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Prof. Concetta Ambrosino

Valeria Nittoli¹, Federica De Vita^{1,2}, Flammia Raffaella³, Reale C¹, Russo Filomena¹, Russo A. Nicola¹, Rinaldi Laura⁴, Feliciello Antonio¹, Pagnotta Stefano³ and Ambrosino Concetta^{1,3,5}

¹Biogem Scarl, Via Camporeale Ariano Irpino, Italy

²Dipartimento di Medicina di Precisione - Università degli studi della Campania "Luigi Vanvitelli", Via De Crecchio Napoli

³Dipartimento di Scienze e Tecnologie - Università degli studi del Sannio Via De Sanctis Benevento,

⁴Dipartimento di Medicina molecolare e Biotecnologie mediche - Università degli studi di Napoli "Federicoll", Via Pansini Napoli

⁵CNR-IEOS Via Pansini Napoli

PJA2 ubiquitin ligase in glioblastoma development and therapy

Protein ubiquitination regulates several cellular activities deregulated in several cancer, including glioblastoma multiforme (GBM), the most common and lethal human primary brain tumour. Recently it has been evidenced a role also in maintaining the telomere length. Here, we report the result of a study aimed to investigate the role of the E3-ubiquitin ligase Praja2 (PJA2) in molecular pathogenesis processes in GBM, including the telomere length.

The role of PJA2 in maintaining the telomere length was evidenced by bioinformatics analyses of RNA-Seq data from U87-MG cells transfected with PJA2 shRNA and confirmed by analyses of single cells RNA-Seq dataset of GBM (TCGA). It was also confirmed experimentally by measuring telomere length, by qPCR, in Pja2KO U87-MG and control cells. Their shortening was evidenced in the former as well as the reduction of lncRNA TERRA, whose deletion was shown to promote telomere shortening in other cell lines. Concordantly with what observed in GBM samples, we also detected an increase of TERT protein. In the Pja2KO U87-MG also cMyc protein increased, an event previously associated to glioma cancer cell proliferation and survival. Finally, we developed a zebrafish line carrying the glial specific inactivation of the pja2 (Pja2 KO-zebrafish) gene and overexpressing or not cMyc. While the latter did not develop cancer up to 24 months, the former did it at different ages starting from 12 month. Furthermore, we confirmed in zebrafish larvae that cMyc is a target of PJA2, being increased in Pja2 KO-zebrafish vs wild type fishes.

The result suggest that the lowering of Praja2 activity could favour GBM development by two different mechanisms: promotion of the telomere shortening, provoking the telomere crisis and the associated genomic instability, and increase of the cellular content of level of cMyc, an event associated to the proliferation and survival of glioma cancer stem cells.

Biography:

Concetta Ambrosino is an associate Professor of Applied Biology at Department of Science and Technology at the University of Sannio. She is scientific deputy director of Biogem Scarl, where she leads the Gene&Environment Interaction Laboratory. She is also an associate researcher of CNR-IEOS. She is among the BBMRI-experts. She got the PhD in Molecular Oncology at the University of Calabria "Magna Grecia" and post-doc in the Developmental Biology Unit at the EMBL. She is working in the development of cellular and alternative animal model of both diseases, focusing on the dissection of the role that mitochondria and protein ubiquitination could play in both.