OMICS International
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J Cancer Sci Ther 2014, 7:10
http://dx.doi.org/10.4172/1948-5956.C1.061

8th Euro Global Summit on Cancer Therapy

November 03-05, 2015 Valencia, Spain

Tumor suppressive effect driven by cytoplasmic RNA-mediated innate signaling

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The type I interferons (IFNs) including IFN-alphas and IFN-beta are innate cytokines that directly or indirectly regulates antiviral defense. Activation of pattern recognition receptor (PRR) by viral pathogen-associated molecular patterns (PAMPs) such as nucleic acids leads to massive production of IFN-alpha/beta, which confers cells with antiviral state in an IFNAR (IFN-alpha/beta-receptor)-dependent manner. As well as eliciting strong antiviral activities, these cytokines are also known to show antitumor effect and immuno-modulating effect. In this study, we tried to harness cytoplasmic RNA-mediated activation of IFN pathway to directly suppress tumor growth. We first found that among various cancer cell lines tested, human breast cancer MCF-7 cells robustly induced IFN-beta production in response to stimulation with 5'-triphosphate RNA and poly(rI:rC), both of which are synthetic ligands for cytoplasmic RNA sensors such as RIG-I and MDA5, respectively. In addition, MCF-7 cells were found to undergo significant cell death in response to stimulation with these RLR ligands. This tumor cell death was suppressed by blockade of type I IFN signaling with anti-IFNAR-2 antibodies, suggesting that the RLR-ligand-induced cell death is dependent at least in part on type I IFN receptor-mediated signaling. Interestingly, in the absence of RLR ligand stimulation, IFN-beta treatment alone failed to remarkably induce tumor cell death. Consistent with this result, in vivo tumor growth of MCF-7 in nude mice was suppressed by treatment with RLR ligands but not IFN-beta. Thus, our present data suggest that the RLR-mediated signaling is essential to achieve the IFN-dependent cell death of MCF-7, and may provide a new insight into innate signaling-assisted cancer therapy.

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The impact of superoxide-peroxide hydrogen imbalance on chemotherapy response of colorectal cancer cells: an in vitro study

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Introduction: The standard treatment for locally advanced rectal cancer involves neoadjuvant radiochemotherapy before total mesorectal excision. However, tumor response to chemoradiation is highly variable among patients. A previous investigation that searched potential genetic markers that evaluated 128 single-nucleotide polymorphism (SNP) found significant association between superoxide dismutase 2 SNP (rs4880) and associated with radiochemotherapy resistance. The polymorphism that occurs a change of valine (V) to alaline (A) (Ala16Val-SOD2) has been associated with risk of several cancer types. The homozygous genotypes present different SOD2 efficiency causing increase in O_2- levels (VV) or increase of H_2O_2 (AA). Cellular control of superoxide anion (O_2-) and hydrogen peroxide (H_2O_2) concentrations is considered crucial to the cell because at low concentrations ROS can work as intracellular signal molecule related to homeostatic regulation, whilst at high levels they can cause cellular dysfunction and senescence.

Objetive: Therefore, we evaluated here if an in vitro superoxide-hydrogen peroxide (S-HP) imbalance could to influence the response of colorectal cancer cell (HT-29) resistant to oxaliplatin. Methods: HT-29 cells (ATCC) were cultured in standard conditions and exposed to different concentrations of methylviologen that is a superoxide anion donators as well as porfirin that is a SOD2-like molecule, with and without oxaliplatin. The effect on viability, cell proliferation and cell cycle were evaluated by MTT assay and analysis of apoptosis by annexin V quantification using flow cytometry analysis as well as by apoptosis pathway genes modulation (p53, Bax/Bcl-2 genes ratio, caspases 8 and 3) by qRT-PCR analysis were determined.

Results: The results showed that S-HP imbalance was able to increase cell cytotoxicity and apoptosis induction independent of oxaliplatin treatment. The results corroborate the potencial pharmacogenetic relevance of this polymorphism on colorectal cancer treatment.

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