Post-Translational Modification of LaminB1 as a Regulator of Translesion DNA Synthesis (TLS)

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Translesion DNA Synthesis (TLS) is of great importance, as it allows cells to complete DNA replication following DNA damage. Polymerase(eta) is a key polymerase involved in TLS across UV induced lesions. This study focuses on post translational modification (Farnesylation) of the nuclear protein LaminB1, to characterize its regulatory potential effects on polymerase(eta). To study the influence of the LaminB1 farnesylation, it was inhibited by the drug Tipifarnib, or by overexpression of mutant LaminB1, followed by examination of LaminB1's nuclear location, polymerase(eta) cellular levels and Cells' survival following UV irradiation. Several advanced bio-molecular assays, including Transient Transfection, Immunofluorescence, Luminescent Cell Viability Assay and Fluorescence Activated Cell Sorting were used in various settings. Inhibition of LaminB1 farnesylation by Tipifarnib caused elevation in cellular polymerase(eta) protein levels in a dose dependent manner. Furthermore, I found a different expression pattern of mutant LaminB1 protein compared to the wild type. Tipifarnib treatment was shown to increase the cells' population doubling time however did not cause cell accumulation in a specific cell cycle phase. The results obtained in this study indicate that LaminB1 farnesylation is involved in the regulation of polymerase(eta) dependent TLS. Cancer cells use TLS machinery in order to continue rapid proliferation in the presence of DNA damage. Polymerase(eta) bypasses preferably DNA lesions induced by cysplatin drug. Tipifarnib is a novel chemotherapeutic drug aimed to target Ras oncogene, but as shown in this work might improve also polymerase(eta) dependent TLS. Therefore, a combination of tipifarnib and cysplatin in cancer treatment might not be recommended.

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