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Non canonical roles of BER enzymes in RNA processing: novel perspectives in cancer biology through the study of APE1 RNA- and protein-interactomes

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The Base Excision Repair (BER) pathway, initially studied as a mere DNA repair pathway, has been later found to be implicated in the expression of cancer related genes in human. For several years, this intricate involvement in apparently different processes represented a mystery, which we now are starting to unveil. The BER handles simple alkylation and oxidative lesions arising from both endogenous and exogenous sources, including cancer therapy agents. Surprisingly, BER pathway involvement in transcriptional regulation, immunoglobulin variability and switch recombination, RNA metabolism and nucleolar function is astonishingly consolidating. An emerging evidence in tumor biology is that RNA processing pathways participate in DNA Damage Response (DDR) and that defects in these regulatory connections are associated with genomic instability of cancers. In fact, many BER proteins are associated with those involved in RNA metabolism, ncRNA processing and transcriptional regulation, including within the nucleolus, proving a substantial role of the interactome network in determining their non-canonical functions in tumor cells. Mammalian apurinic/apyrimidinic endonuclease 1 (APE1) is a key DNA repair enzyme in canonical BER involved in genome stability but also in the non-canonical expression of genes involved in oxidative stress responses, tumor progression and chemoresistance. However, the molecular mechanisms underlying APE1's role in these processes are still unclear. Recent findings point to a novel role of APE1 in RNA metabolism. Through the characterization of the interactomes of APE1 with RNA and other proteins, we demonstrate here a role for APE1 in pri-miRNA processing and stability via association with the DROSHA processing complex during genotoxic stress. We also show that endonuclease activity of APE1 is required for the processing of miR-221/222 in regulation expression of the tumor suppressor PTEN. Analysis of a cohort of different cancers supports the relevance of our findings for tumor biology. We also show that APE1 participates in RNA- and protein-interactomes involved in cancer development, thus indicating an unsuspected post-transcriptional effect on cancer genes. Maybe these new insights of BER enzymes, along with their emerging function in RNA-decay, may explain BER essential role in tumor development and chemoresistance and may explain the long-time mystery. Although recent works have provided tremendous amount of data in this field, there are still lot of open questions.