PARALLEL SESSION: BIOLOGY OF NF2 AND SCHWANNOMATOSIS

Chairs: Helen Morrison, PhD, Leibniz Institute on Aging, Germany; Andrea McClatchey, PhD, Harvard University, US; Jeremie Vitte, PhD, UCLA, US

Late Inactivation of Smarcb1 and Additional Nf2 Loss Are Necessary for Schwannoma Development in Schwannomatosis Patients

Monday, 5 November, 16:45 – 17:10

Jeremie Vitte, PhD, *Department of Head and Neck Surgery, University of California, Los Angeles, United States*

Germline mutations of the *SMARCB1* gene are found in schwannomatosis patients developing benign tumors of cranial and peripheral nerves in their adulthood. *SMARCB1* germline mutations are also the hallmark of rhabdoid tumors (RTs), malignant pediatric tumors mostly developing in brain and kidney, and leading to a familial cancer predisposition syndrome. The mechanisms by which *SMARCB1* germline mutations predispose to RTs versus schwannomas are still unknown. To understand the origin of these two types of *SMARCB1*-associated tumors, we generated different tissue- and developmental stage-specific conditional knockout mice carrying *Smarcb1* and/or *Nf2* deletion. We demonstrated the existence of a time window in neural crest cells where early loss of *Smarcb1* was necessary to initiate tumorigenesis in the cranial nerves and meninges with typical histological features and molecular profiles of human rhabdoid tumors. Importantly, the induction of *Smarcb1* loss alone at later developmental stages in the Schwann cell lineage was not tumorigenic and additional biallelic *Nf2* gene inactivation was necessary to initiate schwannoma development, thus generating the first mouse model developing schwannomas with the same underlying gene mutations found in schwannomatosis patients.

Correlation of the Tumor-Suppressive Function and the Confirmation of NF2

Monday, 5 November, 17:10 – 17:35

Tina Izard, PhD, *Scripps Institute, US*

We recently determined the crystal structure of lipid-bound neurofibromin 2, the protein responsible for neurofibromatosis type 2 (NF2). Since neurofibromin 2 is a member of the ezrin, radixin, moesin family of cytoskeletal proteins, it seemed likely that neurofibromin 2 would function similarly to ERM proteins. Our new structural and functional data demonstrated the correlation between the tumor-suppressive function of neurofibromin 2 and its conformation. We show that membrane attachment is necessary for inhibiting cell proliferation and what lessons can be learned from the various neurofibromin 2 structures with respect to NF2.

Parallels Between Nerve Regeneration and Tumour Formation in the Peripheral Nervous System

Monday, 5 November, 17:35 – 18:00

Alison C Lloyd, PhD, *MRC Laboratory for Molecular Cell Biology, University College London, Gower Street, London, WC1E 6BT*

Peripheral nerves have remarkable regenerative properties and there has been great progress in understanding the multicellular processes involved. Underlying this regenerative capacity is the regenerative nature of the major glial cell type of the PNS, the Schwann cell. Mature, adult Schwann cells dedifferentiate to a progenitor-like state following an injury and these cells have multiple roles in orchestrating the multicellular response required to regenerate a nerve. Tumours that arise in the PNS, in both NF1 and NF2, arise mostly from Schwann cells, which appear to be mimicking many of the roles of these progenitor-like Schwann cells in the injured state. However, whereas an injury usually resolves, these tumours resemble an unrepaired wound and therefore increasing our understanding of the resolution of the injury response is an important approach for the development of novel therapeutic approaches for the treatment of these tumours. In this talk, I will discuss our current understanding of how Schwann cells orchestrate the regeneration of peripheral nerves and the implications of these findings for the biology of NF1 and NF2.

References:

Cattin, A.L., and Lloyd, A.C. (2016). The multicellular complexity of peripheral nerve regeneration. Current Opinion in Neurobiology 39, 38-46.

Cattin, A.L., Burden, J.J., Van Emmenis, L., Mackenzie, F.E., Hoving, J.J., Garcia Calavia, N., Guo, Y., McLaughlin, M., Rosenberg, L.H., et al. Lloyd A.C. (2015). Macrophage-Induced Blood Vessels Guide Schwann Cell-Mediated Regeneration of Peripheral Nerves. Cell 162, 1127-1139.

Napoli, I., Noon, L.A., Ribeiro, S., Kerai, A.P., Parrinello, S., Rosenberg, L.H., Collins, M.J., Harrisingh, M.C., White, I.J., et al. and Lloyd A.C. (2012). A central role for the ERK-signaling pathway in controlling Schwann cell plasticity and peripheral nerve regeneration in vivo. Neuron 73, 729-742.