ABSTRACT

N6-isopentenyladenosine (IPA) and its analogue N6-benzyladenosine (N6-BA) are modified nucleosides endowed with potent *in vitro* antitumor activity on different types of human cancers, including colorectal cancer (CRC) and glioblastoma multiforme (GBM). Although the molecules seem to exert their anti-proliferative effects partially through the inhibition of Farnesyl Diphosphate Synthase (FDPS), their precise mechanisms of action remain to be uncovered. The main aim of my PhD project was to investigate the effects of the isoprenoid derivative N6-BA, by comparing them to those of the lead compound IPA, on the modulation of cancer-related pathways. I found that both IPA and N6-BA affect CRC and GBM cell lines proliferation by modulating the expression of the F-box WD repeat domain-containing 7 (FBXW7), widely considered a tumor suppressor since its crucial role in the turnover of many proteins (i.e. c-Myc, SREBPs and Mcl1) contributing to malignant progression.

In CRC, FBXW7/SREBP/FDPS axis was identified as a target of the compounds. IPA was found to induce the ubiquitination of c-Myc, inhibiting its transcriptional activity through the increase of FBXW7/c-Myc binding and N6-BA acts almost in a similar way. Moreover, IPA involvement in chemoresistance was also investigated. IPA synergized with 5-Fluorouracil in FBXW7- and TP53-wild type CRC cells and sensitized GBM cells to the toxic effect of Temozolomide.

Overall, results here showed provide novel insights into the molecular mechanism of the modified adenosines and suggested the existence of an epigenetic regulation underlying their pleiotropic effects in cancer. Restoring of FBXW7 tumor-suppressor represents a valid therapeutic tool, enabling modified adenosines as optimizable compound for patient-personalized therapies in both CRC and GBM.