High nitric oxide exposure causes Upregulation of JUN, FOS & AP1 and may play a role in cancer stem cell formation by pseudogenes expression

Khatja Batool1, Mohannad Zaid Alkilani and James A Radosevich1,2
1University of Illinois, USA
2Jesse Brown VAMC, USA

Hypothesis: The high exposure causes up-regulation of JUN, FOS & AP1; genes in adapted cell lines and over expression of Pseudogenes which has metastatic potential.

Objective: When subjected to high concentration of NO, H&N tumour cell express more aggressive phenotype compared to non-exposed cell. Upon exposure these cells exhibit adaptation causing greater metastatic potential. Five H&N cell lines were adapted to high concentrations of NO. It appears that AP1, which is a transcription factor protein, composed of JUN and FOS family proteins. These proteins are responsible for various cellular process including cell differentiation, proliferation and apoptosis which up regulate these cells. MicroRNA isolation due to CeRNA add to Pseudogenes and their influence on the growth of cancer. One well studied gene is the BRAF pseudogene and its functional BRAF gene. Studies have shown that high levels of the BRAF pseudogene are directly proportional to the formation of aggressive malignancies.

Methods: This study used five human H&N cells lines (SSC-016, SSC-040, SSC-056, SSC-114, and SSC-116). Known pseudogenes were identified in each line, as well as their coding counterparts. Slow exposure of high NO was used on the cell lines to increase quantities of DETA-NONOate (NO donor). Both the parent and NO cell lines were tagged with red/green fluorescent markers and mRNA was isolated. A gene chip analysis was used to assess genome wide gene expression. Via scratch assays cell migration rates were assessed. Within these five cell lines JUN, FOS, and API1 genes were up-regulated when exposed to high NO. Increased migration velocities was demonstrated among all three genes.

Results: The adenocarcinoma cell lines RP6-159A1.2, RP11-255N24.3, AC004490.1, LDHBP, RP11-572H4.2 were down regulated pseudogenes, and there was no up regulated pseudogenes. The squamous cell carcinomas (SCCs) had the following up regulated pseudogenes: RPL37AP1, AC138972.1, RP11-641D5.1, AC005534.6, AC22431.1, RPL26P12, and they had these down regulated pseudogenes: RP6-159A1.2, RP11-255N24.3, RBMXP1, RP11-20O23.1, RP11-551G24.2. All cell lines showing an increase in a pseudogene expression indicating an increase in the corresponding gene (with the exception of the adenocarcinoma cell lines). JUN, FOS and API1 genes showed increased migration velocities with up-regulation compared to the parent cell lines.

Conclusions: The high concentration of CeRNA may reduce expressions of microRNA, which would then lead to high concentrations of pseudogenes (likely due to high levels of HNO). Pseudogenes, along with BRAF, in turn reduce the expression of microRNA. Therefore, the pseudogenes and BRAF take the same role as the CeRNA. This results in a feedback loop of over expression of the coding gene. Within these cell lines JUN, FOS, and API1 genes had an increased migration velocities which demonstrated an increased tumour aggressiveness.

Biography

Khatja Batool graduated with her Bachelor of Medicine and Bachelor of Surgery from Gulf Medical University, UAE. She started her research at UIC-Chicago, IL where she studied the effects of nitric oxide in cancer stem-cell lines. Additionally, she is a certified expert in Botulinum Toxin, Dermal Fillers and Facial reconstruction. Her distinguished efforts led her to be a part of the organizing committee at the 43rd ISOBM annual conference in Chicago, IL which was attended by Nobel laureate Dr. Ferid Murad and other well-known scientists. She has also had her works published in research journals such as Tumor Biology. Furthermore, Khatja is on the reviewer board for international journals like Tumor Biology and JCMT, Board member at Oncomarks.org and a member of professional societies like ASCO and ISOBM. She has an active interest in oncology research especially in the studies of nitric oxide and telomerase shortening in cancer stem cells.

sania2050@gmail.com