Cancer Research

Time for a "Plan B" in Peritoneal Metastatic Disease

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Peritoneal involvement in cancer is the harbinger of a particularly unfavorable prognosis. The peritoneal cavity microenvironment is skewed toward immunoregulatory conditions promoted by macrophage populations and innate-like B-1 B cells, which provide immune privilege to malignant cell foci. In this issue of *Cancer Research*, Haro and colleagues demonstrate that triggering innate IgM-mediated B-1a immune responses via pathogen- or danger-associated molecular pattern recognition exerts antitumor effects on peritoneal metastases by inducing classical complement cascade activation. Exploitation of innate B-1 humoral responses and noncellular immunity is a promising strategy to counter the "castling" of metastatic tumor cells in the peritoneal immunoprivileged site.

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Our understanding of cancer dynamics continues to grow and so does our awareness of its complexity. Cancer progression is a result of the evolution of malignant clones that is entwined with changes in the tumor microenvironment. It has been reported that mutations in functional driver genes in primary lesions and metastatic foci are relatively homogeneous, suggesting that the cell-of-origin determines the context for malignant transformation that influences the phenotypic outcome of cancers beyond the mutational landscape (1). In this scenario, efforts in improving the efficacy of treatment strategies are expanding beyond the genetics of clones to look at features in the tumor microenvironment; however, successful treatment of metastatic disease remains an unmet goal.

Malignant cells originate from tissues and organs with dramatically different cellular composition and function, providing malignant cells with multiple routes for homing and extravasation, stromal remodeling, and immune escape. Recently, the deconstruction of the tumor microenvironment of peritoneal high-grade ovarian cancer metastatic foci using cellular, biomechanical, and molecular methods revealed gene and protein profiles predicting the extent of disease, stromal remodeling, and patient survival (2). These data hint at common microenvironmental programs in metastatic disease across different tumor histotypes and the clinical relevance of the localization of metastatic disease as a predictor of particularly dismal prognosis.

The peritoneal cavity shares microenvironmental features with other sites of metastatic colonization, such as the central nervous system (CNS) and the bone marrow, that confer immune privilege to malignant cells due to local tissue barriers and/or immunosuppressive resident cell populations. Tumor cell localization in these areas induces local conditions that negatively impact the prognosis, such as involvement of functionally relevant anatomic structures in CNS metastases, long-term dormancy of metastatic cells in bone marrow, and dynamic solid-to-liquid-phase growth and widespread colonization of ascites in peritoneal metastases. Peritoneal colonization is a critical issue in clinical oncology as demonstrated by the remarkably high incidence of peritoneal metastatic disease in patients with ovarian cancer, pancreatobiliary tract cancers, intestinal and gastric cancers, as well as by the occurrence of peritoneal involvement in patients with extra-abdominal primary malignancies, including breast and lung cancers, and lymphomas. The presence of tumor cells within the peritoneal cavity alters normal lymphatic drainage and plays a role in the formation of ascites, limiting the effects of systemic treatment on malignant cell colonies.

The peritoneal cavity immune microenvironment in mice and humans is populated by macrophages, which are derived from peripheral blood monocytes. These macrophages exist as different subsets that differ in terms of antigen presentation complex molecules, complement and Ig receptors, and costimulatory receptors. The macrophage subsets also have the capability to promptly respond to pathogen- and other danger-associated molecular patterns through a dual host-protective and tissue-normalizing response involving iNOS and IL10 (3). Within such a skewed immunoregulatory environment, mouse B lymphocytes show a relative enrichment in B-1 B cells, a diversified subset of innate-like lymphocytes characterized by high Ig-secretion in response to T-cell–independent antigen recognition (4). $CD5^{+}$ B-1a cells have been demonstrated to be highly reliant on NFκB activation by microenvironmental stimuli including B-cell trophic cytokines (BAFF, IL21) and toll-like receptor (TLR) ligands (dsDNA, alarmins) for their expansion and Ig secretion. These cells are involved in inflammation-associated lymphomagenesis and endorse IL10-driven regulatory functions (4, 5).

In this issue of *Cancer Research*, Haro and colleagues (6) elegantly demonstrated that B-1a humoral response could be exploited against peritoneal metastatic foci associated with neoplastic ascites. By combining a pathogen-associated molecular pattern molecule–mimicking TLR and C-type lectin receptor (CLR), the authors were able to demonstrate peritoneal disease regression in mice, which they showed requires competent innate B-1 cells and secretion of IgM reactive against tumor-associated carbohydrate antigens. The proposed effector of the innate

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doi: 10.1158/0008-5472.CAN-18-3553

system–triggered immunotherapy described in their study is the complement cascade. The classical complement pathway is initiated by the assembly of the C1 complex that occurs when the recognition molecule C1q, a member of the C1 complex, binds to immune complexes. The binding of C1q is followed by the assembly of C3 convertase, C5 convertase, and terminal membrane attack complex (MAC). Multiple complement regulatory proteins (CRP) such as CD46 (membrane cofactor protein), CD55 (decay accelerating factor), and CD59 (MAC-inhibitory protein) can interfere with key steps in the assembly of C3 convertase, C5 convertase, and MAC. Regulation of complement activation results from the balance between inducing and restraining signals, a balance that may be variably skewed in the tumor microenvironment by the overexpression of CRPs in malignant cells, expression of complement decoy factors on tumor-associated vasculature, or modulation of complement-interacting pattern recognition proteins, such as pentraxin-3 (7–8). Indeed, if complement can exert an antitumor function by driving the effector activity of tumor antigen–targeting antibodies through MAC-mediated lysis and/or augmentation of antibody-dependent cell-mediated cytotoxicity, noncanonical functions of complement factors may paradoxically promote tumor progression. C1q has been shown to support angiogenesis of highly anastomotic neovessels in a wound healing type of stromal response and to modify the quality of the extracellular matrix sensing by malignant cells, eventually promoting invasion and metastasis. This action was shown to be independent of its role in complement activation (9). Additional components of complement activation, such as C3a and C5a, have been implicated in promoting tumor progression and immune escape by activating mitogenic pathways in malignant cells and coopting inflammatory and/or immunosuppressive myeloid populations (10).

In the study by Haro and colleagues, the positive effects of TLR/CLR agonism on survival were not observed in hosts unable to mount IgM responses or deficient in C3 or C4, which suggests that at least C3 cleavage through the classical complement pathway was required for such a beneficial effect. Although the induction of innate-like B-1a immune memory is a debated issue and the adoptive transfer of TLR/CLR agonist-primed B-1a cells was ineffective in ameliorating survival, the potential induction of local memory cell populations through complement bridging function between innate and adaptive responses represents an intriguing option. The highly promising results of the study from Haro and colleagues suggest the opportunity of undertaking a "plan B" for the immune-mediated treatment of peritoneal metastatic disease. Nevertheless, translation into the human setting will face the challenge of a largely incomplete understanding of human B-1 cell development, distribution, and function, and the need for shared traits in the immune interface of peritoneal metastatic foci in patients with cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

C. Tripodo is supported by the Italian Association for Cancer Research (AIRC) 5 × 1000 special program 12162 (Extension).

Received November 9, 2018; accepted November 9, 2018; published first January 2, 2019.

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Cancer Res 2019;79:5-6.