Translational research: molecular diagnostics and therapeutics

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The research group of Prof. Maurizio Bifulco is focused on the antitumor and immunomodulatory effects of N6-isopentenyladenosine (iPA) and its derivatives, in Glioblastoma (GBM), mevalonate pathway, tumor microenvironment, anti-tumor immune response. iPA inhibits the activity of the farnesyl diphosphate synthase (FDPS) enzyme of mevalonate pathway, which catalyzes the synthesis of geranyl pyrophosphate and farnesyl pyrophosphate substrates required for the post-translational modification of proteins involved in signal transduction and cellular proliferation. Moreover, iPA arrests the proliferation of primary glioblastoma cell lines *in vitro* and *in vivo* via downregulation of epidermal growth factor receptor (EGFR) oncogene-driven pathways.
The results of the research group highlighted a potent iPA-antiglioma effect by blocking EGFR pathway and hence, alone or in association with EGFR-TKIs, it might be a promising therapeutic tool in GBM. Moreover, the observations of a dynamic nature of NK subsets shuttling between tumors' peripheral margins mainly EGFRwt and the EGFRmut-expressing core of GBM, enriched by resting NK with an abnormal functional program, suggests a new dangerous EGFR-NK interplay perturbing GBM microenvironment to drive immune escape and tumor progression (Ciaglia E, *et al.,* 2018. Ciaglia E, *et al.,* 2017).
Currently, our research group is evaluating the effects of iPA and its analogues in GBM to explore the correlation between EGFR signaling, mitochondrial metabolism and tumorigenesis on GBM biology and to better understand the role of the mevalonate pathway on generation and function of Treg cells in cancer and to better understand how this metabolic pathway affects the ability of cancer cells to induce immune escape mechanisms. iPA and its analogues can influence adaptive immune responses, in particularTreg cells, thus allowing identification of new therapeutic combinations to target in parallel tumor and immune cells.
Furthermore, to learn more about the antitumor and immunomodulatory effects of iPA, we are collecting specimens, obtained from a cohort of stage III-IV glioma patients undergoing surgical resection at the Neurosurgery Units of "A. Cardarelli" of Napoli Hospital to obtain primary cell lines and tumor-infiltrating lymphocytes (TIL).

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