Integrins drive synaptic assembly at the neuromuscular junction

1st May, 1pm
June Lloyd Seminar Room (PUW4), ICH

ABSTRACT

Neurotransmission at the neuromuscular junction (NMJ) depends on the coordinated release of synaptic vesicles at specific sites of the nerve terminal called active zones. Here we demonstrate that the formation of active zones is regulated by integrin-α3, a laminin receptor that localizes to the presynaptic terminal. Using genetically modified mice, we show that integrin-α3 is essential for the recruitment of active zone components bassoon and piccolo, for efficient synaptic vesicle release and sensitivity to Ca2+. Unexpectedly, we also find that integrin-α3 is important for the structural integrity of the synapse: mutant NMJs present with defects that include the detachment of nerve terminals from the synaptic cleft, and abnormalities that resemble those found in aged animals and in a number of mouse models with NMJ defects. Overall, these results identify integrin-α3 as a key presynaptic receptor for the regulation of multiple aspects of NMJ development and integrity. To our knowledge, this is the first report of a cell surface receptor the anchorage of pre- and postsynaptic elements at the NMJ.

BIOSKETCH

Francesco was awarded his PhD in 2004 from KCL/Cancer Research UK, for work done in the Cell Adhesion & Disease Laboratory headed by Prof. Kairbaan Hodivala-Dilke. As a postdoctoral fellow he worked at The Scripps Research Institute in La Jolla from 2004 until 2009, CA, in the laboratory of Prof. Ulrich Mueller. He joined ICH in 2009 on a fellowship awarded by the NIHR
Biomedical Research Centre, and is now a principal investigator at the ICH Dubowitz Neuromuscular Centre.

His main area of interest is how cell adhesion to the extracellular matrix drives development. Specifically, during his PhD he uncovered novel roles for the superfamily of integrin adhesion receptors in epidermal development and wound healing; since his postdoc, his interest has focused on development of the neuromuscular system, and he found novel mechanisms underlying cytoskeletal development of skeletal muscle, cell-cell fusion, and synaptic transmission at the neuromuscular junction. He also developing new gene therapy approaches to correct duplications in dystrophin using CRISPR/Cas9 nucleases. His work is supported by the French Association against Myopathies, NIHR, and Duchenne Parent Project.