Role HSP70-HSP90 organizing protein in the regulation of DNA damage and DNA damage response

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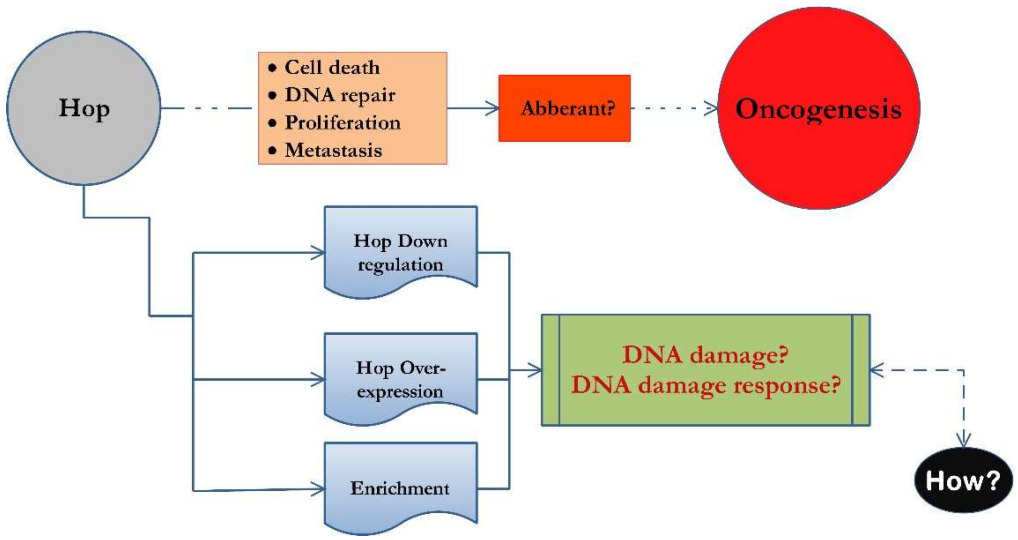

Figure 1: Preliminary data demonstrate that either loss of HOP, HOP overexpression or enrichment of HOP in the cytoplasm or nucleus results in the activation of the DNA damage and DNA damage response (DDR).

Introduction: Eukaryotic organisms are constantly exposed to exogenous and endogenous agents that induce cellular stress. Hsp70-Hsp90 Organizing Protein (HOP) modulates essential cellular processes that play a role in oncogenesis by influencing the fate of numerous proteins and thus regulates fundamental cancer cell biology properties such as cell death, proliferation, metastasis, and DNA damage (Bhattacharya and Picard, 2021). However, there is still a limited understanding of molecular mechanisms underlying many of these processes.

Methodology: Alkaline comet assay was conducted on HOP wildtype, knockout, and overexpressing cell lines. Cell viability was evaluated using resazurin assay. The ability to survive the DNA damage pathways activation was done using a clonogenic assay. SCE assay was used to monitor DNA damage and repair status. We used immunofluorescence microscopy to determine the subcellular distribution of DDR proteins. Western blot was used to detect DDR proteins.

Results: HOP KO had increased levels of DNA fragmentation. There was also a significant increase in SCE eventsin HOP KO cells. HOP WT had better cell viability than KO and survived activation of DNA damage pathways. There were notable differences in morphology and localization of DDR proteins as well. SMC1 and MRE11 were elevated inHOP KO under basal conditions.

Discussion and Conclusions: Taken together, these findings highlight a dysfunctional DDR and an intrinsic genomic instability in HOP deficient cells. In the next stage of this project, we shall conduct a mechanistic analysis on how HOP regulates DDR.

Reference:

Bhattacharya, K. and Picard, D. (2021) 'The Hsp70–Hsp90 go-between Hop/Stip1/Sti1 is a proteostatic switch and may be a drug target in cancer and neurodegeneration', *Cellular and Molecular Life Sciences 2021 78:23*. Springer, 78(23), pp. 7257–7273. doi: 10.1007/S00018-021-03962-Z.

Key Words: Hsp70-Hsp90 organizing protein (HOP), DNA damage response (DDR), sister chromatid exchange (SCE), wild type (WT), knock out (KO)