Internship proposal 2025

Electro-mechanical activity in neural crest cell migration: from fundamentals to pathology.

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Project description :

Neural crest cells (NCCs) are a population of totipotent, highly migratory cells common to all vertebrates. They colonize developing embryonic tissues to form a wide range of derivatives: the adrenal gland, cardiac valves, bones (ear, jaw), Schwann cells (myelin) of the peripheral nervous system (PNS), melanocytes (skin pigments), and the enteric nervous system (ENS, intrinsic innervation of the intestine). NCC migration defects give rise to more than 20 different syndromes known as neurocristopathies, that lead to severe intestinal, cranio-facial, nervous, cardiac or skin impairements. Hirschsprung disease (HD) is the most prevalent neurocristoptahy (1:3000-4000 newborns) and is characterized by the lack of enteric nervous system in the colon, due to defective migration of NCCs in this tissue during embryogenesis.

At MSC, using a transgenic mouse model that expresses a fluorescent intracellular calcium reporter specifically in neural crest cells, we have been able to show that the main molecules / signaling pathways involved in the pathogenesis of HD are tightly linked to the spontaneous calcium activity of the migrating NCCs. Blocking the receptor for endothelin 3 for example, an important peptide whose mutation induces HD, completely abolishes Ca^{2+} activity in neural crest cells. We have further shown that calcium transients induce cellular movements, presumably by activating the contractile machinery responsible for migration. These new links between cell electrical activity and neurocristopathy suggest that neural crest cells behave in a similar way to muscle during migration, and then differentiate to non-contractile neurons. 50% of HD cases do not have a known genetic causal factors and the involvement of electrical activity (ion channels) has so far not be considered in genetic screens.

The internship aims at **deciphering the link between the spontaneous electrical activity and cellular force generation that drives cell migration**. It will include:

- performing Traction Force Microscopy combined with calcium imaging experiments on NCCs, to measure the force generated by migrating cells and how these are modified by calcium activity.

- performing inter-cellular force measurements, using FRET or membrane tension sensors, by fluorescence lifetime microscopy.

If time allows, we will also be interested in performing galvanotaxis experiments on NCCs combined with calcium imaging. NCCS are known to be galvanotactic, i.e., they migrate directionally in an applied electric field. One of our hypothesis is that galvanotaxis and chemotaxis (attraction of cells by chemical substances, like GDNF in the gut) are two sides of the same coin: chemotactic agents may induce voltage differentials across cells or groups of cells, which drive migration.

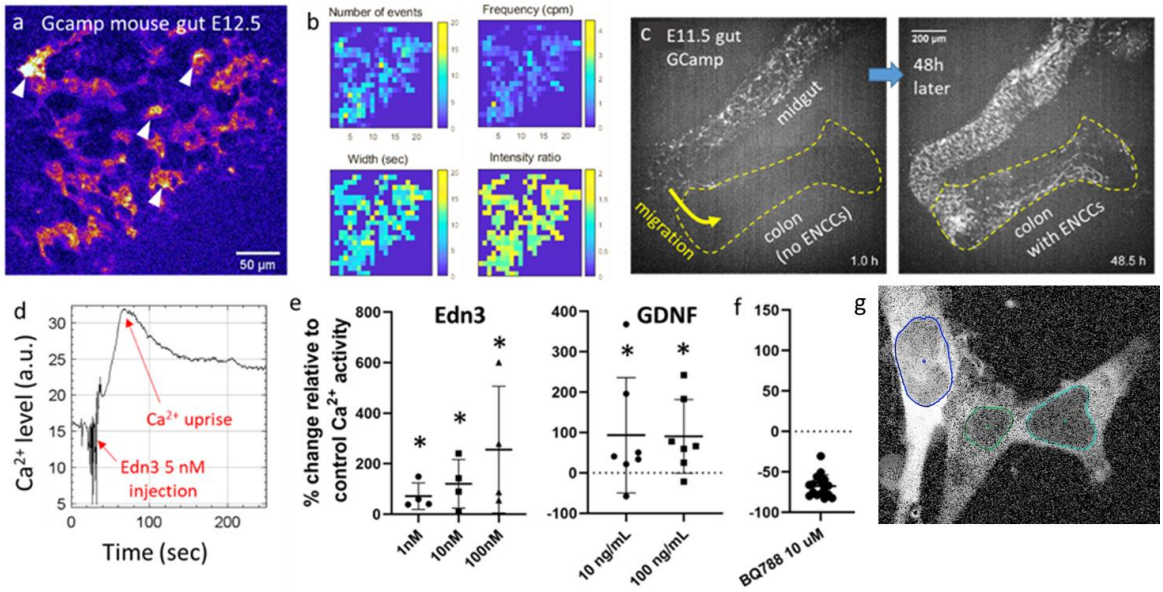

Figure 1. (a) Ca^{2+} transients in ENCCs. (b) Automated analysis of transients. (c) 2-day NCC migration in the colon, ex-vivo. (d) Ca^{2+} uprise induced by endothelin 3 (e) Ca^{2+} spikes are stimulated by endothelin 3 and GDNF, 2 proteins critical in HD pathogenesis (f) The blocker of the endothelin receptor BQ788 inhibits activity, (g) cell movements can be tracked with deep-learning segmentation approaches.

We are looking for motivated, talented, rigorous students, interested in embryogenesis and experimentation on mouse embryonic organs. Fluency or skills in image analysis under ImageJ and Matlab will be an asset. Skills to be acquired over the course of the internship include dissection, organ culture, confocal microscopy, calcium imaging & analysis, immunohistochemistry, artificial intelligence-assisted tracking of cells. The internship may be followed up by a PhD recruitment.