MuSK as the Master Organizer of Neuromuscular Junction Development

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Although myasthenia gravis was originally identified as an autoimmune disease in which the acetylcholine receptor (AChR) was the primary antigenic target (Meriggioli, 2009), other antigens can produce a similar clinical phenotype. As noted in the text, another antigenic target that can produce the clinical symptoms of myasthenia is MuSK, a muscle specific receptor tyrosine kinase (Shigemoto, 2007) (Chapter 26). In both cases, there is a loss of normal clustering of AChR at the neuromuscular junction. An appreciation of the role played by MuSK in organizing the neuromuscular junction (Wu et al., 2010) illuminates why two antigens that do not stably interact can result in similar clinical presentations.

MuSK is a receptor tyrosine kinase with a cytoplasmic tyrosine kinase domain and an extracellular domain with immunoglobulin-like repeats and a cysteine-rich domain (Forrester, 2002). Clustering of AChRs at the neuromuscular junction requires the interaction of agrin, MuSK and a member of the low-density lipoprotein receptor family (Lrp4). Agrin does not bind directly to MuSK, but Lrp4 appears to be a coreceptor interacting with both agrin and MuSK (Kim et al., 2008; Zhang et al., 2008). This interaction dimerizes and activates the MuSK tyrosine kinase activity as well as triggering endocytosis of the MuSK complex (Zhu et al., 2008).

However, MuSK has a much larger set of interacting proteins, involving both physical (i.e., acting as a scaffold) and functional (i.e., downstream signaling) interactions. Examples of the MuSK scaffolding functions include an interaction with rapsyn, which can also interact with and aggregate AChRs, and with ColQ, which is important for localization of acetylcholinesterase to the synaptic cleft (chapter 13). Activation of MuSK by agrin stimulates the interaction of

rapsyn with surface AChRs and with the actin cytoskeleton through α-actinin. Interestingly, rapsyn mediates phosphorylation of AChR by MuSK after agrin activation, a step required for aggregation (Lee et al., 2008. Activation of the MuSK pathway also leads to tyrosine phosphorylation of rapsyn carboxy terminal. Rapsyn may also activate Src family nonreceptor tyrosine kinases, linking it to the downstream signaling functions of MuSK in the neuromuscular junction.

Examples of downstream signaling pathways associated with MuSK include activation of Abl and Src family nonreceptor tyrosine kinases, CK2, Pak1, and Rho GTPases (Wu et al., 2010). Abl activates Rho GTPase, which can alter actin dynamics through the WASP pathway (Chapter 6), but Rho GTPase can also activate Pak1 kinase and ROCK (Chapter 25). Pak1 also affects actin filament dynamics through activation of the serine/threonine LIM kinase 1, which inhibits the ADF/Cofilin pathway. ROCK affects myosin function. These represent only a fraction of the physiological interactions and related signaling pathways mediated directly or indirectly by the MuSK complex, but they illustrate the intricate network required to generate and maintain the AChR clusters in the NM.

While the combined functions of activating these signaling pathways downstream of MuSK kinase activity and of scaffolding lead to clustering and stabilization of AChRs, many of the participating proteins are rapidly turned over at the NMJ. Loss of MuSK signaling leads to a rapid degradation of rapsyn and other elements that stabilize AChR clusters. For example, denervation and associated secretion of agrin from the motor neuron leads to a dispersal of AChR from the NMJ. Similarly, antibodies against MuSK that interfere with agrin binding or with other aspects of MuSK signaling would be expected to produce the characteristic muscle weakness of myasthenia gravis (Shigemoto, 2007). Patients with anti-MuSK antibodies represent

about 6% of all myasthenia cases. Unlike the situation with anti-AChR antibodies (Meriggioli, 2009), patients with anti-MuSK antibodies have a similar number of AChR in the muscle, but these receptors fail to cluster at the NMJ in the junctional folds.

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