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EXPERT VIEWS

Beyond Lactylation: Interrogating ATR's Role and Model Consistency in DNA Damage Response

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Recently, on invitation, I read with keen interest the article by Chen et al., titled "Metabolic regulation of homologous recombination repair by MRE11 lactylation" published in Cell 2024; 187(2): 294–311. In brief, the authors concluded that "Lactic acid induces MRE11 lactylation in cancer cells, leading to overactivation of homologous recombination and chemotherapy resistance. This discovery reveals the link between cellular metabolism and double strand break repair, as well as the impact of Warburg effect on chemotherapy resistance."

While I greatly appreciate the intriguing observation presented in this study, after thoroughly reading the article, I would like to highlight three crucial questions that it raises. First, when reviewing the mechanism map, a key question arises: what about the expression level and functional status of ATR besides those of ATM? As we know, ATR plays a more significant role than ATM in intra-S-phase checkpoint activation following IR, with DNA-PKcs facilitating recovery [1]. Even in the context of double-stranded DNA (dsDNA) damage, there is notable interplay between ATM and ATR in sensing and signaling DNA double-strand breaks [2]. However, authors did not present any data to exclude the involvement of ATR in the DNA damage repair, and the map only depicts ATM responding to DNA damage without including ATR.

Secondly, the authors used cisplatin and ionizing radiation (IR) to treat cell models *in vitro* and animal models *in vivo*, respectively, to validate their claims. While both cisplatin and IR treatment can cause DNA damage, including single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) breakage [3], they do so with different mechanisms. The former is through inter-chain and/or intra-chain cross-linkage, whereas the latter is the dosage–and/or time–dependent breakage. Thus, the *in vivo* and *in vitro* experiments in the article cannot mutually confirm or support each other due to these differing mechanisms.

Lastly, the authors mentioned that MRE11 contains two DNA-binding domains (DBDs), enabling it to bind both single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA). For double-stranded breakage (DSBs), MRE11 lactylation plays a key role in regulating MRE11 DNA-binding ability and subsequent DNA end resection [4], which is essential for the generation of homology and the subsequent steps of the HR process [5]. Particularly in the case of DNA double strand breaks (DSBs) and replication stress, three PI3-kinase related protein kinases—ATM, ATR and DNA-PKcs—are recruited to and activated at the DNA damage sites by their respective sensor protein complexes: MRE11/RAD50/NBS1 for ATM, RPA/ATRIP for ATR and KU70–KU80/86 (XRCC6/XRCC5) for DNA-PKcs. Upon activation, ATM, ATR, and DNAPKcs phosphorylate a wide range of partially overlapping substrates to promote efficient and accurate DNA repair while also coordinating DNA repair with other DNA metabolic events (*e.g.*, transcription, replication and mitosis) [6]. It is also crucial to explain how SSB from intra-chain crosslinking by cisplatin treatment is repaired. Without this clarification, genomic instability will persist, especially in cases of metabolic abnormalities, further laying the groundwork for the deterioration of cancer other than cure or relief.

In summary, understanding whether and how MRE11 acetylation affects the expression and functional status of ATR, as well as ensuring consistency between cell modeling and animal modeling treatment conditions will strengthen the scientific rigor of this research and contribute to a more comprehensive understanding of DNA repair pathways in cancer.

Conflicts of Interest

The author declares no conflicts of interest.

Declaration of AI Use

During the preparation of this work, the author used AI-assisted language tools solely for grammar correction, spelling checks, and improving readability of text originally written by the author.

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