Progress in Neurobiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Review article

Functional integration of complex miRNA networks in central and peripheral lesion and axonal regeneration

M. Ghibaudi*, M. Boido, A. Vercelli

Department of Neuroscience "Rita Levi Montalcini", Neuroscience Institute Cavalieri Ottolenghi, University of Torino, Italian Institute of Neuroscience, Italy

ARTICLE INFO

Article history:
Received 25 January 2017
Received in revised form 24 July 2017
Accepted 28 July 2017
Available online xxx

Keywords:
Spinal cord injury
Axotomy
Neuroinflammation
Apoptosis
Cooperation
Convergence

ABSTRACT

New players are emerging in the game of peripheral and central nervous system injury since their physiopathological mechanisms remain partially elusive. These mechanisms are characterized by several molecules whose activation and/or modification following a trauma is often controlled at transcriptional level. In this scenario, microRNAs (miRNAs/miRs) have been identified as main actors in coordinating important molecular pathways in nerve or spinal cord injury (SCI). miRNAs are small non-coding RNAs whose functionality at network level is now emerging as a new level of complexity. Indeed they can act as an organized network to provide a precise control of several biological processes. Here we describe the functional synergy of some miRNAs in case of SCI and peripheral damage. In particular we show how several small RNAs can cooperate in influencing simultaneously the molecular pathways orchestrating axon regeneration, inflammation, apoptosis and remyelination. We report about the networks for which miRNA-target bindings have been experimentally demonstrated or inferred based on target prediction data: in both cases, the connection between one miRNA and its downstream pathway is derived from a validated observation or is predicted from the literature. Hence, we discuss the importance of miRNAs in some pathological processes focusing on their functional structure as participating in a cooperative and/or convergence network.

Abbreviations: AAV(s), adeno-associated virus(es); ADAM, a disintegrin and metalloprotease; AGO(2), argonaut (2); AKT, protein kinase B; APC, adenomatous polyposis coli; ASO(s), antisense oligonucleotide(s); ATF3, activating transcription factor 3; BBB, blood brain barrier; BCAA, branched chain amino acids; BCAT2, branched-chain aminotransferase; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; C11Orf9, myelin regulatory factor; CAND1, cullin-associated and neddylation-dissociated 1; CREB, cAMP response element binding protein; DGCR8, DiGeorge Syndrome critical region 8; DHA, docosahexaenoic acid; Dkk-1, Dickkopf-related protein 1; DLK, dual leucine zipper kinase; DRG, dorsal root ganglion; Egr2, early growth response 2; FADD, Fas-Associated protein with Death Domain; FAP-1, FAS associated phosphatase-1; FAS, associated protein with death domain; FAS-L, associated protein with death domain ligand; FGF2, fibroblast growth factor 2; FGF9, fibroblast growth factor 9; FGFR2, fibroblast growth factor receptor 2; FoxJ3, forkhead box J3; FOXO, Forkhead box O; Foxp(12), Forkhead box O p(1,2); GAP-43, growth associated protein 43; GFAP, glial brillary acidic protein; GSK-3(β), glycogen synthase kinase 3(β); Hes5, hes family bHLH transcription factor 5; HspB1, heat shock protein B1; IkBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; IKK, inhibitor of kappa kinase complex; IL-1, interleukin 1; IL-1α, interleukin 1α; IL-1β, interleukin 1β; IL-6, interleukin 6; IRAK1, interleukin 1 receptor associated kinase 1; JNK, c-Jun N-terminal kinase; KLF(6), Krueppel-like factor (6); LIF, leukemia inhibitory factor; LNA, locked nucleic acid; LV, lentiviral vectors; MAG, myelin-associated glycoprotein; MAP1B, microtubule associated protein 1B; MAPK, mitogen-activated protein kinase; MBP, myelin basic protein; MCAo, middle cerebral artery occlusion; MecP2, methyl CpG binding protein 2; miRNA(s) or miR(s), microRNA(s); MRF, myelin regulatory factor; mTOR, mechanistic target of rapamycin; NCAM, neural cell adhesion molecule; NeuroD1, neuronal differentiation D1; Neurog2, Neurogenin 2; NF-kB, nuclear factor kappa B; NGF, nerve growth factor; NPC, neuronal progenitor cell; NSCs, neural stem cells; OLs, oligodendrocytes; OPCs, oligodendrocyte progenitor cells; p250GAP, Rho GTPase activating protein 32; p53, tumor protein p53; p73, tumor protein p73; PAK, p21-activated kinases; PDK1/2, phosphatidylinositol-dependent kinase 1/2; PDZ-RhoGEF, Rho guanine nucleotide exchange factor 11; PI3K, phosphoinositide 3-kinases; PMP-22, peripheral myelin protein 22; PRKAG3, protein kinase AMP-activated non-catalytic subunit gamma 3; PTEN, phosphatase and tensine homolog proteins; PUMA, p53 upregulated modulator of apoptosis; rAAV, recombinant AAV; Rac1, Ras-related C3 botulinum toxin substrate 1; REST, RE1-Silencing Transcription factor; RhoA, Ras homolog gene family member A; RISC, RNA-induced silencing complex; ROCK1, rho-associated coiled-coil-containing protein kinase 1; RVG, rabies virus glycoprotein; SARM-1, sterile alpha- and armadillo-motif-containing protein-1; SC(s), Schwann cell(s); SCI, spinal cord injury; SCZ, schizophrenia; siRNA, small interfering RNA; SMA, spinal muscular atrophy; SMAC, second mitochondria-derived activator of caspases; SMAD2, mothers against decapentaplegic homolog 2; SMAD3, mothers against decapentaplegic homolog 3; SOD1, superoxide dismutase 1; Sox(24,6,9,10,11), SRY-box (2,4,6,9,10,11); Sox2, SRY-box 2; Sox4, SRY-box 4; Sox6, SRY-box 6; SPCs, Schwann progenitor cells; STAT3, signal transducer and activator of transcription 3; TDP-43, TAR DNA-binding protein 43; TF, transcription factor; TGF-β, transforming growth factor-β; TGF-β, transforming growth factor-β; TIAM1, T-cell lymphoma invasion and metastasis 2; TLX, tailess; TNF-α, tumor necrosis factor alpha; TRAF6, TNF receptor associated factor 6; TRBP, trans-activation response RNA-binding protein; wnt, wingless-related integration site; XIAP, x-linked inhibitor of apoptosis protein; ZFP238, zinc finger protein 238.

* Corresponding author at: Neuroscience Institute Cavalieri Ottolenghi, University of Turin Regione Gonzole 10, 10043, Orbassano, TO, Italy.
E-mail address: matilde.ghibaudi@unito.it (M. Ghibaudi).

http://dx.doi.org/10.1016/j.pneurobio.2017.07.005
0301-0082/

Contents

1. Peripheral and central axon degeneration after injury

Peripheral and central injury (due to motor vehicle accident, falls or sporting injuries) may severely damage axons and/or neurons, leading to a partial or complete motor, sensory and/or autonomic dysfunction, and considerably compromising the patient quality of life. Depending on the injury severity, neural death, inflammation and retrograde degeneration occur at different extent as consequence of specific molecular degenerative mechanisms. We summarize the key events and pathways taking place upon PNS/CNS damage and leading to degeneration.

As concerns PNS, during the first phases after injury, axon and myelin damage occurs both at the proximal and distal segments of the nerve in a process called Wallerian degeneration. In the first hours after the injury the end of the axon swells and in two days the increase of intracellular Ca^{2+} induces axon degeneration through calcium dependent proteolytic enzymes such as calpain (George et al., 1995). The increased Ca^{2+} influx leads to kinase activation such as dual leucine zipper kinase, c-Jun N-terminal kinase (JNK), inhibitor of kappa kinase complex (IKK) and glycogen synthase kinase 3 (GSK-3) whose inhibition protect axons in dorsal root ganglion (DRG) neuron culture (Gerdts et al., 2011; Michaelevski et al., 2010). Pathways involving transforming growth factor-β (TGF-β)/mothers against decapentaplegic homolog 2/3(SMAD2/SMAD3) and sterile alpha- and armadillo-motif-containing protein-1 have been identified as negative signals limiting axonal ability to regrowth (Gerdts et al., 2013; Patent number US7524640B2).

The growth pathway involving phosphoinositide 3-kinases-protein kinase B (PI3K-AKT), whose inhibition is associated with poor growth ability, is repressed by phosphatase and tensin homolog (PTEN) after peripheral nerve injury. Indeed its *in vivo* inhibition in a rat sciatic nerve injury model accelerates axon outgrowth (Christie et al., 2010). Despite the molecular signals inhibiting regeneration, the axons of a peripheral nerve show an intrinsic growth capacity. Within hours from injury, genes with regenerative capabilities are activated: JUN, FOS, activating transcription factor 3 (ATF3) and cAMP response element binding protein (CREB). CREB3 knock out (KO) in DRG culture significantly reduces neurite elongation, demonstrating its fundamental role after injury (Ying et al., 2014). Locally released cytokines, such as leukemia inhibitory factor (LIF) and interleukin-6 (IL-6), activate the downstream growth associated protein 43 (GAP-43) after DRG peripheral injury (Cafferty et al., 2004). GAP-43 is the first recombination activating gene originally discovered by Skene and Willard (1981), whose induction after sciatic nerve injury strongly correlates with regeneration (Skene and Willard, 1981). LIF also activates the Janus kinase 2-*signal transducer and activator of transcription 3* (JAK2-STAT3) pathway in DRG neurons: STAT3 is specifically associated to the early phase of axon regeneration in PNS (Bareyre et al., 2011).

While axon degeneration/regeneration occur, T cells, neutrophils and macrophages infiltrate the injury site, increasing the level of early inflammatory cytokines, tumor necrosis factor alpha (TNF-α) and interleukin-1α (IL-1α) (Wagner and Myers, 1996). In the following days the inflammatory reaction is amplified by macrophages, mast cell recruitment and endothelial cell activation. Macrophages remove myelin debris and myelin associated molecules (like myelin-associated glycoprotein, MAG) that inhibit regeneration (Baichwal et al., 1988; da Costa et al., 1997). Resident macrophages (4% of the total number) rapidly respond to the injury and then circulating macrophages (chemokine c–c motif receptor 2) are recruited to the lesion side where they constitute the main cell components of the bridge for the new growing tissue (Siebert et al., 2000). Moreover they are also recruited by chemokine (c–c motif ligand 2) secreted by SCs that is fundamental in regulating the axonal regrowth program via LIF/STAT3 mechanism. Notably, two distinct populations of macrophages are described: M1 with a proinflammatory function and M2 working in the opposite direction (Ydens et al., 2012).

SCs after injury break off from the damaged axons, dedifferentiate, secrete cytokines and promote immune cell infiltration. JUN is the main factor responsible for the initial transition from myelinating to non-myelinating SCs that allow a complete clearing of the tissue for a successful regeneration. This is consistent with the downregulation of myelin genes (MBP, MAG and peripheral myelin protein 22-PMP-22) and the upregulation of immature SC markers such as neural cell adhesion molecule (NCAM), p75 neurotrophin receptor and glial fibrillary acidic protein (GFAP) (Chen et al., 2007; Jessen and Mirsky, 2008). On the other hand, a set of trophic factors inactive in normal or developing SCs [for instance glial cell line-derived neurotrophic factor, artemin, brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) (Boyd and Gordon, 2003)] appear. In addition, the products of early axon degeneration stimulate SCs to remove myelin debris and recruit macrophages by the toll-like receptors nuclear factor kappa-light-chain-enhancer of activated B cells. Due to the separation from the axons, SCs synthetize TNF-α, IL-1α and

Please cite this article in press as: M. Ghibaudi, et al., Functional integration of complex miRNA networks in central and peripheral lesion and axonal regeneration, Prog. Neurobiol. (2017), http://dx.doi.org/10.1016/j.pneurobio.2017.07.005