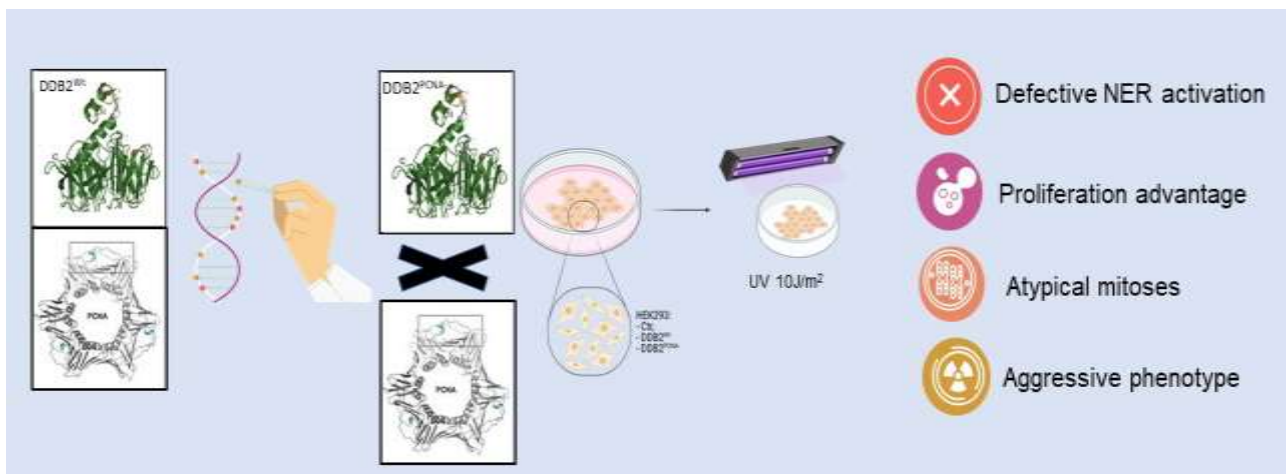


Studying interactions between proteins involved in cell cycle regulation and DNA replication and repair

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The DNA must be replicated and transmitted properly to avoid genomic instability, pathogenetic basis of several human diseases, such as cancer; to this end, cells have developed a complex system to monitor and signal DNA damage (checkpoints), and DNA repair systems. For many years the research of the laboratory has been directed to some proteins that regulate the cell cycle and appear also to be involved in the processes of DNA repair. Among these proteins, the cyclin-dependent kinase inhibitors p21^{CDKN1A} plays a very important role in cell cycle control, mainly in the "checkpoint" of G1 phase and in the inhibition of DNA synthesis by associating with PCNA, a cofactor necessary for the activity of many enzymes involved in the DNA metabolism. Recently, our research has demonstrated that p21, in cooperation with p27, an important member of CDK-inhibitor family, is involved in the induction in controlling the entry/exit from the temporary cell cycle (quiescence). In addition, p21 appear to promote the efficiency of DNA repair processes, like the Nucleotide Excision Repair (NER). In fact, p21 seems to be required to regulate the acetylation of some factors involved in NER. Among these, we are studying the protein that binds to damaged DNA (DDB2), which, combined with DDB1 in the DDB complex, plays a role in the recognition of DNA damage induced by UV in the Global Genome Repair (GGR-NER). In the last years we have demonstrated that DDB2 protein interact directly with PCNA and, the loss of this interaction, affects DNA repair and confers proliferative advantages, along with an increased invasion ability of cells expressing DDB2^{PCNA-} mutant.

Aim of the PhD project is to investigate new molecular network including DDB2 and PCNA, which may help dissecting gene expression pathways determining increased cell proliferation and acquisition of invasion ability. In particular, specific goals are: i) to define the DDB2 interactome; ii) to evaluate biophysical properties of cells expressing DDB2^{Wt} and DDB2^{PCNA-} forms, in order to investigate how mechanical aspects may influence the DNA damage response and migration properties of these cells.



Techniques: Cell culture, gene cloning, transfection protocols, cell-free systems, gene silencing, DNA replication and repair study, epigenome and interactome analysis, immunofluorescence techniques and microscopy analysis, evaluation of invasion and metastatic capability.