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PERSPECTIVE

Aminoacyl tRNA synthetases and their relationships with peripheral nerve degeneration and regeneration

Following damage resulting from mechanical injury, viral infection, or autoimmunity, peripheral nerves degenerate and a variety of complications, including sensory loss, muscular paralysis, skin thinning, and a loss of tendon reflexes, can manifest. If these complications persist, they can cause a number of debilitating personal and/or social problems. For example, Guillain-Barre syndrome is induced by the degradation of myelin sheaths, and if the symptoms are not controlled the disease can be life-threatening due to the demyelination of respiratory muscle nerves. To date, effective treatment strategies that can inhibit the demyelination of peripheral nerves in the early stages of disease have yet to be developed. Thus, as with severe cases of Guillain-Barre syndrome, devices that alleviate the symptoms of respiratory muscular paralysis, including breathing machines, must be utilized until a cure can be developed.

Wallerian degeneration, which occurs following peripheral nerve injury, includes axonal degradation and demyelination. During this process, demyelination begins with fragmentation of the myelin into small ovoid structures induced by the mechanical strength of Schwann cells (Jung et al., 2011). Axonal debris and myelin fragments, which can affect axonal regeneration, are engulfed by Schwann cells and macrophages that are recruited to the site of injury on peripheral nerves from nearby blood vessels. However, a full understanding of the exact mechanisms underlying Wallerian degeneration is essential to effectively aid in the regeneration of injured nerves due to the tremendous influence this process has on nerve regeneration. In addition to their myelin-related activities in the peripheral nervous system, Schwann cells play important roles during axonal degradation, regeneration, and reinnervation. Therefore, defining the roles that Schwann cells play during peripheral nerve degeneration and regeneration is important for resolving the issues associated with nerve-related degenerative diseases such as type 2 Charcot-Marie-Tooth disease and diabetic peripheral neuropathy.

During Wallerian degeneration, Schwann cells in the distal stumps of injured neurons display complicated transcriptional interactions as well as morphological changes throughout the demyelination process. Following nerve injury, the expression of positive regulators, including krox-20, Oct-6, Sox-10, Brn2, and NF-κB, is decreased whereas the expression of negative regulators, including c-jun, Notch, Sox-2, Pax-3, and Id2, is increased in denervated Schwann cells (Jessen and Mirsky, 2008). These changes influence the transition of myelinated Schwann cells into non-myelinated Schwann cells. Denervated Schwann cells that lack any interaction with axons are in a dedifferentiated state and are referred to as Büngner cells (Arthur-Farraj et al., 2012). These dedifferentiated Schwann cells exhibit multiple molecular changes that are not present in differentiated Schwann cells. For example, dedifferentiated Schwann cells show increased lysosomal activation, increased expression of neurotrophic receptors, and enhanced MAPK activation (Jung et al., 2014).

During peripheral nerve regeneration, dedifferentiated Schwann cells undergo proliferation in the endoneurium where they build up regeneration tracks, called bands of Büngner, and guide the regrowth of axon terminals in order to reinnervate the skin and muscles. Additionally, the proliferated Schwann cells undergo apoptosis and the selected Schwann cells wrap around the regenerating axon to once again form myelin sheaths. Ultimately, the regenerated nerves begin to exhibit saltatory conduction to effector cells.

Aminoacyl-tRNA synthetases (AARSs) are enzymes that acylate tRNAs with amino acids. Because AARSs play important roles during the transfer of genetic information from nucleic acids to proteins, they must have arisen early in evolution. Although it is known that AARSs are essential for catalytic activation and the maintenance of cell viability, the multifunctional or non-canonical roles of AARSs have only gradually become clear. For example, AARSs are important contributors to RNA processing/trafficking, rRNA synthesis, apoptosis, cell proliferation, transcriptional control, translational control, inflammation, and angiogenesis (Park et al., 2005).

The discovery that the secretion of AARSs into the extracellular space induces cell signaling has increased interest in the non-canonical functions of AARSs. Non-canonical roles of AARS system is an essential for a variety of living cell events (Park et al., 2005). Tyrosyl-tRNA synthetase (YARS) is secreted into the extracellular space and is divided into two fragments by polymorphonuclear elastase. The N-terminal fragment (mini-YARS) and C-terminal fragment (C-YARS) influence the production of tumor necrosis factor and myeloperoxidase and the recruitment of immune cells, respectively. Tryptophanyl-tRNA synthetase (WARS) is structurally similar to YARS and is divided into N-terminal mini-WARS and T2-WRS, which subsequently influence angiogenesis. Additionally, lysyl-tRNA synthetase (KARS), phenylalanyl-tRNA synthetase (FARS), threonyl-tRNA synthetase (TARS), and seryl-tRNA synthetase (SARS) are associated with the activation of DNA replication while glutamyl-prolyl-tRNA synthetase (EPRS) and glutaminyl-tRNA synthetase (QARS) are associated with inflammation and apoptosis. However, additional studies are necessary to further elucidate the non-canonical functions of AARSs, which are ubiquitously expressed in living cells, particularly in the nervous system.

Dysfunction within the AARS system is an important contributor to a variety of human diseases (Park et al., 2008). KARS is related to human immunodeficiency virus-1 and degenerative amyotrophic lateral sclerosis. In some cases of myositis and scleroderma, auto-antibodies for alanyl-tRNA synthetase, glycyl-tRNA synthetase (GARS), histidyl-tRNA synthetase, isoleucyl-tRNA synthetase (IARS), and methionyl-tRNA synthetase (MARS) can be identified. Additionally, Charcot-Marie-Tooth (CMT) disease may be caused by mutations in the genes encoding KARS, GARS,

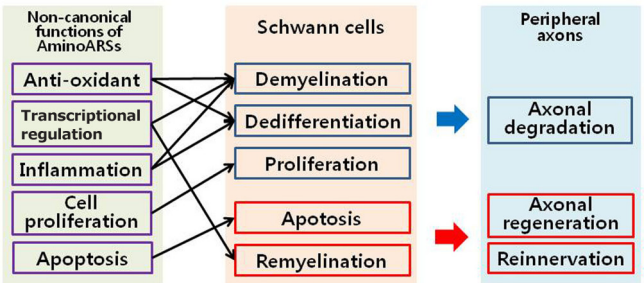

Figure 1 Aminoacyl-tRNA synthetases (AARSs) and their relationships with peripheral nerve degeneration and regeneration.
It was hypothesized that the non-canonical functions of AARSs serve as key factors that regulate demyelination, remyelination, and Schwann cell dedifferentiation, proliferation, and apoptosis during peripheral nerve degeneration and regeneration. Additionally, Schwann cell dynamics may influence axonal degradation, regeneration, and reinnervation *via* the action of AARSs. Blue box: Wallerian degeneration processes; red box: nerve regeneration processes; purple box: non-canonical functions of AARSs related to Schwann cell dynamics.

and YARS. Leucyl-tRNA synthetase (LARS) affects type 2 diabetes mellitus and bradyacusia, while cysteinyl-tRNA synthetase (CARS), EPRS, FARS, IARS, and MARS are related to carcinogenesis.

As mentioned above, AARSs perform specific functions involved in the fate of living cells through particular molecular pathways, and alterations of their non-canonical roles may result in diseases of the nervous system. The relationships of some hereditary peripheral neuropathies with AARS protein mutations have recently been identified using genetic analyses (Antonellis and Green, 2008). For examples, G240R and P244L, and L129P and H418R mutations in GARS gene cause CMT type 2D and distal spinal muscular atrophy type V (dSMA-V), respectively (Antonellis and Green, 2008). D500N mutation in GARS gene affects both CMT2D and dSMA-V (Antonellis and Green, 2008). Two missense mutations (G41R and E196K) and one deletion (V153_V156del) in YARS gene are associated with dominant intermediate CMT type C (Antonellis and Green, 2008). Although AARSs are expressed ubiquitously for the canonical functions, these previous results indicate that some non-canonical functions of AARSs affect the specific cell types. However, the pathophysiologies and non-canonical effects of these diseases have yet to be determined. Additionally, some research groups have attempted to construct animal models to investigate the symptoms of human hereditary peripheral neuropathies; however, these studies have been unable to determine the pathophysiologies and non-canonical effects of the diseases (Seo et al., 2014). Thus, investigating the non-canonical functions of AARSs during peripheral nerve degeneration and regeneration is important for identifying effective treatments for disorders of the nervous system, particularly the peripheral nervous system.

Changes in the patterns of AARS activity in the dorsal root ganglion (DRG) following peripheral nerve injury have previously been investigated by our research group (Park et al., 2014). We observed decreased expression of KARS and QARS mRNA in injured DRG neurons, suggesting that these proteins have neuroprotective properties. Furthermore, our findings suggested the possibility that KARS and QARS act as neurotransmitters that transfer normal sensory signals to the spinal dorsal horn. Thus, AARSs may possess a variety of non-canonical functions in the peripheral nervous system, and AARS dysfunction may be integrally involved in peripheral nervous system disorders.

Our research group is presently focusing on Schwann cells to identify the non-canonical functions of AARSs in the peripheral nervous system. The present article discussed peripheral nerve degeneration and regeneration because the relationships of AARSs with peripheral nerve degeneration and regeneration may be dependent on Schwann cell activity. One of the phenotypes that occur in Wallerian degeneration is demyelination. Demyelination is induced by a variety of factors, including reactive oxygen stress, transcriptional regulation *via* positive and negative regulators, and inflammatory events influenced by macrophages and Schwann cells. These factors are also associated with remyelination during peripheral nerve regeneration. Thus, the non-canonical functions of AARSs in Schwann cells are likely essential for myelin dynamics during nerve degeneration and regeneration (**Figure 1**).

The non-canonical functions of AARSs may also be related to Schwann cell dedifferentiation because this process is induced by the denervated state of Schwann cells, which means that Schwann cells cannot receive some signals from normal axons. AARSs have the ability to be secreted into the extracellular space and influence various cellular reactions (Park et al., 2005). Thus, we suggest that the non-canonical functions of AARSs are related to the interaction between Schwann cells and axons, and that AARS dysfunction may induce Schwann cell dedifferentiation (**Figure 1**). Additionally, Schwann cells undergo cellular proliferation during axonal regeneration and apoptosis during remyelination throughout the nerve regeneration process (**Figure 1**). Proliferation and apoptosis are two non-canonical functions that AARSs contribute to in other living cells. Therefore, the possible relationships between Schwann cell dynamics and the non-canonical functions of AARSs may be important targets for the control of peripheral nerve degeneration and regeneration.

As mentioned previously, our research group has produced preliminary results demonstrating the effects of AARSs on peripheral nerve degeneration and regeneration in Schwann cells. A previous study (Park et al., 2015) does not mean that only KARS and QARS affect peripheral nerve degeneration and regeneration, but not the others. Recently, we found that other AARSs can manage the expression of negative transcriptional regulators during Wallerian degeneration (unpublished data). However, we are not sure which mechanisms are exactly associated with the effect of AARSs on Wallerian degeneration and nerve regeneration because we just set up the study in Schwann cells. Thus, additional experiments through AARSs dynamics in Schwann cells may be sufficient to provide the evidence necessary for the development of novel therapeutic strategies to control peripheral demyelinating diseases and degenerative nerve diseases. These studies should aim to determine the specific AARSs that are essential for the effective regulation of peripheral nerve degeneration and regeneration.

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