ASO Author Reflections: ATMIN Altering the WNT Signaling Pathway via PARP1 in MSI-High Colorectal Cancer

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PAST

The nucleolus has emerged as a central guiding hub in many cancer development processes, such as DNA damage response, stress sensing, proteostasis, and cell cycle control. Overall, 10–20% of colorectal carcinomas found in patients will be categorized as having defective DNA mismatch repair systems (microsatellite instability [MSI]-high). Microsatellite stability status is clinically important and such carcinomas respond differently to 5-fluorouracil-based adjuvant chemotherapy and anti-PD1/PDL-1.¹ Small-molecule poly(ADP-ribose) polymerase 1 (PARP1) inhibitors (including olaparib, niraparib, rucaparib, and talazoparib) have already been approved by the European Medicines Agency and the US FDA to treat cancers with germline loss-of-function mutations of BRCA.^{2,3}

PRESENT

In our study recently published in *Annals of Surgical Oncology*, we investigated a DNA double-strand breaks marker, ataxia-telangiectasia mutated interactor (ATMIN), focusing on its expression and clinical characteristics in MSI patients. We demonstrated that perturbation of ATMIN changes the activities of the PARP1/transcription factor 4 (TCF4)/ β -catenin complex.⁴ The PARP1 molecule plays an essential role in cancer biology processes, i.e. genome maintenance, chromatin remodeling, transcription, replication,

energy metabolism, inflammation and immunity, and cell death.⁵ Moreover, since PARP1 represents a feasible target for pharmacological PARP inhibitors in various cancer types, we explore its specific role in colorectal cancer.

FUTURE

By specifically targeting cancers, PARP1 inhibitors afford a promising step towards precision medicine in oncology. It is believed that PARP inhibitors can be more widely used and will soon have a place in chemotherapy regimens. They may even be effective in a broader range of cancer types than originally anticipated. However, based on our findings, microsatellite states also need to be considered when using PARP1 inhibitors in colorectal cancer.

DISCLOSURE None of the authors declare any conflicts of interest.

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