abstracts: poster presentations

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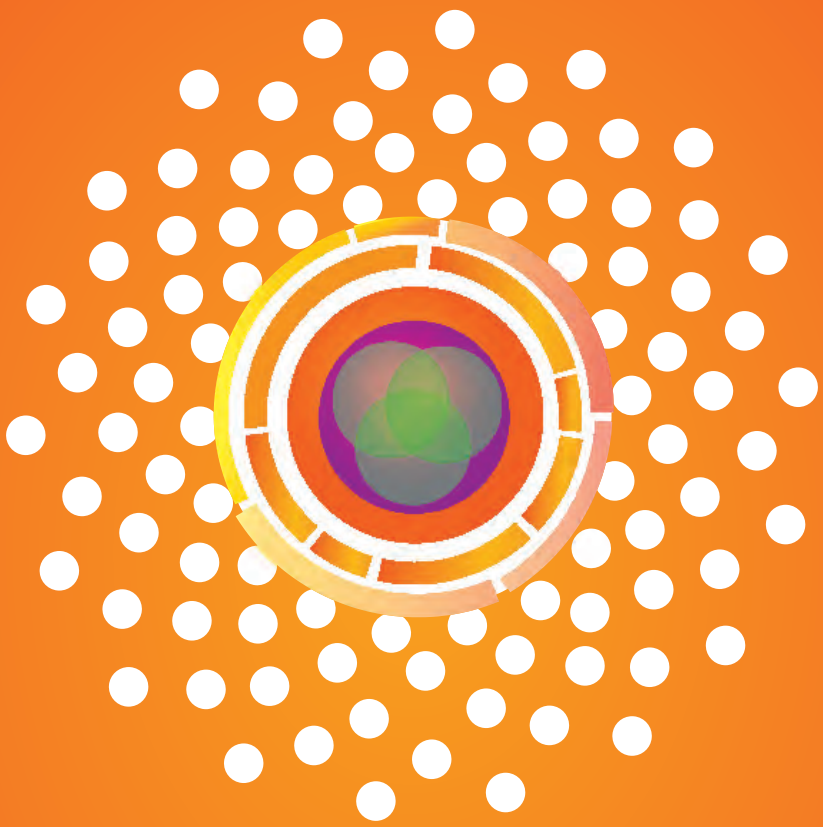

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vivo, cell lines with simple aneuploidies developed recurrent chromosomal aberrations that were absent from their euploid counterparts and that were associated with enhanced growth. Thus, the genome-destabilizing effects of single-chromosome aneuploidy may facilitate the evolution of balanced, high-complexity karyotypes that are frequently found in advanced malignancies.

P1115

Board Number: B510

Prion like propagation of p53 amyloid leading to cancer.

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The protein p53 is critical in cell where it regulates the cell cycle and functions as a tumor suppressor protein. In 50% of human cancer, p53 undergoes a loss of function. This is owing to p53 gene mutations, mainly missense point mutations, positioned in the central DNA binding domain. The mutant proteins have been earlier shown to accumulate as aggregate in multiple cancer cell types, and its aggregation also has been demonstrated in vitro. These observations suggest a role of aggregation as a plausible cause for loss of p53 function and cancer development. Here, we provide evidences that functional human p53 can be inactivated by exogenous addition of p53-derived peptides PILTIITL fibrils (P8) in budding yeast as well as human derived mammalian cells lines, SH-SY5Y. This inactivation was due to amyloid formation and resulted in cytoplasmic sequestration, which required the presence of innate p53 presumably for intracellular seeding to occur. p53 amyloid formation was studied with purified p53 core domain and its mutant R175H in vitro. R175H being a structural mutant was observed to aggregate faster suggesting the fact that amyloid formation of p53 is augmented on mutation. We have observed not only the functional inactivation of p53 but also gain-of-function effects in cells, upon amyloid formation. Interestingly the p53 amyloid formation in one cell can inactivate the functional p53 in another cell upon cellular fusion suggesting for an infectious nature of this mode of inactivation similar to prions. Thus the overall study implies that the loss of function of even wild-type human p53 can occur upon seeded aggregation and a prion like behavior of these aggregates may provide an explanation for the spreading of cancer. Importantly this study indicates that aggregation-causing residues of p53 or anti aggregating agents may serve as a potential target for cancer therapy.

P1116

Board Number: B511

Novel isatin-Schiff base copper (II) complexes as potential p53-activating pro-apoptotic agents.

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Activation of tumor suppressor p53 is considered as a promising therapeutic approach in cancer treatment. E3 ubiquitin ligase MDM2, the major negative regulator of p53, is overexpressed in many types of tumor cells. Therefore, one of the main mechanisms to activate p53 and trigger apoptosis in tumor cells is to use small-molecule inhibitors of MDM2. In this study we performed molecular and cell-based studies to investigate the potential pro-apoptotic properties of the novel isatin Schiff base copper (II) complexes. The compounds were designed to target MDM2 and result in p53 activation. Several tumor cell lines were used in the study. A range of experimental approaches were implemented,

including colorimetric cell proliferation assay, immunoblotting, real-time polymerase chain reaction, flow cytometry. Oxidation of key biogenic thiol, glutathione, was analyzed using UV spectroscopy. The results suggest that metal-based compounds, such as isatin Schiff base copper (II) complexes, represent a promising new scaffold for development of potent anti-tumor agents. The work was supported by the Russian Foundation for Basic Research, grant 16-34-50250.

P1117

Board Number: B512

The differential RBBP6 (retinoblastoma binding protein 6) expression predicts p53-induced apoptosis in human breast cancer cell lines.

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Breast cancer incidence rate has increased beyond that of lung cancer, making it the most common malignancy among women. Breast tumour progression is partly as a result of p53 inactivation by overexpressed ubiquitous regulatory proteins that possess p53 binding domain. RBBP6 forms a member of such protein since it has an E3 ligase activity due to its RING finger-like domain. And its overexpression in several malignancies makes it a potential target in cancer management. However, it is not clearly defined whether or not RBBP6 interaction with p53 promotes cancer progression. The present study therefore aims at evaluating the apoptotic response of breast cancer cell lines that differently express p53 to RBBP6 targeting and co-treatment with anticancer agents. Following treatments, apoptosis was evaluated by confocal microscope and flow cytometry using Annexin V staining. And it was further confirmed by measuring mitochondrial ATP content and caspase 3/7 activity. Cell proliferation and cell cycle arrest were evaluated using xCELLigence assay and flow cytometry through staining with propidium iodide, respectively. The wt. p53-expressing MCF-7 cell line was more susceptible to apoptosis induction as opposed to the mt. p53-expressing MDA-MB-231. RBBP6 silencing led to a significant accumulation of p53 expression in MCF-7 as compared to MDA-MB-231. Co-treatment with GABA and camptothecin seemed to sensitize the cells to apoptosis induction rather than cell cycle arrest. Overexpression of RBBP6 seemed to promote cell cycle progression and cell proliferation. These results predict the p53 genotypic status of MCF-7 and MDA-MB-231 breast cancer cell lines to play a major role in their responsiveness to RBBP6 targeting and co-treatment with apoptosis-inducing agents.

P1118

Board Number: B513

PA28γ expression affects the acquisition of cancer phenotypes.

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Although cancers arise through unique mutations, there exist common phenotypes amongst all cancers including uncontrolled proliferation, avoidance of apoptosis, genetic and genomic instability, and contact-independent growth. PA28γ is a proteasome activator that is commonly overexpressed in many cancers, and is correlated with all four of the aforementioned phenotypes. The transcriptional regulator, p53, is responsible for a myriad of cell fate decisions and is mutated in as many as half of all cancers. PA28γ stabilizes and controls localization of p53 in cells, which may also contribute to the carcinogenic transformation process. In order to further study the role of PA28γ in the acquisition of different phenotypes of cancer, PA28γ (+/+) and PA28γ (-/-) murine embryonic fibroblast (MEF) cells were