World Academy of Science, Engineering and Technology
International Journal of Bioengineering and Life Sciences
Vol:13, No:04, 2019

Profiling of the Cell-Cycle Related Genes in Response to Efavirenz, a Non-Nucleoside Reverse Transcriptase Inhibitor in Human Lung Cancer

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Abstract : The Health-related quality of life (HRQoL) for HIV positive patients has improved since the introduction of the highly active antiretroviral treatment (HAART). However, in the present HAART era, HIV co-morbidities such as lung cancer, a non-AIDS (NAIDS) defining cancer have been documented to be on the rise. Under normal physiological conditions, cells grow, repair and proliferate through the cell-cycle as cellular homeostasis is important in the maintenance and proper regulation of tissues and organs. Contrarily, the deregulation of the cell-cycle is a hallmark of cancer, including lung cancer. The association between lung cancer and the use of HAART components such as Efavirenz (EFV) is poorly understood. This study aimed at elucidating the effects of EFV on the cell-cycle genes' expression in lung cancer. For this purpose, the human cell-cycle gene array composed of 84 genes was evaluated on both normal lung fibroblasts (MRC-5) cells and adenocarcinoma (A549) lung cells, in response to 13μM EFV or 0.01% vehicle. The ±2 up or down fold change was used as a basis of target selection, with $p < 0.05$. Additionally, RT-qPCR was done to validate the gene array results. Next, In-silico bio-informatics tools, Search Tool for the Retrieval of Interacting Genes/Proteins (STRING), Reactome, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Ingenuity Pathway Analysis (IPA) were used for gene/gene interaction studies as well as to map the molecular and biological pathways influenced by the identified targets. Interestingly, the DNA damage response (DDR) pathway genes such as p53, Ataxia telangiectasia mutated and Rad3 related (ATR), Growth arrest and DNA damage inducible alpha (GADD45A), HUS1 checkpoint homolog (HUS1) and Role of radiation (RAD) genes were shown to be upregulated following EFV treatment, as revealed by STRING analysis. Additionally, functional enrichment analysis by the KEGG pathway revealed that most of the differentially expressed gene targets function at the cell-cycle checkpoint such as p21, Aurora kinase B (AURKB) and Mitotic Arrest Deficient-Like 2 (MAD2L2). Core analysis by IPA revealed that p53 downstream targets such as survivin, Bcl2, and cyclin/cyclin dependent kinases (CDKs) complexes are down-regulated, following exposure to EFV. Furthermore, Reactome analysis showed a significant increase in cellular response to stress genes, DNA repair genes, and apoptosis genes, as observed in both normal and cancerous cells. These findings implicate the genotoxic effects of EFV on lung cells, provoking the DDR pathway. Notably, the constitutive expression of this pathway (DDR) often leads to uncontrolled cell proliferation and eventually tumourigenesis, which could be the attribute of HAART components' (such as EFV) effect on human cancers. Targeting the cell-cycle and its regulation holds a promising therapeutic intervention to the potential HAART associated carcinogenesis, particularly lung cancer.

Keywords : cell-cycle, DNA damage response, Efavirenz, lung cancer
Conference Title : ICGMB 2019 : International Conference on Genetics and Molecular Biology
Conference Location : Cape Town, South Africa
Conference Dates : April 16-17, 2019