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An anti-cancer drug impair and repair mechanism (Methotrexate induced mucositis and its prevention in rat model)

Kasthuri Natarajan and **Premila Abraham**
Tamil Nadu Dr. M.G.R. Medical University, India

Methotrexate (MTX) is widely used as a chemotherapeutic agent for leukemia and other malignancies as well as non-malignant diseases. The efficacy of this drug is often limited by mucositis and intestinal injury which are the major causes of morbidity in children and adults. Despite many studies, the precise mechanism of MTX induced mucositis is still not fully understood. Therefore, currently, there is no definitive prophylaxis or therapeutic treatment for MTX induced mucositis. The present study is aimed to identify the possible mechanism of inflammation and prevention in MTX induced mucositis using a rat model. The experimental rats received three daily intraperitonial injections of 7 mg/kg body weight of methotrexate. Control rats received vehicle alone. For the intervention studies, aminoguanidine was used. Twenty four hours after the final dose of MTX/vehicle, the rats were sacrificed and the small intestine was removed for the studies. Histologically, MTX treated rat small intestine revealed moderate to severe mucosal damage with abscess formation. We found increased levels of iNOS, nitric oxide and superoxide levels which lead to nitrosative stress. Western blot analysis revealed the activation of NFkB and its downstream proteins of inflammatory mechanism and the release of cytochrome c into cytosol, activation of caspases, PARP and DNA fragmentation indicating apoptosis mechanism in response to MTX treatment. Aminoguanidine, a selective iNOS inhibitor, attenuate nitrosative stress, improved MTX induced morphological changes, inhibited NFkB inflammatory pathway and intrinsic apoptotic pathway. Thus, aminoguanidine has a protective role against MTX induced small intestinal damage. In conclusion, these results provide an evidence for the role of oxidative stress, nitrosative stress, activation of inflammatory and apoptosis pathway cause small intestinal damage in the pathogenesis of methotrexate induced mucositis. Thus, aminoguanidine pretreatment deteriorate the methotrexate induced mucositis, reduce side effects and improve efficacy of the drug. This combinational sequence therapy of drugs has a promising output that can be extrapolate to human with further clinical trials.

kasthuri.jrf@gmail.com

Differential mi-RNAs expression profiles classify mucin 1(+)/ (-) human breast cancer stem cells

Madhulika Singh, Sanjay K Mishra and **Yogeshwer Shukla**
CSIR-Indian Institute of Toxicology Research, India

Background: Mucin-1 (Muc1) is a secreted, oncogenic mucin that is aberrantly over expressed in breast cancer cells but its potential role in breast cancers stem cells (BCSCs) have not been explored. Micro-RNAs (mi-RNA), small non-coding RNAs that play critical roles in normal stem cell functions during development, have emerged as important regulators of BCSCs as well.

Methods: Muc positive (+)/ (-) cells were isolated from patient-derived cancer (n=25), and normal BC tissues (n=15) and propagated in non-adhesive suspension cell culture to assess their phenotypic characteristics. Further mi-RNAs expression profiling was done by using micro-RNA Taq Man® Low Density Array Cards v2.0 based on qReal-Time PCR array.

Results: Significantly altered expression of mi-RNAs were found (17 up-regulated and 29 down regulated) in Muc (+) BCSCs as compared to Muc (-) ($p<0.05$). All these mi-RNAs were having significant role in BCSCs self renewal, proliferation potential and were also involved in cancer metastasis. Further, selected miRNAs expression levels were individually tested and validated in mammospheres generated from tissue samples. Muc (+) BCSCs were showing higher level of miRNAs -9, -16, -34a, -195-5p and -454 as compared to Muc(-) BCSCs. Significantly down regulated expression of miR-106a, -125b and -218 was also noted in Muc (+) BCSCs as compared to adhered and Muc(-) cell population.

Conclusions: These mi-RNAs can potentially be used to develop a panel for classification and prognosis in order to better predict the progression of the disease and facilitate the choice of treatment strategy.

madhulika.anil@gmail.com