N6-isopentenyladenosine, an Endogenous Isoprenoid Derivative, Induces Autophagy and Apoptosis in a Cooperative Manner in Melanoma Cells, Through the Activation of AMPK

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N6-isopentenyladenosine (iPA) is a modified adenosine characterized by an isopentenyl chain derived by dimethylallyl pyrophosphate (DMAPP), an intermediate of mevalonate pathway. iPA is a promising isoprenoid derivative with pleiotropic biological effects, including a direct anti-tumor and anti-angiogenic activity. However, its mechanism of action is still unknown. Since angiogenesis is a key process for growth and spread of solid tumors, the effect of iPA on tumor angiogenesis was investigated employing A375 human melanoma cells, well known for their highly angiogenic phenotype, co-cultured with endothelial cells. Moreover, we analyzed its action on melanoma cells using proliferation assays, flow cytometry and WB analysis.

iPA was able to affect angiogenic phenotype of melanoma cells. Noteworthy, iPA, in its active phosphorylated form iPAMP, inhibited the proliferation of melanoma cells, with a cell cycle arrest in G1 phase (2.5-10 µM). iPAMP, behaving as an AMP mimetic, was able to activate AMPK, leading to the induction of autophagy. In our cell system autophagy didn’t appear as protective mechanism but as preliminary step to cell death induction. Indeed, the analysis of peculiar markers in time course suggested that the autophagy was set up before apoptosis. The monophosphorylation of iPA into iPAMP by adenosine kinase (ADK) is crucial for its biological activity, since the pre-treatment with 5-Itu, selective inhibitor of ADK, reverted all the observed effects.

These results indicate for the first time that iPA exerted anti-melanoma activity, leading a concomitant induction of autophagy and apoptosis processes, both involved in cell death.