). The majority of injured CNS axons bifurcate in vicinity of lesion site, but they do not cross the scar and consequently do not lead to functional recovery (Deumens et al., 2010a; Devor, 1975; Devor, Wall, 1976). It was shown that CNS axons can regenerate if appropriate support is provided, e. g. after application of part of peripheral nerve, embryonic neural tissue, Schwann cell inclusions or other suitable substrate (Deumens et al., 2010a; Giger et al., 2010; Deumens et al., 2010b). Such regeneration capabilities impose importance of environmental factors for successful initiation and motion

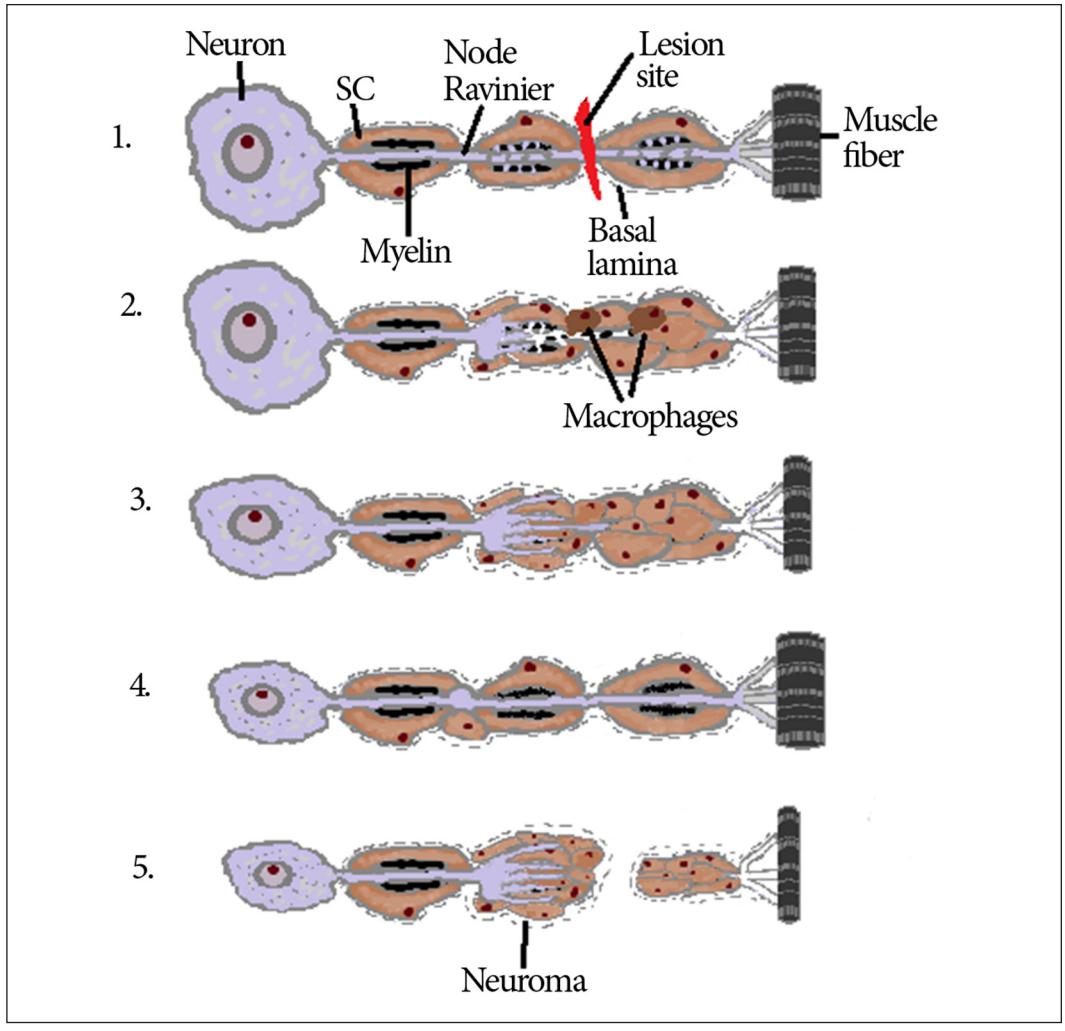

Fig. 1. PNS axon injury and regeneration. 1. During the first days after injury degeneration of myelin and axon occurs at both sides of a lesion. 2. During the next step of regeneration (days to weeks after injury) anterograde degradation of axon occurs leading by mitotic division of Schwann cells (SC) as well as macrophages invading to the endoneural tube. Soma of neuron undergoes chromatolytic changes encouraging sprouting of injured part of neurite. Muscle fibers innervated by injured axon start to undergo atrophy, but do not die. 3. After the removal of the remaining injured part of axon, sprout of regenerating axon correctly re-entered endoneural tube leads to recovery of neural wiring which can last up to a few months. Meanwhile the innervated tissue proceeds to undergo atrophy as a consequence of lack of innervation. 4. After correct reinnervation of the target tissue and formation of neuromuscular junction, uninvolved axon sprouts retract. Moreover, after re-establishment of innervations atrophy of innervated cell reverses as well as soma of affected neuron starts to recover to its native state. 5. In case of failure of axon sprouts to cross the formed cell barrier and re-enter endoneural tube, neuroma will form. Reinervated cell will undergo severe atrophy and soma of neuron will remain in regenerative state. Figure was prepared based on data from Deumens et al., 2010

of axon growth in lesion area. Furthermore, successful regeneration of CNS axons suggests that neurons in CNS maintain re-growth capability, but rely on expressed environmental factors (Kadoya et al., 2009; Lu et al., 2004). It is also supported by observations that regenerated CNS axons do not re-enter CNS and consequently do not form functional junctions with their targets after reaching the end of aforementioned growth patterns (Kadoya et al., 2009).

DRGs bind CNS and PNS and therefore are a very challenging model in understanding differences between CNS and PNS regeneration. In case when axon injury occurs amid vertebral column and DRG as shown in Fig. 2, axons will regenerate as long as they are in the PNS, but will not enter into spinal cord (Hagg, 2005; Roth et al., 2009), contrariwise if injury occurs in distal or peripheral part of DRG axons, functional recovery of the affected areas will be restored after regenerated axons will reach their targets (Marmigere, Ernfors, 2007; Lallemend, Ernfors, 2012; Davis, 2013). Studies revealing that axon repelling molecules such as EphB3 (Miranda et al., 1999; Mann et al., 2003; Egea et al., 2009), Slit2 (Piper et al., 2006), Sema3A (Dent et al., 2011; Tojima et al., 2010) and some others (Chilton, 2006) are abundantly expressed in lesion site of CNS imply that regeneration capabilities are mainly impaired by these repulsive molecules.

Development and regeneration of DRG axons

Dorsal root or spinal ganglions start developing as early as E9.5 as shown in Fig. 3 (Marmigere and Ernfors, 2007).

DRGs belong to PNS and basically consist of afferent neurons, glia cells and connective tissue. The key difference between CNS neurons and neurons residing in DRGs is that DRG neurons are pseudounipolar exposing single axon with two branches, one reaching targets in periphery, another entering spinal cord and transmitting

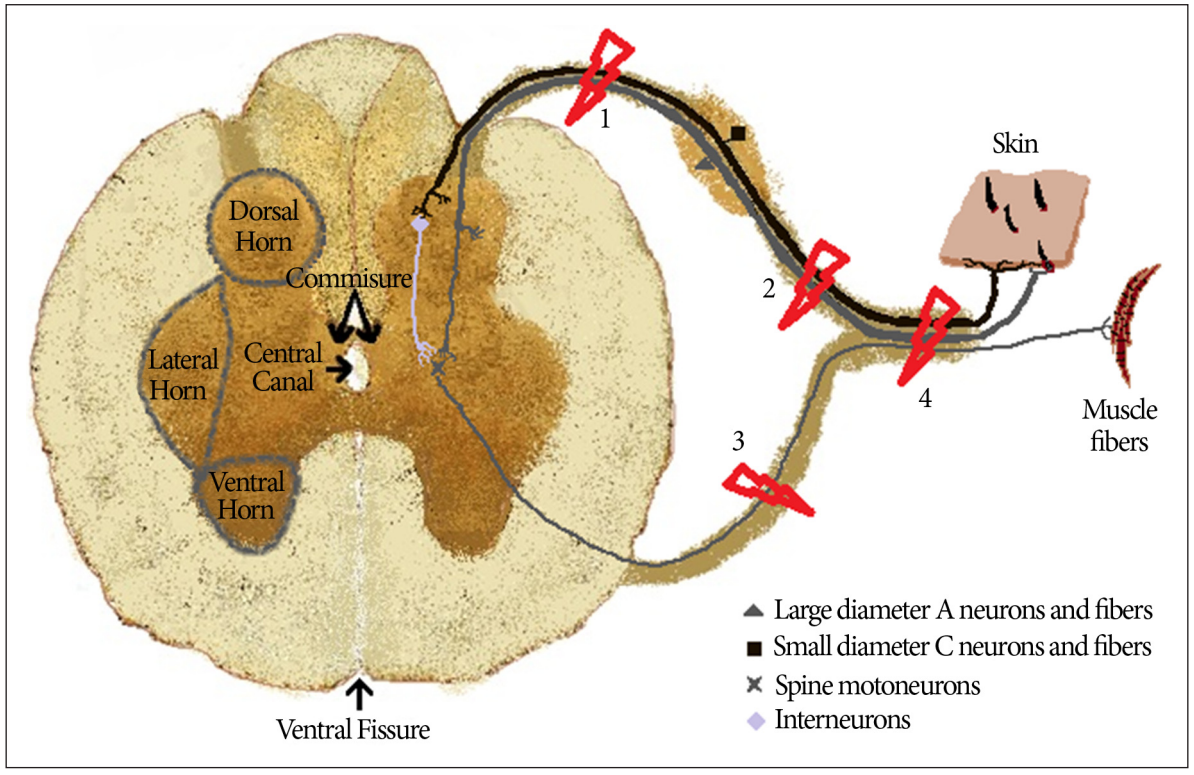

Fig. 2. DRG axon lesions and functional recovery. Afferent neurons residing in DRGs can be divided into two types: big neurons possessing myelinated (fast response, A type) axons mainly responsible for low intensity non-noxious stimuli and small neurons possessing non-myelinated (slow response, C type) axons basically responsible for noxious stimuli. Lesions of PNS affecting only afferent axons (2), only efferent axons (3) or both (4) induce temporary loss of perception or motor activity of areas affected. Injuries of axons in PNS do not lead to scar formation and therefore regenerate relatively successfully. Injuries of afferent axons growing towards spinal cord (1) are rare, but regeneration of axons ceases as long as they reach CNS environment, and therefore this kind of injuries lead to a permanent loss of sensations of the affected areas. Figure was prepared based on data from Lallemend and Ernfors, 2012

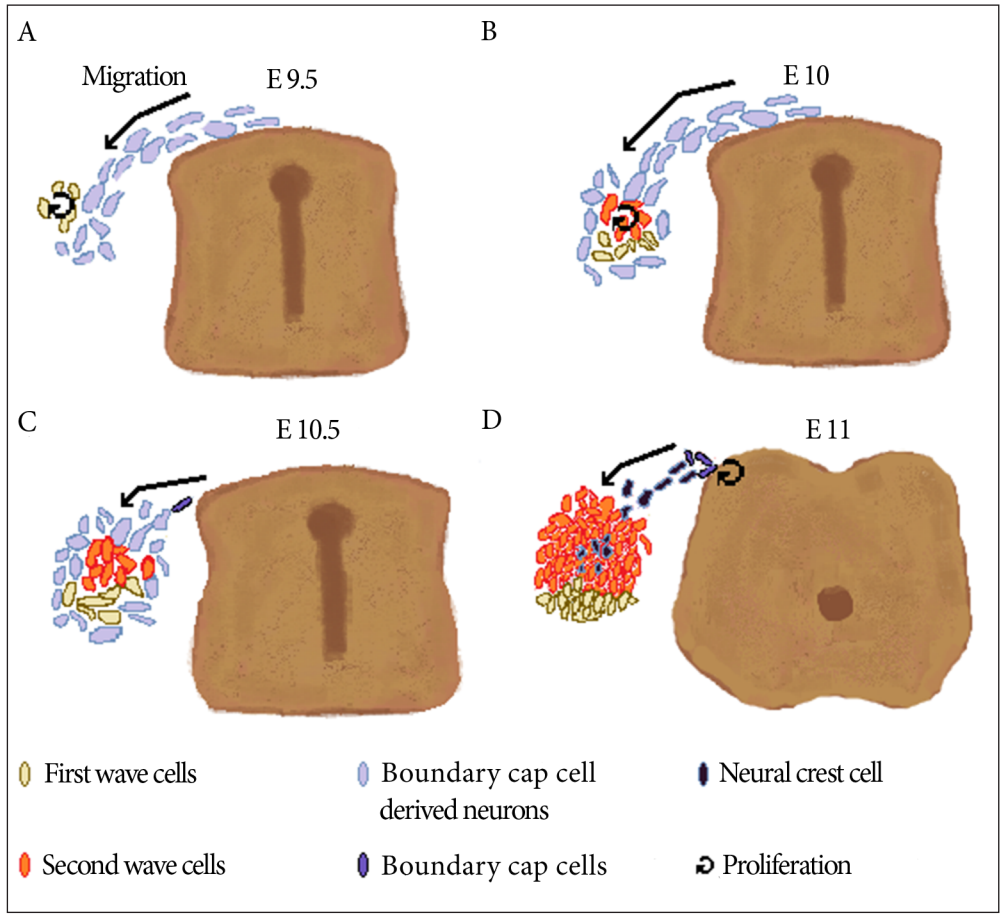

Fig. 3. Steps of DRG formation. Development of DRG neurons proceeds in three waves of neurogenesis. In chick DRG large proprioreceptive neurons followed by small neurons migrate and mature first. Two types of neural crest cell (NCC) with different fates are present. A) Multipotent NC cells migrate to the rostral part of the dorsal somatic lip during the first wave of migration (Montelius et al., 2007). NCC maturate, giving rise of mechanoreceptive and proprioreceptive neurons. B) During the second wave NCCs with high rate of proliferation as opposing to the first wave of low proliferation rate NCCs migrate to DRG. At this stage neurogenesis occurs in post-migratory cells and results in sensory neuron formation. C) Multipotent boundary cap cells derived from neural crest cells can be identified as early as E 10.5 at the DRG axon entry to spinal cord site (Hjerling-Leffler et al., 2005; Maro et al., 2004). D) Boundary cap cells proliferate and migrate into the DRG giving rise to small TrkA positive sensory neurons. Final maturation of DRG mainly related to neurite development and maturation of cells. Arrows indicate the highest rates of proliferation during different steps of DRG formation. Figure was prepared based on data from Marmigere and Ernfors, 2007

signals to neurons in CNS. During development DRGs strongly rely on different neurotrophic factors, such as NGF (Caroll, Rothenberg, 1992; Glebova, Ginty, 2005) or BDNF (Fukuoka et al., 2001) as well as on guidance molecules such as Semaphorins (Raper, 2000; Tanelian et al., 1997; Kawasaki et al., 2002), Netrins (Jiang et al., 2003), Slit (De Bellard et al., 2003), and Ephrins (Mizobuchi et al., 2013; Krull, 2001). Correct axon navigation during the development as well as regeneration after injury is essential for functional activity. It has been shown that incorrect connection or disconnection from either target or CNS neurons leads to apoptosis of DRG neurons (Lo et al., 1995a; Lo et al., 1995b). DRG neurons usually are injured at three possible sites: nerves

reaching distal targets, neuron bodies residing in DRG and axons entering vertebral column. Lesions of either neuron bodies or axons growing in direction of vertebral column are rare, but more severe, inducing permanent loss of sensory function. Axons reaching periphery targets do regenerate successfully as long as neural shaft remains intact (Deumens et al., 2010a). The difference between regeneration capabilities of the same axon reaching different targets supports the hypothesis that proper regeneration is strongly dependant on extracellular signaling and neurotrophic molecules.

Guidance molecules in regeneration

Major progress has been made during recent years in identifying signaling cues and factors involved in axon regeneration (Giger et al., 2010). It was shown that both attractive and repulsive cues are important for successful regeneration and recovery of function. Moreover, Song and Poo (2001) identified major factors important for axon regrowth and navigation as well as for cell migration to the site of lesion. Among the most important guidance molecules the families of semaphorins, netrins, ephrins and slits are identified as crucial for correct navigation and regeneration. During the development of neural system these cues along with growth factors such as NGF, BDNF or GDNF play the main role in the development of both PNS and CNS. Understanding of signal transduction mechanisms and roles that these molecules are playing in axon regeneration is crucial for the successful development of patient treatment methods after CNS and PNS lesions.

Semaphorins

Semaphorins constitute a large family of proteins that are divided into eight groups all sharing the same conservative sema domain composed of about 500 amino acids (Roth et al., 2009; Pasterkamp, Kolodkin, 2003). Both types, secreted and membrane bound semaphorins, transfer their signal through plexin and neuropilin receptor complex (Kawasaki et al., 2002; Young et al., 2004). Importance of Sema3A in both PNS and CNS survival, regeneration and development has been demonstrated a decade ago (Roth et al., 2009; Chedotal et al., 1998; Raper, Kapfhammer, 1990; Raper, Grunewald, 1990; Luo et al., 1995; Bagnard et al., 2004). Adult mammal motoneurons constantly express Sema3A and its co-receptor NRP1 throughout the lifespan. Contrary to CNS injuries, lesions of PNS do not initiate elevation of Sema3A and its receptor expression at the injury site (Pasterkamp, Verhaagen, 2006; Pasterkamp et al., 1998a). Furthermore, low Sema3A expression in PNS is observed throughout all regeneration process. In case of correct reinnervations of the target, Sema3A expression recurs to basal level (Pasterkamp et al., 1998b). Biological meaning of NRP1 / PlexA1 complex and Sema3A co-expression in the same neuron is not clear. Hypothesis is based on analogy with ephrins state that signaling molecules can functionally modulate the expression of their receptors (Hornberger et al., 1999). If this is also true for reduction of Sema3A expression, this would implement increased sensitivity for Sema3A from other sources (De Winter et al., 2002a). It was also shown that in case of a successful reinnervation of target, Schwann cells surrounding junction start expressing higher levels of Sema3A increasing the stability of connection (De Winter et al., 2002b). Recovery after PNS injury is related not only to axon regeneration but also rearrangement of efferent and afferent fibers in the dorsal and ventral horns of spinal cord. As sensory neurons in DRGs express NRP1 at constant levels throughout regeneration a decreased expression level of Sema3A by motoneurons is an indispensable condition for successful recovery of the function (Woolf et al., 1992; Gavazzi et al., 2000).

Netrins

Netrins are a family of proteins composed of a conservative sequence of about 600 amino acids (Dickson and Keleman, 2002). It is noteworthy that they are partly homologous to laminine – basal lamina proteins involved in cell migration, differentiation, adhesion and survival (Timpl et al., 1979). It has been shown that netrins can act either as attractive or repulsive guidance cues depending on receptors they interact with. To date, two main families of netrin receptors are identified. UNC5 is involved in axon repulsion and DCC family is mainly shown to be important for attraction (Bonnin et al., 2007; Bashaw, Klein, 2010). Moreover, it was shown that netrins induce depolarization of membrane and induces Ca^{2+} influx through voltage gated calcium

channels (VGCC), that are important for netrin-induced midline crossing (Shim et al., 2005; Wu et al., 2006). Conditional mutations of netrins or their receptors lead to commissural axon misguiding in CNS and therefore should be taken into account in treatment of severe CNS injuries (Briancon-Marjollet et al., 2008).

Slits

Slits are a family of secreted proteins in vertebrates encoded by three genes Slit1, Slit2 and Slit3 (Hohenester, 2008). Slits are identified by four leucine-rich repeated domains, conserved N- terminal domain, C- terminus cysteine knot domain and nine EGF-like repeats (Wong et al., 2002; Hohenester et al., 2006) and are mainly expressed in spinal cord floor-plate of mammals (Long et al., 2004). Slits canonically interact with Robo (roundabout) receptors and act as repulsive cue for commissural axons preventing them from re-crossing midline in the spinal cord. There are three identified vertebrate members of the Robo receptor family: Robo 1, 2 and 3. Slit2 is one of the most important repulsive cues in axon regeneration (Piper et al., 2006). Cytoskeleton reorganization induced by Slit2 acting through p38 and p42 / p44 MAPK pathways is shown to be one of the factors of axon inability to cross cell scar formed after injury in CNS (Zheng et al., 2001). Additionally, it has been shown that Slit2 signaling involves local axonal protein synthesis, important for rapid response and cytoskeleton reorganization. The same axonal protein synthesis was found to be important in Sema3A and Netrin-1 induced repulsive axon responses (Campbell, Holt, 2001).

Ephrins

Ephrins also known as ephrin ligands are a family of membrane-bound proteins (Himanen and Nikolov, 2003a, b) that are best known as repulsive cues in guidance of axonal growth cones (Egea, Klein, 2007). The major structural characteristic of ephrins is a presence of N-terminal receptor binding domain which is bound to the membrane through a linker of about 40 amino acids. There are two major subclasses of Ephrins: ephrin-A subclass is bound to membrane through GPI linkage, whereas ephrin-B subclass is attached to membrane through a single transmembrane domain containing PDZ-motive. Currently identified eight ephrins are divided into two subclasses: ephrinAs (ephrinA 1–5) and ephrinBs (ephrinB 1–3). Ephrins transduce their signal through transmembrane Eph receptors. Recently there are 14 identified Eph receptors that are mainly characterized by a conserved N-terminal domain, a cysteine-rich region, extracellular domain of two fibronectin type III repeats, a conserved kinase domain, a sterile alfa motive (SAM) domain and a PDZ-binding motif residing in the cytoplasmic region. Eph receptor family is divided into two subfamilies based on sequence and binding affinities for the ephrin ligands. EphA subfamily (EphAs 1–8) predominantly interacts with ephrinA, and the EphB subfamily (EphBs 1–6) interacts with ephrinB. Moreover, it has been found that both receptors and ligands can act as signaling cue causing bi-directional responses of axon navigation (Petros et al., 2010; Marquardt et al., 2005). It has been recently shown, that during axon regeneration EphB receptors play a crucial role in axon-glia cell interaction, as both of them express ligands and receptors of Ephrin B subfamilies. This interaction is mainly involved in shaping neuronal structures and preventing axons to cross glia cell scar formed in CNS or in rare cases in PNS (Egea et al., 2009; Egea, Klein, 2007).

Growth factors in regeneration

Growth factors are described as molecules involved in cell proliferation, migration, growth and survival. Although growth factors are essential for neuronal cell survival, they can also act as guidance cues in neurodevelopment and axon regeneration (J. Wordinger, Clark, 2008). Growth factors are expressed by both neuronal and non-neuronal cells and thereby can induce cell response via paracrine, autocrine and juxtacrine mechanisms. In axon regeneration after SCI three main growth factors NGF, BDNF and GDNF play an important role not only by providing survival signals but also as attractants for axons, and cell migration to injury site (Kawamoto, Matsuda, 2004). The interplay between these properties of growth factors is a key element for preventing formation of glia scar and supporting a correct regeneration of axons.

NGF

Nerve growth factor is a dimer of 13 kDa polypeptide chains. NGF belongs to the neurotrophin

family molecules sharing structural homology. In addition to NGF, the family includes brain-derived neurotrophic factors (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) (Butte et al., 1998; Robinson et al., 1999). Survival of CNS and PNS neurons is developmentally dependent on availability of NGF. On the other hand, these neurons become independent of NGF once they have established their connections and maturate. Although NGF-responsive mature neurons become independent of growth factor for survival, they undergo atrophic changes if subjected to long term NGF withdrawal (Sofroniew et al., 2001). In peripheral nerve injury meylinating and non-myelinating Schwann cells (SC) de-differentiate and reenter the cell cycle. Proliferating SC produce cytokines, NGF and other factors that are important for axon regeneration and nerve repair (Mirsky, Jessen, 1999; Frostick et al., 1998). During altered conditions SC expression of NGF is highly increased (Mirsky, Jessen, 1999). PNS injury also leads to infiltration of inflammatory cells to lesion site. Among these, macrophages, mast cells, and T cells are shown to have the capacity to express NGF. The role and function of NGF for different cell types in response to PNS injury are not fully clear. Effect of exogenously administered NGF *in vitro* increases myelination capacity of regenerating axons. On the other hand, NGF promotes Schwann cell migration that precedes and promotes axon elongation into entubation repair sites (Sofroniew et al., 2001). This double effect of NGF is an important property which can help in developing a strategy for applying growth factors after CNS or PNS injuries in a timely manner.

BDNF

BDNF is a secreted neurotrophic factor essential for survival of sensory neurons, as well as certain cholinergic neurons, motoneurons and part of dopaminergic neurons. In CNS, it was shown that synthesis of BDNF is affected by neuronal activity and is important for synaptic plasticity. Strengthening of synaptic pathways intensifies the connections between neurons, resulting in increased formation of synapses for both axon collaterals and dendritic spines. Recently it has been shown that *in vitro* application of BDNF after conditional lesion of DRG axons significantly increases regeneration rate and recovery after injury. Moreover, the application of BDNF antiserum suppresses enhanced neurite outgrowth, suggesting that BDNF plays an important role in recovery after nerve system lesions (Song et al., 2008). Reduction in BDNF levels has been associated with a number of neurodegenerative, developmental and neuropsychiatric conditions including Alzheimer's disease (Peng et al., 2005), Parkinson's disease (Howells et al., 2000), schizophrenia (Favalli et al., 2012) and depression (Castren et al., 2007).

GDNF

A glial cell line-derived neurotrophic factor (GDNF) family influences both neural migration and neurite outgrowth (Hashino et al., 2001). GDNF, artemin and neurturin belonging to the same family of growth factors are important guidance cues in the development of enteric, sympathetic and parasympathetic nervous systems (Wang et al., 2006; Sariola, Saarma, 2003; Tian et al., 2013; Allen et al., 2013). GDNF ligands signal through a receptor complex Ret tyrosine kinase and a binding sub-unit specific for each ligand (GFRα1 for GDNF, GFRα2 for neurturin and GFRα3 for artemin). Neural cell adhesion molecule (NCAM) was also identified as a signaling receptor for GDNF-family ligands (Paratcha et al., 2003). GDNF and NCAM binding results in Schwann cell migration as well as promotion of axon growth in the hippocampus and cortex. Moreover, GDNF was found to have trophic properties and protective effects on noradrenergic neurons, as well as peripheral motor neurons, promoting possibilities for its therapeutic potential. It was also found that GDNF induces functional improvements after chemical lesion of the striatum in the CNS. This recovery is found to be due to neurochemical changes in paleostriatum and substantia nigra (Lapchak et al., 1997). Local application of GDNF was also shown to partly recover motor functions after chemical lesions of CNS (Kirik et al., 2001). The interplay between different growth factor families that are shown to have therapeutic properties should be investigated for possible use in SCI treatment.

CONCLUSIONS

Depending on the severity of CNS or PNS injury consequences can lead to temporal or permanent

loss of function of the regions affected. *In vitro* and *in vivo* studies based on rodent dorsal root ganglions and other types of neuronal tissue have provided a strong impetus towards development of new strategies for treatment of affected patients. Current progress made in understanding of cellular and molecular events triggered by SCI provided tools to manipulate mechanisms allowing successful regeneration of injured CNS neurons. The ultimate goal of the CNS injury studies is to understand causes of failure for successful regeneration and to overcome barriers preventing reestablishment of functional activity. In both SCI and some neurodegenerative diseases, the major reason of neural system dysfunction is loss of functionally active connections between neurons. In patients diagnosed with partial spinal cord lesion or protrusion reestablishment of circuitry can be established by introducing factors and cues that induce short distance axonal sprouting and formation of a new synaptic contact. This can lead to relatively fast recovery of function of areas affected. Spatio-temporal drug application therapies are among most perspective strategies of successful treatment of SCI. Combination of growth promoting and growth inhibiting molecules as well as factors involved in cell migration and survival are essential for developing treatment that could enhance successful return to active life after rehabilitation procedures of both neurodegenerative disease affected patients and patients with SCI. As aforementioned recent advances in the field of CNS and PNS regeneration are based on research of rodent models, additional studies need to be performed to adapt them for clinical practice. Tenable steps which should be made for further advances in neural system treatment after occurrence of malfunction of CNS involve experiments with human-like primates in order to develop protocols suitable for human clinical treatment.

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SVARBIAUSIOS MOLEKULĖS AKSONŲ REGENERACIJOJE

Santrauka

Suaugusių žinduolių centrinės nervų sistemos (CNS) vystymasis glaudžiai siejasi su spontaniško gebėjimo regeneruoti po pažaidų praradimu. Savo ruožtu periferinės nervų sistemos (PNS) aksonai gebėjimą regeneruoti po pažaidų išlaiko visą gyvenimą. Santykis tarp augimą skatinančių ir augimą slopinančių veiksnių, ekspresuojamų tiek nervinių, tiek ir ne nervinių ląstelių pažaidos aplinkoje, sąlygoja regeneracijos sėkmę. Dalis signalinių molekulių, taip pat ir augimą reguliuojantys veiksniai, yra gaminamos per visą gyvenimą, tačiau kai kurių jų raiška ypač padidėja po CNS pažaidos, kai jos riboja aksonų augimą bei paveikia kitų ląstelių elgseną. Efrinų, Semaforinų, Slit ir Netrinų klasės molekulės yra pagrindiniai veiksniai, trukdantys sėkmingai CNS regeneracijai ir funkcijų atkūrimui. PNS neuronai inicijuoja reparacijos mechanizmus iš karto po pažaidos atsiradimo ir sėkmingai atkuria savo funkcijas net tada, kai pažaidos plotas siekia kelis centimetrus. Skirtumų tarp PNS ir CNS regeneracijos mechanizmų ir juose dalyvaujančių veiksnių suvokimas yra svarbūs tiek tiriant nervų sistemos plastiškumą, tiek taikant naujas nervų sistemos pažaidų atkūrimo strategijas.

Raktažodžiai: nugaros smegenų pažaidos, nervų regeneracija, nugaros smegenų regeneracija, nugaros nervai