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N-F1 RACE - Neurofibromatosis type 1: Role of Amino acids in Cancer Eradication

Neurofibromatosis type 1 (NF1) is a tumor-predisposing disorder caused by heterozygous mutations in the Nf1 gene encoding for the tumor suppressor neurofibromin. Biallelic Nf1 inactivation in Schwann cells leads to the onset of neurofibromas, benign neoplasms that can cause severe medical complications and give rise to malignant peripheral nerve sheath tumors (MPNSTs), for which no treatment exists. Mitochondria sustain bioenergetic changes underlying malignant transformation of neurofibroma cells. My pilot experiments indicate that in MPNST cells the mitochondrial chaperone TRAP1 takes part into amino acid metabolism and autophagy. N-F1 RACE aims at i) dissecting the molecular mechanisms behind TRAP1-dependent alterations in amino acid concentrations and autophagic activity observed in MPNST cells; ii) investigating the impact of these processes on tumor progression. To achieve these goals, I will implement a multidisciplinary strategy, encompassing the fields of mitochondrial physiology, metabolomics, cell oncology and pharmacology. I will study amino acid sensing mechanisms regulating autophagy and assess MPNST cell features, including proliferation rate and differentiation, after inhibiting autophagy. I will search for novel TRAP1 client proteins involved in amino acid metabolism and measure their activities through dynamic flux analysis, following TRAP1 pharmacological inhibition or genetic ablation. I will test whether the combined inhibition of TRAP1 and autophagy is effective in hindering MPNST cell tumorigenicity, both in in vitro experiments, and by using the most effective compound combination on tumor growth in mouse xenograft models. I foresee this dual targeting strategy to be more efficient than the administration of a single agent. N-F1 RACE will uncover new molecular details of TRAP1-mediated metabolic adaptations supporting cancer cell growth, opening new horizons in the development of therapeutic strategies.