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# Colorectal cancer: the first neoplasia found to be under immunosurveillance and the last one to respond to immunotherapy?

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The first study demonstrating that human colorectal carcinoma (CRC) is under robust immunosurveillance was published a decade ago. Today, it is clear that CRC patients with Stage III lesions abundantly infiltrated by effector memory T cells have a better prognosis than subjects with Stage I neoplasms exhibiting no or poor immune infiltration. Thus, immunological parameters have a superior prognostic value for CRC patients than TNM staging or the Dukes classification. In spite of the fact that CRC is the first neoplasia found to be under immunological control, most attempts made so far to cure this malignancy with immunotherapy have failed. With the exception of a minority of lesions characterized by microsatellite instability (MSI), CRC seems to be insensitive to the blockade of immunological checkpoints with monoclonal antibodies (mAbs) specific for cytotoxic T lymphocyte-associated protein 4 (CTLA4), programmed cell death 1 (PDCD1, best known as PD-1) and the PD-1 ligand CD274 (best known as PD-L1). Thus, CRC stands in contrast with an increasing number of malignancies that respond to checkpoint blockers. Efforts should therefore be dedicated to the development of strategies to (re)instate immunosurveillance in patients with MSI$^-$ CRC, perhaps based on the identification of novel, locally relevant immunological checkpoints.

Blocking the immunological checkpoints mediated by PD-1 and CTLA4 has recently emerged as a highly promising option for the treatment of an ever-increasing number of malignancies, including (but not limited to) melanoma, non-small cell lung carcinoma, bladder carcinoma, Hodgkin lymphoma, triple-negative breast carcinoma, as well as head and neck cancer.[1] Admittedly, only a fraction of individuals with these neoplasms respond to checkpoint blockers, and definitive cures are still an exception. However, robust and durable objective responses entailing the complete disappearance of neoplastic lesions and no relapse are not considered miraculous anymore. In other words, with the advent of checkpoint blockers, curing cancer has become an attainable - rather than a merely utopian - goal.[1]

Nonetheless, there are a few cancer types that appear to be rather refractory to checkpoint blockers, and CRC is one of them. As a notable exception, patients with mismatch repair-deficient CRC lesions obtain clinical benefits from the administration of a PD-1-targeting mAb.[2] Perhaps, this is because defects in mismatch repair favor MSI, a state of genomic instability that largely increases the incidence of somatic mutations and hence the immunogenicity of cancer cells.[3] The fact that CRC does not respond to checkpoint blockers appears somehow paradoxical, since the first sophisticated analyses of the immunological tumor microenvironment have been performed on CRC specimens, yielding the conclusion that the "immune contexture" has a critical impact on the fate of patients.[4,5] The term "immune contexture" refers to the density, distribution and function of the immune infiltrate, which globally constitutes the most robust prognostic parameter for overall survival in CRC patients undergoing standard surgery and/or chemotherapy. Thus, immunological variables including the so-called "immunoscore" supersede in importance all traditional classifications of MSI$^-$ CRCs, including TNM staging and the Dukes score.[6-9] Corroborating this notion, it has been found that oxaliplatin, a platinum derivative that is widely employed in adjuvant or neoadjuvant chemotherapeutic regimen against CRC,[10,11] exerts optimal effects only in the presence of a functional immune system.[12,13] Indeed, CRCs that develop in mice lacking T cells or Toll-like receptor-4 (Tlr4) fail to respond to oxaliplatin-based chemotherapy.[14,15] Moreover, CRC patients treated with oxaliplatin have a particularly high chance of experiencing disease relapse if they bear a

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loss-of-function allele of *TLR4*.[15] Thus, immunological parameters have not only a prognostic but also a predictive value for CRC patients treated with standard chemo- or radiotherapeutic regimens.

Based on the abovementioned preclinical and clinical findings, one may have predicted that mAbs targeting immunological checkpoints would be particularly efficient in CRC patients. However, neither the blockade of CTLA4 (with ipilimumab/Yervoy™) nor that of the PD-1/PD-L1 axis (with nivolumab/Opdivo™ or pembrolizumab/Keytruda™) has conferred any major clinical benefits to patients bearing mismatch repair-proficient CRC.[16-20] Rather, only mismatch repair-proficient $MSI^+$ CRC lesions (which generally display an abundant immune infiltrate) are likely to respond to pembrolizumab.[2] The etiology of mismatch repair-deficient $MSI^+$ CRCs is very different from that of their mismatch repair-proficient $MSI^-$ counterparts. In particular, only the former are prone to accumulate somatic mutations, and this may significantly increase their immunogenicity (and hence explain their sensitivity to pembrolizumab, at least in part). Of note, other cytological events may lead to genomic instability, including tetraploidization. Supporting an etiological relationship between the amount of somatic mutations and immunogenicity, tetraploidization has also been shown to elicit immunosurveillance mechanisms (although it does not cause MSI).[21,22]

What might be the reason(s) why checkpoint blockers are not efficient in subjects with $MSI^-$ CRC? There are several speculative answers to this question. First, in CRC lesions that are massively infiltrated by effector memory T cell, immunological checkpoints might be intrinsically inactive. In such a scenario, the exogenous administration of checkpoint blockers would simply be useless. Second, CRC lesions with limited T-cell infiltration may not respond to checkpoint blockers because they cannot be properly invaded, recognized or eliminated by the cellular immune system. This may reflect the antigenic properties of malignant cells, their inability to dispatch immunostimulatory danger signals in the course of oncogenic and/or chemotherapeutic stress, or the activation of yet to be discovered immunological checkpoints that actively suppress immunosurveillance against CRC.

Further preclinical and clinical studies are warranted to understand which among the aforementioned (and mutually non-exclusive) possibilities apply. Is immunosurveillance against CRC controlled by novel immunological checkpoints that are not regulated by CTLA4 and the PD-1/PD-L1 axis? Is it necessary to combine clinically approved checkpoint blockers with additional immunotherapeutic measures including immunostimulatory compounds,[23,24] therapeutic vaccines,[25] or immunogenic cell death inducers?[26-28] Is it a requirement to intervene on the gut microbiota, which shapes the local tumor microenvironment, to reinstate failed immunosurveillance?[29] Patients with $MSI^-$ CRC are impatiently awaiting answers to these questions.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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