Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

Institute of Psychiatry and Neuroscience of Paris

UNIVERSITÉ PARIS DESCARTES

Psychiatry and Neuroscience Seminar Series

Dr Eric Chevet

(Host T GALLI)

Inserm U1242, Chemistry, Oncogenesis, stress, Signaling, Rennes

Complexity of IRE1 signaling in tumor development and therapeutic opportunities

Friday October 12th, 2018, noon

Room R04-45, 102-108 rue de la santé - 75014 Paris

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Proteostasis imbalance is emerging as a major hallmark of cancer, driving tumor aggressiveness. Genetic and pharmacological evidence suggest that the endoplasmic reticulum (ER), a major site for protein folding and quality control, plays a critical role in cancer development. This concept is valid to glioblastoma multiform (GBM), the most lethal primary brain cancer with an overall survival of 15 months and no effective treatment. We previously demonstrated that the ER stress sensor IRE1a (referred to as IRE1) contributes to GBM progression, impacting tissue invasion and tumor vascularization. IRE1 is an RNase that signals by catalyzing the splicing of the mRNA encoding the transcription factor XBP1, in addition to regulate the stability of certain miRNAs and mRNAs through a process known as Regulated IRE1 Dependent Decay (RIDD). Somatic mutations in the IRE1 gene have been identified in GBM and other forms of cancer. Here we investigated the contribution of IRE1 signaling to GBM based on the systematic comparison of mutant forms identified in cancer, and demonstrated its significance to the disease. We also uncovered a novel mutation associated with GBM with functional consequences to tumor formation. Taking advantage of the specific signaling outputs of the RNase domain of IRE1 engaged by distinct GBM-related mutations, we defined specific expression signatures that were confronted to human GBM transcriptomes. This approach allowed us to demonstrate the antagonistic roles of XBP1 mRNA splicing and RIDD on tumor outcomes. This study provides the first demonstration of a dual role of IRE1 downstream signaling in cancer and opens a new therapeutic window to abrogate tumor progression.

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Avril T, et al. CD90 Expression Controls Migration and Predicts Dasatinib Response in Glioblastoma. Clin Cancer Res. 20173)

Obacz J et al. Endoplasmic reticulum proteostasis in glioblastoma-From molecular mechanisms to therapeutic perspectives. Sci Signal. 2017