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Mechanisms of neuroblastoma cell growth inhibition by CARP-1 functional mimetics (Article) (Open Access)

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Abstract

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Neuroblastomas (NBs) are a clinically heterogeneous group of extra cranial pediatric tumors. Patients with high-risk, metastatic NBs have a long-term survival rate of below 40%, and are often resistant to current therapeutic modalities. Due to toxic side effects associated with radiation and chemotherapies, development of new agents is warranted to overcome resistance and effectively treat this disease in clinic. CARP-1 functional mimetics (CFMs) are an emerging class of small molecule compounds that inhibit growth of diverse cancer cell types. Here we investigated NB inhibitory potential of CFMs and the molecular mechanisms involved. CFM-1, -4, and -5 inhibited NB cell growth, in vitro, independent of their p53 and MYCN status. CFM-4 and -5 induced apoptosis in NB cells in part by activating pro-apoptotic stress-activated kinases (SAPKs) p38 and JNK, stimulating CARP-1 expression and cleavage of PARP1, while promoting loss of the oncogenes C and N-myc as well as mitotic cyclin B1. Treatments of NB cells with CFM-4 or -5 also resulted in loss of Inhibitory κB (IκB) α and β proteins. Micro-RNA profiling revealed upregulation of XIAP-targeting miR513a-3p in CFM-4-treated NB, mesothelioma, and breast cancer cells. Moreover, exposure of NB and breast cancer cells to CFM-4 or -5 resulted in diminished expression of antiapoptotic XIAP1, cIAP1, and Survivin proteins. Expression of anti-miR513a-5p or miR513a-5p mimic, however, interfered with or enhanced, respectively, the breast cancer cell growth inhibition by CFM-4. CFMs also impacted biological properties of the NB cells by blocking their abilities to migrate, form colonies in suspension, and invade through the matrix-coated membranes. Our studies indicate anti-NB properties of CFM-4 and 5, and suggest that these CFMs and/or their future analogs have potential as anti-NB agents. © 2014 Muthu et al.

SciVal Topic Prominence

Topic: Melanoma-Specific Antigens | Cells | cancer cell

Prominence percentile: 69.625

Indexed keywords

EMTREE drug terms: antineoplastic agent, cell cycle and apoptosis regulator 1, cell cycle and apoptosis regulator 4, cell cycle and apoptosis regulator 5, microRNA, miR513a 5p, miR513a 5p antibody, protein p53, survivin, unclassified drug, X linked inhibitor of apoptosis, antineoplastic agent, APC2 protein, human, apoptosis regulatory protein, benzodiazepine derivative, BIRC5 protein, human, CCAR1 protein, human, cell cycle protein, CFM 1, cytoskeleton protein, growth inhibitor, I kappa B kinase, immunoglobulin enhancer binding protein, inhibitor of apoptosis protein, microRNA, MIRN513 microRNA, human, mitogen activated protein kinase p38, Myc protein, MYC protein, human, nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase, PARP1 protein, human, protein binding, stress activated protein kinase, X linked inhibitor of apoptosis, XIAP protein, human

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EMTREE medical terms:

apoptosis | article | cell count | cell growth | cell loss | cell migration | cell oncogene | cell viability | concentration response | controlled study | drug efficacy | drug mechanism | growth inhibition | human | human cell | in vitro study | neuroblastoma cell | oncogene c myb | protein cleavage | protein expression | protein targeting | upregulation | antagonists and inhibitors | biomimetics | biosynthesis | Breast Neoplasms | cell motion | cell proliferation | cell survival | drug effects | enzyme activation | female | genetics | metabolism | neuroblastoma | oncogene myc | pathology | phosphorylation | procedures | signal transduction | tumor cell line | tumor invasion

MeSH:

Antineoplastic Agents | Apoptosis | Apoptosis Regulatory Proteins | Benzodiazepinones | Biomimetics | Breast Neoplasms | Cell Cycle Proteins | Cell Line, Tumor | Cell Movement | Cell Proliferation | Cell Survival | Cytoskeletal Proteins | Enzyme Activation | Female | Genes, myc | Growth Inhibitors | Humans | I-kappa B Kinase | Inhibitor of Apoptosis Proteins | JNK Mitogen-Activated Protein Kinases | MicroRNAs | Neoplasm Invasiveness | Neuroblastoma | NF-kappa B | p38 Mitogen-Activated Protein Kinases | Phosphorylation | Poly(ADP-ribose) Polymerases | Protein Binding | Proto-Oncogene Proteins c-myc | Signal Transduction | X-Linked Inhibitor of Apoptosis Protein

Chemicals and CAS Registry Numbers:

survivin, 195263-98-0; X linked inhibitor of apoptosis, 391965-84-7; I kappa B kinase, 209902-66-9; nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase, 58319-92-9; stress activated protein kinase, 155215-87-5;

Antineoplastic Agents; APC2 protein, human; Apoptosis Regulatory Proteins; Benzodiazepinones; BIRC5 protein, human; CCAR1 protein, human; Cell Cycle Proteins; CFM 1; Cytoskeletal Proteins; Growth Inhibitors; I-kappa B Kinase; Inhibitor of Apoptosis Proteins; JNK Mitogen-Activated Protein Kinases; MicroRNAs; MIRN513 microRNA, human; MYC protein, human; NF-kappa B; p38 Mitogen-Activated Protein Kinases; PARP1 protein, human; Poly(ADP-ribose) Polymerases; Proto-Oncogene Proteins c-myc; X-Linked Inhibitor of Apoptosis Protein; XIAP protein, human

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