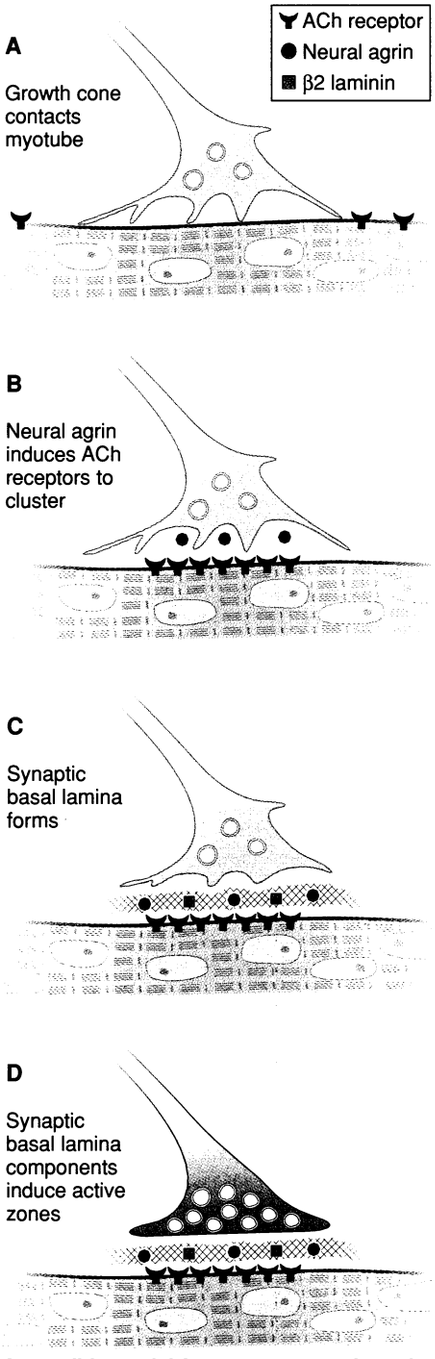

A possible model for synaptogenesis at the neuromuscular junction.

tic signals that initiate this process and of the proteins that recognize the localization domain on the β2 chain remain projects for the future.

What does the concentrated β2 laminin do at the synapse? Two recent papers from the Sanes and Merlie laboratories indicate that it helps mediate presynaptic differentiation and may direct regenerating axons to find the original synaptic site. The first observations (*8*) reveal the consequences of synaptogenesis without the β2 chain. In a β2 knockout mouse synapses form, but are simpler and lack presynaptic specialization. Synaptic vesicles are evenly distributed in the nerve terminal, rather than being concentrated near the site of nerve-muscle contact, and the number of active zones, the site of rapid transmitter release by exocytosis, is drastically reduced. The second report shows that β2 laminin may serve as a stop signal to ingrowing motor axons (*7*). When cultured on laminin as a substrate, motor neurons extend neurites. When cultured on the β2 chain, they adhere but do not extend neurites; moreover, in mixtures, β2 laminin inhibits neurite growth of motor neurons (but not of other neuronal types). When motor neurons are cultured on alternating strips of laminin and the β2 chain, neurites extend on the laminin surface but stop at or slightly beyond the laminin-β2 border. These experiments led Sanes and his colleagues to the idea that the β2 chain may help attach resident terminals to the postsynaptic surface during synaptogenesis. During regeneration, neurites growing on the laminin-rich extrasynaptic surface of muscle fibers would stop at the synapse site. β2 chains could thus trap and confine growing terminals to the appropriate place.

Competition experiments with synthetic peptides derived from the β2 laminin sequence identify a site that appears to mediate neurite adhesion and inhibition of neurite extension. The tripeptide LRE, a sequence that occurs three times in the β2 laminin chain (and is also found in several other components of the synaptic basal lamina but is not in the β1 chain), is an effective inhibitor of both neurite adhesion and of neurite extension on a laminin substrate (*9*, *13*). The inhibition appears to be specific for motorneurons, as neurite growth of dorsal root ganglion cells and PC12 cells on laminin is unaffected by the peptide. Remarkably, LRE is part of the 16-amino-acid sequence responsible for synaptic localization of the β2 laminin. Two ideas flow from this observation: LRE may be part of a general signal targeting a variety of components to the synaptic basal lamina, and the resulting concentration of LRE sites at the synapse could identify it to the growth cones of motor axons.

Present knowledge of the two components of the synaptic basal lamina—agrin and laminin β2—suggests a simplified narrative of basal lamina signaling during synaptic differentiation (see the figure). First, agrin secreted from the growth cones of ingrowing motor axons causes ACh receptors to cluster at sites of nerve-muscle contact. Second, the muscle fiber forms a synaptic basal lamina in association with the ACh receptor clusters by the local accumulation of laminin β2, along with other components of the extracellular matrix (acetylcholinesterase, heparin sulfate proteoglycan, and muscle agrin). Third, laminin β2 and possibly other synaptic basal lamina components induce synaptic vesicle accumulation and the formation of active zones in the presynaptic terminals. According to this scheme, laminin β2 may be a key link in the signaling pathway that assures the precise registration of presynaptic and postsynaptic structures.

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John Merlie (1945–1995)

On 27 May, John Merlie suddenly and unexpectedly died of a heart attack. The news was doubly shocking, because John was in midstride of what many thought the most important work of an already distinguished career. Merlie was a pioneer in the use of molecular methods to study the synapse. In a series of experiments that began in the laboratory of Jean-Pierre Changeux, he and his colleagues defined the pathways by which the subunits of the nicotinic acetylcholine receptor subunits are synthesized, folded, assembled, and transported to the surface. This work stands as a model for understanding how oligomeric ion channels are synthesized and how their synthesis is regulated. Later, he turned to problems of synaptogenesis, and once again set the pace for others to follow. He cloned rapsyn and demonstrated its role in acetylcoline receptor clustering and, with Josh Sanes, gave vivid demonstration to the idea that nuclei at the neuromuscular junction differentially express mRNAs for synaptic proteins. Most recently, he and Sanes had embarked on an ambitious program using knockout mice to define the role of synaptic proteins. This work, much of it still in progress and eagerly awaited, promises to raise our understanding of synaptic differentiation by a quantum jump. Unassuming and modest, John never sought the limelight, but let his work speak for itself. With its eloquent voice, he has left an indelible mark on our field.