Professor Juha Peltonen

NF1 Tumor Suppressor/ Histogenesis Factor

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The neurofibromatosis 1 syndrome (NF1), caused by mutations of the NF1 gene, affects ~1/3000 individuals worldwide. A mutation in the NF1 gene can cause an astonishingly wide array of ailments affecting the whole body and different cell types. The changes in NF1 include neurofibroma tumors, pigmented macules of the skin, cardio-vasculopathies, hamartomas of iris, gliomas, learning difficulties, predisposition to malignancies, and typical bone defects, such as pseudarthrosis. Dental and oral development is often disturbed.

The Turku Neurofibromatosis Consortium is composed of Cell and molecular biology research at the Institute of Biomedicine, the Neurofibromatosis clinic (Department of Dermatology), and the NF research at the Department of Oral Diseases. All three components of the consortium are located in the same campus which makes the transfer of biological samples from the operating room to cell culture facility easy. The scientific aim is to increase understanding of NF1 gene in cellular differentiation and the effect of inactivation of one, or two, NF1 alleles on the reading of the whole genome.

Neurofibromas are composed of all elements of peripheral nerve, but disorganized in haphazard manner. Experiments with transgenic mice have revealed that loss of both NF1 alleles in Schwann cell lineage is a prerequisite for neurofibroma growth, but tumors only develop in NF1 +/- background, that is, if the other cell types of the tumor carry NF1 mutation in one allele. Skeletal anomalies in NF1 are primary lesions, not caused by adjacent tumors. In analogy to neurofibromas, bone lesions of NF1 contain multiple cell types such as osteoclasts, osteoblasts, and osteocytes. The best known function of the protein product of the NF1 gene, neurofibromin, is to accelerate the switch of active Ras-GTP to inactive Ras-GDP in many cell types. Our recent findings indicate that neurofibromin also acts as a Ras-GAP during ossification in NF1+/+ and NF1+/- mice.

Our aim is to characterize new molecular functions of NF1 tumor suppressor/histogenesis factor in the development and repair of neural and skeletal connective tissues. At the cellular level, this study focuses on the action of the NF1 Ras-GAP on the formation of cellular contacts and the role of NF1 in Ca^{2+} mediated signaling between cells. The results will elucidate fundamental fields of ossification and neurobiology, including axonal growth, differentiation preceding myelination, and thus the pathogenesis of human neurofibromatosis syndrome.

The analyses utilize blood and neurofibroma samples from neurofibromatosis patients and cell cultures derived from the samples. Conditional NF1 knock-out mice are used to create and analyze cell type specific NF1 deficient animals. Neural anomalies are addressed using neurofibroma cell cultures. Mouse Schwann cells and neurons separately and in co-cultures allows us to combine healthy or NF1-deficient Schwann cells with healthy or NF1-deficient neurons. We expect to find that the mutation of

the NF1 gene causes defective communication between Schwann cells and axons, as estimated by altered calcium-mediated cell signaling and aberrant expression of cell contacts. The expected findings are important for the understanding of nerve development and tissue repair.

Recent publications:

Kuorilehto, T., Pöyhönen, M., Bloigu, R., Heikkinen, J., Väänänen, K. and Peltonen, J. (2005) Decreased bone mineral density and content in neurofibromatosis type 1: Lowest local values are located in the load carrying parts of the body. *Osteoporosis Int*. 16: 928-936.

Koivunen, J., Aaltonen, V., Koskela, S., Lehenkari, P., Laato, M. and Peltonen, J. (2004) Protein kinase C alpha/beta inhibitor Go6976 promotes formation of cell junctions and inhibits invasion of urinary bladder carcinoma cells. *Cancer Res*. 64: 5693–5701.

Kuorilehto, T., Nissinen, M., Koivunen, J. and Peltonen, J. (2004) NF1 tumor suppressor protein and mRNA in skeletal tissues of developing and adult normal mouse and NF1 deficient embryos. *J. Bone Mineral Res*. 19: 983-989.

Korkiamäki, T., Ylä-Outinen, H., Koivunen, J., Karvonen, S.-L. and Peltonen, J. (2002) Altered calcium mediated cell signaling in keratinocytes cultures from patients with neurofibromatosis type 1. *Am. J. Pathol*. 160: 1981-1990.

From left to right: Vivian Visnapuu, Elina Heikkilä, Heli Ylä-Outinen, Juha Peltonen, Kati Pummi, Elisa Lepistö, Sirkku Peltonen, Maria Alanne