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DOCK4 PROMOTES LOSS OF PROLIFERATION IN GLIOBLASTOMA PROGENITOR CELLS THROUGH NUCLEAR BETA-CATENIN ACCUMULATION AND SUBSEQUENT miR-302-367 CLUSTER EXPRESSION

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Glioblastomas (GBM) are lethal primitive brain tumours characterized by a strong intra-tumour heterogeneity. We observed in GBM tissues the coexistence of functionally divergent micro-territories either enriched in more differentiated and non-mitotic cells or in mitotic undifferentiated OLIG2 positive cells while sharing similar genomic abnormalities. Understanding the formation of such functionally divergent micro-territories in glioblastomas (GBM) is essential to comprehend GBM biogenesis, plasticity and to develop therapies. Here we report an unexpected anti-proliferative role of beta-catenin in non-mitotic differentiated GBM cells. By cell type specific stimulation of miR-302, which directly represses cyclin D1 and stemness features, beta-catenin is capable to change its known proliferative function. Nuclear beta-catenin accumulation in non-mitotic cells is due to a feed forward mechanism between DOCK4 and beta-catenin, allowed by increased GSK3-beta activity. DOCK4 over expression suppresses selfrenewal and tumorigenicity of GBM stem-like cells. Accordingly in the frame of GBM median of survival, increased level of DOCK4 predicts improved patient survival.

BIOGRAPHY

Thierry Virolle is a Research Director (permanent position) at Institut National de la Santé et de la Recherche Médicale (INSERM), Head of the Team Cancer Stem Cell Plasticity and Functional intra-tumor Heterogeneity at the Institute of Biologie Valrose (iBV). He is Co-Founder of the French National Sud Cancer Stem Cell Network, SUNRiSE dedicated to the study of cancer stem cell.

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