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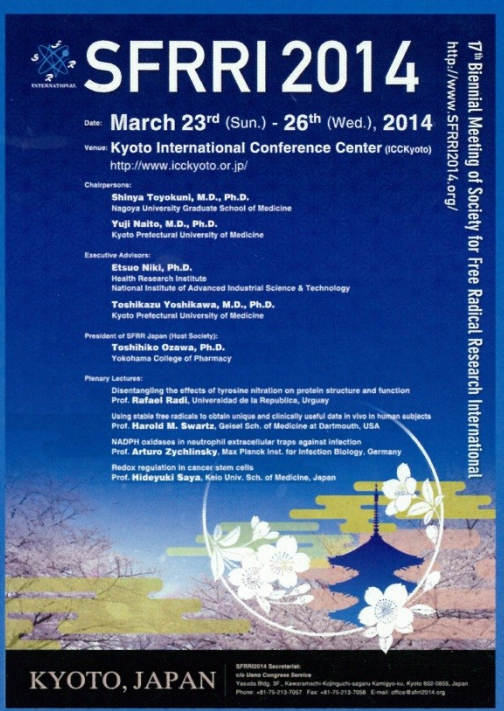

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The effect of Fermented Papaya Preparation on radioactive exposure

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Background: Radiation (radioactive, UV) damages cells, leading to death or mutagenesis. The damage is mediated in part by reactive oxygen species (ROS). Fermented Papaya Preparation (FPP), a yeast fermentation product of Carica papaya Linn, acts as an anti-oxidant by scavenging ROS and by chelating excess cellular labile iron (LI). We studied the effects of FPP on radiation-induced damage in cultured cells and mice.
Methods: FPP (10-100 μg/ml) was added to cultured cells before or after irradiation (0-18 Gy). After 1-3 days, survival was estimated by a proliferation assay; apoptosis - by staining for phosphatidylserine exposure (with Annexin V) and propidium-iodide uptake; ROS - by staining with dichlorofluoresceine-diacetate, and LI - by calcein-AM. DNA oxidation was estimated by measuring 8-oxyguanine and DNA stability - by the "comet assay". Mice were treated with FPP (in the drinking water) before or after irradiation. Their survival and their marrow cells were analyzed.
Results: FPP significantly ($P<0.05$) ameliorated the radiation-induced increase in LI, ROS, 8-oxyguanine and DNA instability. Apoptosis was decreased and, consequently, cell survival - increased. About 60% of 14 Gy-irradiated mice who received 100 μg/ml FPP survived.
Conclusions: FPP was shown to protect cultured cells and mice against various aspects of radiation-induced damage.

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Oxidative stress and cell differentiation: monochloramine affects differentiation of K562 erythroleukemia cell line

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Background: Cell differentiation is an important issue not just for normal development and aging but for cancer progression and treatment. We report that a physiologically attainable oxidant, monochloramine (NH_2Cl), affects differentiation of K562 erythroleukemia cell line, which suggests that leukemic cell differentiation can be manipulated by redox control.
Methods: K562 cells (5×10^4 cells/ml) in RPMI 1640 + 10% FBS were added with NH_2Cl (60 μM), and cultured in a CO_2 incubator for the indicated times. Differentiation marker proteins (CD235, CD71, γ-globin, CD41, CD42b, CD61, CD11b and CD14, 3 d) and ERK1/2 phosphorylation (2 h) were analyzed by a flow cytometer using specific antibodies. Cell morphology was also observed by a light microscope.
Results: Erythroid markers (CD235, CD71 and γ-globin) were all increased by NH_2Cl, whereas megakaryocyte markers (CD41, CD42b and CD61) as well as myeloid markers (CD11b and CD14) did not show detectable expression. ERK phosphorylation was decreased by NH_2Cl. Interestingly, NH_2Cl induced large cells with multiple or lobulated nuclei, which was characteristic to megakaryocyte.
Conclusion: NH_2Cl increased erythroid markers in K562 cells, and the decrease in ERK phosphorylation might be involved in the mechanism. Oxidative stress may be effective in inducing leukemic cell differentiation.

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Variation in glucose availability induces reactive oxygen species and increased P-gp mediated multi-drug resistance to chemotherapeutics

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Background: The multidrug resistance (MDR) protein, P-glycoprotein (P-gp), reduces tumor cell sensitivity to chemotherapeutics. Moreover, within a tumor, there exists a considerable spatial and temporal gradient of glucose, rendering cells exposed to a stressful environment that the tumour needs to respond to.
Methods: After variation in glucose concentrations, reactive oxygen species (ROS) were measured by flow cytometry using the cellular and mitochondrial stress markers DCFH-DA and MitoSOX, respectively. Stress induced protein activation was determined by RT-PCR, western blotting and immunofluorescene. The effect of glucose variation on chemotherapeutic cytotoxicity was determined *via* MTT assays.
Results: Elevated and restricted glucose availability induced mitochondrial superoxide production and cytosolic stress. ROS activated the transcription factor, NF-κ β. The active p65 subunit of NF-κ β was observed to translocate into the nucleus, resulting in enhanced HIF-1α transcription. ROS also prevented PHD degradation of active HIF-1α. Interestingly, this lead to increased plasma membrane P-gp protein expression and function. Consequently, this resulted in greater drug resistance to Doxorubicin, which was reduced by the P-gp inhibitor elacridar.
Conclusion: A more aggressive MDR phenotype can result from glucose stress induced superoxide production.

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Nitric oxide derived from chronic inflammatory environment causes conversion of human colonic adenoma cells to adenocarcinoma cells

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We determined a mechanism of inflammation-related carcinogenesis in our established a mouse model. FPCK-1-1 cells, derived from a colonic polyp in a patient with familial adenomatous polyposis, were non-tumorigenic when 5×10^6 cells were injected subcutaneously into nude mice. However, when 1×10^5 of FPCK-1-1 cells, attached to a piece of plastic plate, were implanted in a subcutaneous space in nude mice, they were converted into adenocarcinoma cells in the chronic inflammation induced by the foreign body, a plastic plate. We found that highly proliferative fibrous stroma, formed from the plate implantation, was essential for the conversion. Further we revealed that nitric oxide (NO) derived from the fibrous stroma was the primary cause for the conversion. The conversion was inhibited by administration of NO synthase inhibitor, aminoguanidine. And FPCK-1-1 cells continuously exposed to chemically generated NO acquired tumorigenicity and resistance to anoikis (apoptosis resulting from loss of cell-substrate interactions). These results confirmed that NO was one of the causative factors for the acceleration of colon carcinogenesis, especially in the conversion from adenoma to adenocarcinoma in the chronic inflammatory environment.