



Novel therapeutic compound acridine–retrotuftsins action on biological forms of melanoma and neuroblastoma

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Abstract

Purpose As a continuation of our search for anticancer agents, we have synthesized a new acridine-retrotuftsins analog HClx9-[Arg(NO₂)-Pro-Lys-Thr-OCH₃]-1-nitroacridine (named ART) and have evaluated its activity against melanoma and neuroblastoma lines. Both tumors develop from cells (melanocytes, neurons) of neuroectodermal origin, and both are tumors with high heterogeneity and unsatisfactory susceptibility to chemotherapies. Thus, we analyzed the action of ART on pairs of biological forms of melanoma (amelanotic and melanotic) and neuroblastoma (dopaminergic and cholinergic) with regard to proliferation, mechanism of cell death, and effect on the activity of tricarboxylic acid cycle (TAC) enzymes.

Methods The cytotoxicity of ART was evaluated by XTT and trypan blue tests. Cell death was estimated by plasma membrane structure changes (phosphatidylserine and calreticulin externalization), caspase activation, presence of ROS (reactive oxygen species), activity of tricarboxylic acid cycle enzymes (pyruvate dehydrogenase complex, aconitase, and isocitrate dehydrogenase), NAD level, and ATP level.

Results ART influences the biological forms of melanoma and neuroblastoma in different ways. Amelanotic (Ab) melanoma (with the inhibited melanogenesis, higher malignancy) and SHSY5Y neuroblastoma (with cholinergic DC cells) were especially sensitive to ART action. The Ab melanoma cells died through apoptosis, while, with SH-SY5Y-DC neuroblastoma, the number of cells decreased but not as a result of apoptosis. With Ab melanoma and SH-SY5Y-DC cells, a diminished activity of TAC enzymes was noticed, along with ATP/NAD depletion.

Conclusion Our data show that the biological forms of certain tumors responded in different ways to the action of ART. As a combination of retrotuftsins and acridine, the compound can be an inducer of apoptotic cell death of melanoma, especially the amelanotic form. Although the mechanism of the interrelationships between energy metabolism and cell death is not fully understood, interference of ART with TAC enzymes could encourage the further investigation of its anticancer action.

Keywords Acridine · Retrotuftsins · Melanoma · Neuroblastoma · Apoptosis · Tricarboxylic acid cycle enzymes

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Introduction

The acridine family includes a wide range of tricyclic molecules with various biological activities, such as anticancer, antiinflammatory, antimicrobial, antiparasitic, antiviral, and fungicidal activities (Gensicka-Kowalewska et al. 2017; Kukowska 2017). Acridines influence many biological processes, e.g., proliferation, pH homeostasis, and secretion of neurotransmitters. These compounds intercalate between base pairs in the double-stranded DNA structure (Kitchen et al. 1985; Pommier et al. 1987), influence activity of the topoisomerases that control the chromatin structure (Ferguson and Denny 1991) and affect the activity of telomerases and cyclin-dependent kinases (Gunaratnam et al. 2007;