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Immunomodulatory Role of Heat Killed Mycobacterium indicus pranii against Cervical Cancer

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Abstract : Background: Cervical cancer is the third major cause of cancer in women and the second most frequent cause of cancer related deaths causing 300,000 deaths annually worldwide. Evasion of immune response by Human Papilloma Virus (HPV), the key contributing factor behind cancer and pre-cancerous lesions of the uterine cervix, makes immunotherapy a necessity to treat this disease. Objective: A Heat killed fraction of Mycobacterium indicus pranii (MIP), a non-pathogenic Mycobacterium has been shown to exhibit cytotoxic effects on different cancer cells, including human cervical carcinoma cell line HeLa. However, the underlying mechanisms remain unknown. The aim of this study is to decipher the mechanism of MIP induced HeLa cell death. Methods: The cytotoxicity of Mycobacterium indicus pranii against HeLa cells was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Apoptosis was detected by annexin V and Propidium iodide (PI) staining. The assessment of reactive oxygen species (ROS) generation and cell cycle analysis were measured by flow cytometry. The expression of apoptosis associated genes was analyzed by real time PCR. Result: MIP could inhibit the proliferation of HeLa cell in a time and dose dependent manner but caused minor damage to normal cells. The induction of apoptosis was confirmed by the cell surface presentation of phosphatidyl serine, DNA fragmentation, and mitochondrial damage. MIP caused very early (as early as 30 minutes) transcriptional activation of p53, followed by a higher activation (32 fold) at 24 hours suggesting prime importance of p53 in MIP-induced apoptosis in HeLa cell. The up regulation of p53 dependent pro-apoptotic genes Bax, Bak, PUMA, and Noxa followed a lag phase that was required for the transcriptional p53 program. MIP also caused the transcriptional up regulation of Toll like receptor 2 and 4 after 30 minutes of MIP treatment suggesting recognition of MIP by toll like receptors. Moreover, MIP caused the inhibition of expression of HPV anti apoptotic gene E6, which is known to interfere with p53/PUMA/Bax apoptotic cascade. This inhibition might have played a role in transcriptional up regulation of PUMA and subsequently apoptosis. ROS was generated transiently which was concomitant with the highest transcription activation of p53 suggesting a plausible feedback loop network of p53 and ROS in the apoptosis of HeLa cells. Scavenger of ROS, such as N-acetyl-L-cysteine, decreased apoptosis suggesting ROS is an important effector of MIP induced apoptosis. Conclusion: Taken together, MIP possesses full potential to be a novel therapeutic agent in the clinical treatment of cervical cancer.

Keywords : cancer, mycobacterium, immunity, immunotherapy.
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