DISRUPTION OF HP1-KAP1 INTERACTION LEADS TO FORMATION OF LARGE NUCLEAR BODIES AND DECREASES HP1 MOBILITY IN THE NUCLEUS

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Introduction: Posttranslational modifications are playing crucial roles in cellular mechanisms. SUMOylation is a reversible posttranslational modification of target proteins by the attachment of a small ubiquitin-like protein. The consequences of SUMOylation are widely variable, depending on the physiological state of the cell and the attached SUMO isoform. Accumulating recent findings have revealed a prominent role of SUMOylation in molecular pathways that govern senescence and ageing. It has been proven the link between SUMO attachment events and cellular processes that influence senescence, including promyelocytic leukaemia (PML) nuclear body, telomere function and reactive oxygen species (ROS).

Methods: The biotin ligase BirA was fused to the protein of interest, and the Biotin Acceptor Peptide (BAP) was fused to SUMO to make the detection of its biotinylation possible by confocal microscopy.

Results: KAP1 protein which mediates transcriptional control by interaction with the Kruppel-associated box repression domain found in many transcription factors was proposed to be involved in gene silencing via its recruitment of HP1 to particular sites in the genome. This simple model predicts that loss of the KAP1-HP1 interaction would weaken HP1 binding to chromatin, resulting in its higher intranuclear mobility. We used the HP1BD fragment of KAP1 as a dominant negative tool to test this prediction. Contrary to our expectations, we observed a decrease in HP1 mobility upon the disruption of the interaction between endogenous KAP1 and HP1. Moreover, large nuclear HP1-containing domains were formed under these conditions. Despite previously reported association between HP1 and PML bodies known to be highly enriched in SUMOylated proteins, we found no colocalization of PML with these HP1 domains. We conclude that the interaction between HP1 and KAP1 preserves HP1 in a more mobile and homogeneously distributed state in the nucleus.

Conclusion: We demonstrated that disruption of the KAP1-HP1g interaction leads to formation of remarkable matrix-associated nuclear domains that are enriched in HP1g and not identical to PML bodies. Overall, this part of the work illustrates how the identification of SUMO-modified proteins in proximity to a protein of interest could provide fresh clues revealing additional insights into the biology of these proteins.