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Abstract Topic: - Cancer

Abstract Title: - Altered dynamics of STN1 and Repair proteins: An in-silico study to uncover its role in telomeric instability

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Aims: - STN1, also known as (DNA polymerase) -accessory factor AAF44, is a part of the discovered Ctc1/Stn1/Ten1 complex and has a role in telomere maintenance which is under-explored. Telomeres are hotspots for the formation of secondary genomic structures, such as T-loop, D-loop, G-quadruplexes, and R-loops. STN1 is known to maintain telomeric integrity at the replication fork and a dysregulated expression of STN1 may contribute to alternative lengthening of telomere (ALT) in cancer by assisting the localization of ALT-associated PML bodies (APBs). This study focuses on STN1 and its interaction with DNA repair proteins to better understand the delicate interplay that encourages telomeric instability leading to cancer.

Methods: - To understand the collaboration of STN1 with various DNA repair proteins, a network analysis was performed. Simultaneously, fold change in stn1 expression was extracted from TCGA database and extensive mutational profiling was carried out for mutations mined from COSMIC database. Further, detrimental SNPs of stn1 and its DNA repair interacting partners were docked using multiple in silico tools. Finally, a correlation was established between the gene expression and drug sensitivity for STN1, WRN, BRCA1, TP53BP1, SMC5, and SMC6 using GSCA database to assimilate the current clinical interventions available and search for novel molecules in future.

Results: - STN1 interacts with multiple proteins such as WRN, TP53BP1, BRCA1, SMC5, and SMC6 involved in Non-homologous End-joining and Homologous recombination repair mechanisms. A significant correlation was found in the differential expressed STN1 and interacting partners. In skin and large intestine tissues, it was upregulated while in lung and liver, it was showing a decreasing trend. Two of 93 non-synonymous SNPs were found to be highly detrimental to the protein function and the docking showed altered dynamics of the binding partners compromising the telomeric integrity. Overexpressed STN1 with its upregulated binding partners WRN, BRCA1, and SMC6 was found to be sensitive to various small molecule/drugs used in the treatment of cancer.

Conclusions: - These findings elucidate that STN1 dysregulates through changes in expression or due to mutations leading to altered dynamics with certain repair proteins. Any imbalance of repair proteins and CST complex at telomere can disrupt the telomeric integrity leading to progression of cancer and onset of ALT-mechanism. It also makes STN1 a viable therapeutic target to prevent cancer cell immortalization.

Keywords: - STN1 interacts with multiple proteins such as WRN, TP53BP1, BRCA1, SMC5, and SMC6 involved in Non-homologous End-joining and Homologous recombination repair mechanisms. A significant correlation was found in the differential expressed STN1 and interacting partners. In skin and large intestine tissues, it was upregulated while in lung and liver, it was showing a decreasing trend. Two of 93 non-synonymous SNPs were found to be highly detrimental to the protein function and the docking showed altered dynamics of the binding partners compromising the telomeric integrity. Overexpressed STN1 with its upregulated binding partners WRN, BRCA1, and SMC6 was found to be sensitive to various small molecule/drugs used in the treatment of cancer.