The Reaction-Diffusion Model as Applied to Neuronal Synapse Formation

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Patten formation, or morphogenesis, is a fundamental process in the development of an organism. In 1952, Alan Turing proposed the reaction-diffusion model as an explanation of the chemical basis of morphogenesis. This model depicts that two diffusible morphogens, if allowed to regulate each other's activity through reactions, can lead to the generation of complex biological patterns. We found that this model offers good theoretical basis for understanding the development of the neuromuscular junction (NMJ). During NMJ development, motor axons contact skeletal muscle cells to induce the clustering of acetylcholine receptors (AChRs) to extremely high density (~10,000/μm^2) at the postsynaptic membrane. This remarkable molecular and structural specialization of the plasma membrane is accomplished by a muscle-intrinsic mechanism in conjunction with signals from the innervating motor axon. Studies over the past decade have suggested the following paradigm: motor axons secret the heparan-sulfate proteoglycan agrin to cause the local activation of a tyrosine kinase receptor MuSK (muscle-specific kinase) to initiate a signaling cascade leading to the assembly of a postsynaptic cytoskeletal scaffold that clusters AChRs through a diffusion-mediated process. With quantum-dot nanoparticles, this process can now be directly visualized. Agrin-mediated MuSK activation leads to the postsynaptic assembly of the F-actin cytoskeleton, through the activation of cortactin and Rho-family GTPases, which interacts with AChRs via the associated cytosolic protein rapsyn to cause their "trapping" and clustering. In addition to the kinase pathway, the function of tyrosine phosphatase (PTP) has been elucidated recently. The PTP is also activated as a result of synaptogenic stimulation of muscle. PTP signal locally checks the spread of the kinase signal in effecting a sharp boundary of AChR clustering. In addition, it also globally suppresses the formation and maintenance of AChR clusters in the extrajunctional area. This indicates that PTP serves as a negative regulator in postsynaptic development and its influence is both local and global. Our recent work has shown that MuSK, Src family kinase, and the SH2 domain-containing PTP Shp2, together with its activating protein, are integral components of the mechanism for the propagation of the PTP signal. Thus, a locally activated kinase signal coupled with a diffuse and propagating PTP inactivator enables the muscle to form a spatially discrete and preeminent postsynaptic specialization for highly efficacious neurotransmission. This scheme offers an application of the reaction-diffusion model on intracellular signaling in the development of the nervous system.

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