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CD47 as a potential predictive biomarker in colorectal cancer

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ABSTRACT

In this week's Journal for ImmunoTherapy for Cancer, Arai and colleagues analyzed next-generation sequencing data for DNA and RNA from 14,287 patients with colorectal cancer (CRC) categorized by median CD47 expression level, and showed that CD47, a key component of innate immunity in deflecting phagocytosis, is associated with molecular subtypes of CRC, cell damage-associated molecular pattern-related genes, major oncogenic pathways, and adaptive immune checkpoint genes. Taken together, they concluded that CD47 expression is associated with activation of oncogenic pathways and an immune-engaged tumor microenvironment. Clinical outcomes data also demonstrated that high CD47 is associated with prolonged survival in patients treated with antiangiogenic and checkpoint inhibitor therapy. Biomarker studies such as this will enable broader application of immuno-oncology to patients with CRC and other malignancies.

There is promise that novel immune therapy strategies, particularly those targeting the innate immune system, will extend the benefits of immuno-oncology (IO) to patients with microsatellite stable colorectal cancer (MSS CRC). In this week's Journal for ImmunoTherapy for Cancer, Arai and colleagues analyzed next-generation sequencing data for DNA and RNA from 14,287 CRC cases. They categorized populations by median CD47 expression level and showed that the CD47 level, known as an antitumor "don't eat me signal", is associated with molecular subtypes of CRC, cell damage-associated molecular pattern (DAMP)-related genes, major oncogenic pathways, and adaptive immune checkpoint genes. Taken together, they concluded that CD47 expression is associated with activation of oncogenic pathways and an immune-engaged tumor microenvironment (TME).[1]

MSS or mismatch repair proficient CRCs comprise the vast majority of CRC cases and to date have been largely refractory to currently available adaptive immune checkpoint inhibitors (ICI), including programmed cell death protein-1/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocytes-associated protein 4 inhibitors.[2–8] This lack of response has been attributed to a TME characterized by immune suppressive cell infiltration, including T regulatory cells, myeloid-derived suppressor cells, and tumor-associated macrophages as well as high levels of immune suppressive cytokines.[9] The innate immune system, which activates adaptive immunity and provides non-specific cell protection, works via activation of macrophage and dendritic cells in turn leading to phagocytosis, proinflammatory cytokine release, and downstream T-cell activation.[10 11]

CD47 is a ubiquitous immune regulatory transmembrane protein found on the surface of both hematologic and epithelial cells. In binding to phagocyte-expressed signal regulatory protein alpha (SIRPα),[12] it provides a negative feedback signal to macrophages, thus evading phagocytosis. Upregulated by hypoxia[13] and MYC-signaling cascades,[14] binding of CD47 with SIRPα activates inhibitory SHP-1 and SHP-2 signaling on immune cells. Elevated CD47 expression has been reported in multiple tumor types and higher expression levels have been associated with poorer prognosis[15–17] in other disease states including gastric cancer and hematologic malignancies.

As such, CD47 is a checkpoint for phagocytosis initiation and a target for novel therapeutics focusing on innate immunity. Multiple agents targeting CD47 have been and are under investigation as potential therapeutic interventions, including both direct antagonists and bispecific antibodies. Further combination therapies have demonstrated promising activity in disrupting the CD47-SIRPα pathway and leading to clinical benefit. Earlier initial trials of the CD47 inhibitor magrolimab showed promise in a phase I/Ib trial in combination with cetuximab in KRAS wild type CRC,[18] but further study of this agent was terminated due to futility in phase II and III trials in patients with myelodysplastic syndrome (NCT05079230, NCT04778397). Indeed, myelosuppression in general has been a major issue with the development of anti-CD47 drugs. Current studies, such as a phase II trial of evorpacept (ALX148) in

combination with cetuximab and pembrolizumab for refractory MSS metastatic CRC (NCT05167409), are however focused on developing the next generation of checkpoint inhibitors by focusing on innate rather than adaptive immunity. Recently, the phase 2 ASPEN-06 trial in metastatic gastric cancer showed that the evorpacept combination achieved a confirmed overall response rate of 40.3% compared with 26.6% for the control arm and demonstrated a median duration of response of 15.7 months compared with 7.6 months in the full trial population.[19] Another anti-CD47, SL-172154 is a SIRPα-Fc-CD40L fusion intended to block the CD47 axis at the same time as engaging immunostimulatory CD40, designed to avoid the dose-limiting anemia observed with magrolimab for example. Preclinical and phase I data suggested that CD47 inhibition, in combination with targeted or checkpoint inhibitor antibody therapy, will augment phagocytosis, leading to neoantigen presentation and T-cell activation associated with targeted and PDL1 antibody therapy. Clinical studies targeting this molecule remind us of the difficulties in translating preclinical data on both efficacy and toxicity into the clinic.

The present study by Arai and colleagues, focused on CD47 as a prognostic and predictive biomarker. Formalin-fixed paraffin-embedded tumor samples from 14,287 patients with CRC were assessed for CD47 expression and molecular profiling, and results correlated with clinical outcomes available from an insurance claims database. Next-generation sequencing was performed on extracted DNA and RNA, and pathogenic mutations were identified per established criteria. MSI/MMR and PDL1 status were similarly determined by means of validated and commercially available assays. This represents one of the largest published datasets for molecular assessment in CRC, the major strength of the work.

The authors used median CD47 gene expression level to stratify subjects into high versus low CD47 subgroups. While the median is somewhat arbitrary, there is no established or validated standard for this marker. There were notable differences among the high versus low populations with CD47-high tumors being seen in older adults and at lower frequency in right-sided tumors. Additionally, there were fewer RAS mutations in the CD47-high group, but higher frequencies of TP53, KMT2C, and C1C mutations as well as NTRK1 fusions. CDX2 and FLT1 amplifications were lower in the CD47-high group. Consensus molecular subtype classification assessed by RNA sequencing data differed between the two groups.

Tumor-derived DAMPs reflect cell signaling that precedes phagocytosis. DAMP signature, calculated as a composite of six DAMP-related genes, was also significantly elevated in the CD47-high group compared with the CD47-low group. There was a significant difference in dMMR/MSI-H with CD47-high tumors more likely to exhibit dMMR/MSI-H, although the absolute value of 7.5% is less than that often reported in the CRC literature.[20] The CD47-high group also exhibited higher activity in oncogenic signaling pathways and adaptive immune checkpoint genes, suggesting that CD47 may hold predictive value. While there was no difference in overall survival (OS) among patients with high versus low CD47 levels, interestingly those treated with angiogenesis inhibitors and who had high CD47 levels had a significantly prolonged OS, although the difference was modest 29.9 versus 28.7 months. The difference was more clinically significant among those treated with ICIs with nearly 4-month improvement in OS among those with CD47-high expression.

In aggregate, they present a detailed exploration of CD47 expression, associations with oncogenic and immunogenic signaling pathways, and association with clinical outcomes including therapeutic response. They do so by using a large data set including both molecular and clinical response data. They illustrate a broad role for CD47 in enhancing angiogenesis, promoting tumor cell migration and invasion, and fostering an immune suppressive TME. That there was apparent predictive but not prognostic clinical implications differs from other known factors with prognostic and predictive implications, such as sidedness, RAS and RAF mutations. This also contrasts somewhat with other studies that have shown prognostic value for CD47 expression in other malignancies.

Ultimately, this work may have interventional implications. Already trials are underway exploring novel CD47 inhibitors in combination with ICI and targeted therapies (NCT05167409) as well as bispecific antibodies targeting both CD47 and PDL1 (NCT05780307). These trials, however, do not use CD47 expression as a selection biomarker. The work presented here highlights the need to do so in retrospective analyses of these interventional trials and the potential role CD47 may hold as a selection biomarker.

The promise of immune oncology, in not only increasing response for a select few but of converting an otherwise life-limiting disease into a chronic one, requires continued exploration of novel approaches to address oncogenic pathways and the TME. The mechanistic basis for the variability in response and duration of response to IO in cancer remains poorly understood. Additional biomarker studies will help to elucidate this and enable broader application of IO to patients with CRC and other malignancies. Arai and colleagues here contribute to this worthy goal with a well-designed and conducted study exploring the CD47 biomarker.

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Competing interests From 2020 to present, JS has been Editor-in-Chief of Oncogene and has sat on SABs/advisory boards for Vaccitech, Heat Biologics, Lilly, Alveo Technologies, Pear Bio, Agenus, Equilibre Biopharmaceuticals, Graviton Bioscience, Celltrion, Volvox, Certis, Greenmantle, vTv Therapeutics, APIM Therapeutics, Onconox, IO Labs, Bryologyx, Clinical Ink, Zephyr AI, Benevolent AI, Sable Bio and Linkgevity. He has consulted with Lansdowne partners and Vitruvian.

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