The Roots of Neurofibromas in Neurofibromatosis 1 – A Question of Multipotency, Differentiation and Hiding

Eeva-Mari Jouhilahti
Department of Cell Biology and Anatomy and Department of Dermatology, Faculty of Medicine, University of Turku, and Turku Doctoral Programme of Biomedical Sciences, Turku, Finland. E-mail: emjouh@utu.fi

Eeva-Mari Jouhilahti defended her PhD thesis in Turku, Finland, on 12th October 2012. The thesis was supervised by Professor Juha Peltonen from the Department of Cell Biology and Anatomy, Institute of Biomedicine, University of Turku and Associate Professor Sirkku Peltonen from the Department of Dermatology, University of Turku and Turku University Hospital, Turku, Finland. The opponent was Professor Juha Kere, Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden. The thesis is available at: https://www.doria.fi/handle/10024/80362.

Neurofibromatosis type 1 (NF1) is an autosomal dominant cancer predisposition syndrome that affects about 1 in 3,500 individuals worldwide. NF1 is caused by mutations in the *NF1* gene that encodes the tumour suppressor protein neurofibromin, an inactivator of the Ras oncogene. The hallmarks of NF1 include pigmentary lesions of the skin, Lisch nodules of the iris and cutaneous neurofibromas. Cutaneous neurofibromas are benign tumours composed of all the cell types of normal peripheral nerve. The traditional view of neurofibroma development has been that cutaneous neurofibromas arise from the disruption of the small nerve tributaries of the skin and subsequent proliferation of the resident cells. The second hit mutation in the *NF1* gene has been considered as a prerequisite for neurofibroma development. The second hit is detectable in a subpopulation of primary Schwann cells cultured from neurofibromas.

This thesis challenges the traditional concept of neurofibroma development. The results show that cutaneous neurofibromas are intimately associated with hair follicular structures and contain multipotent precursor cells (NFPs), suggesting that neurofibromas may arise from the multipotent cells which reside in hair follicles. Furthermore, this study presents that human cutaneous neurofibromas contain HLA II-positive cells. *In vitro* studies showed that Schwann cells cultured from human cutaneous neurofibromas express HLA class II genes. The results may indicate the HLA II–positive cells within cutaneous neurofibromas act as non-professional antigen presenting cells which in turn may be the mediators of immune tolerance. Tumour cells can thus hide from the immune system.

This thesis also investigated neurofibroma development in the oral cavity and the use of different biomarkers to characterize cellular differentiation in neurofibromas. The results revealed that oral neurofibromas are not rare, but they usually appear as solitary lesions contrary to multiple cutaneous neurofibromas and present high heterogeneity within and between tumours. The use of class III beta-tubulin as a marker for neuronal differentiation led to an unexpected finding showing that multiple cell types express class III beta-tubulin during mitosis.

Eeva-Mari Jouhilahti defended her PhD thesis on neurofibromatosis 1 in Turku, Finland on 12th October 2012. *Left to right:* Opponent, Professor Juha Kere, PhD Eeva-Mari Jouhilahti, Professor Juha Peltonen, Associate Professor Sirkku Peltonen.

The findings of this study increase the understanding of the previously poorly understood properties and phases of neurofibroma development. The increased understanding of the multipotency of tumour cells, cellular differentiation and ability to hide from immune system will aid in the development of future treatments.