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AUTHOR'S VIEW

Metastasis immune-based scores predict patient survival

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ABSTRACT

Treatment of metastatic colorectal cancer is based upon the assumption that metastases are homogeneous within a patient. A comprehensive analysis of all metastases of each patient revealed the heterogeneity of the colorectal metastatic disease and its clinical impact. Complex tumor-immune interrelations shape the metastatic landscape. Adaptive immune cells and Immunoscore quantified in a random metastatic biopsy predict clinical outcome and their evaluation in the tumor microenvironment of the least infiltrated metastasis most accurately predict long-term survival. The adaptive immune cell infiltration was more informative than tumor regression and pathological response to predict long-term survival. These results highlight the clinical utility of Immunoscore for patient management. The immune response within the tumor microenvironment is an essential diagnostic criterion for colorectal cancer that has recently been integrated into the international WHO classification of Digestive System Tumors.

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The prognostic impact of T- and B-cells on stage IV metastatic patients

The management of metastatic colorectal cancer (CRC) has improved considerably through more effective surgical techniques and systemic treatments that offer potential for long-term complete remission. Despite optimal treatment, the risk of tumor recurrence and subsequent mortality is still high (>50%) after CRC metastases resection. Clinico-pathological prognostic factors like the tumor regression grade (TRG) have been proposed to identify patients who may be at risk for recurrence[1] but none of these markers has been sufficiently informative to correctly predict the outcome of the patients.

Accumulating evidence suggests that tumor progression and metastasis are shaped by the intratumoral immune landscape. From pre-cancer lesions[2] to late metachronous metastases,[3–5] the immune microenvironment plays a central role regarding cancer development and patients' survival. Cytotoxic and memory T cells infiltrating primary CRC tumors predict the survival of patients,[6–9] including early-stage cancer and locally advanced cancer patients.[10,11] Immunoscore is a standardized scoring-system based on densities of two lymphocyte populations (CD3, CD8) infiltrating the tumor (CT) and invasive margin (IM) that has a highly significant prognostic value. The accuracy, reproducibility, and prognostic value of Immunoscore were validated by an international consortium and in an independent analytical validation study.[12] In non-metastatic CRC, time to recurrence and overall survival could be largely governed by the adaptive immune reaction.[6–9] All these data support for the introduction of immune cell quantification in colorectal cancer classification.

The impact of intrametastatic immune infiltration on metastatic patient survival was revealed in a comprehensive analysis including all resected metastases (n = 338) for 153 stage IV patients undergoing complete curative metastatic resection.[4] Whole slide automatic quantification assembled detailed information about the spatial immune cell distribution within metastases. Like primary tumors, metastases were infiltrated with adaptive immune cells like total (CD3), cytotoxic (CD8), memory (CD45RO), and regulatory (FOXP3) T lymphocytes as well as B cells (CD20) in a non-uniform manner. Densely infiltrated areas could be observed in both tumor regions and overall immune densities were higher at the IM. Metastases of the same patient were heterogeneously infiltrated and each responded differently to treatment. Patients achieving pathological and radiological responses had a significantly higher frequency of highly infiltrated metastases. This heterogeneity of the tumor microenvironment in addition to the genetic heterogeneity of metastatic disease seems to relate to treatment response. The amount of infiltrating immune subpopulations and also their variability among all metastases of a patient was important for the survival. A particular importance had the least immune-infiltrated metastasis that could further promote metastatic progression as it is likely least affected by immune-based elimination.[3] This underlines the importance of evaluating immune and tumoral heterogeneity within metastases during clinical trials.

T-cells of a randomly selected metastasis have previously been associated with increased survival and response to chemotherapy.[13,14] A single biopsy accurately identifies low

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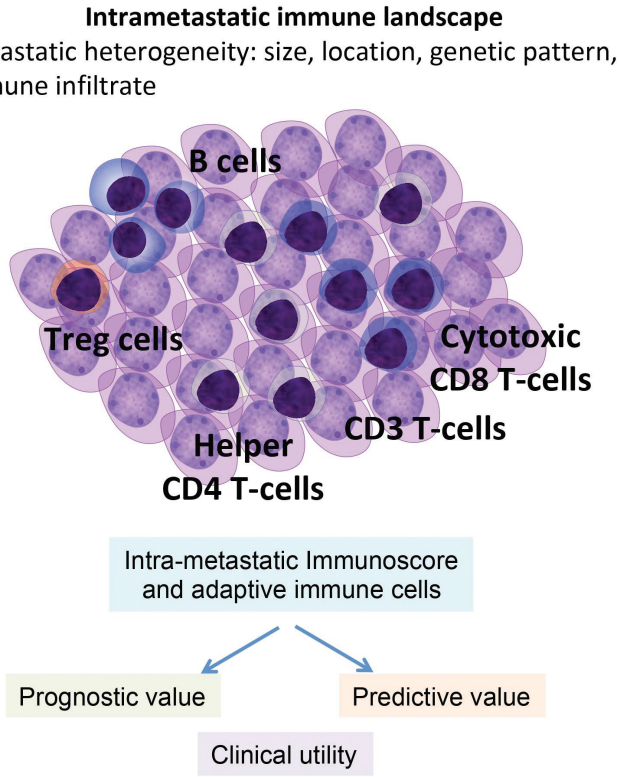

Figure 1. Intrametastatic immune infiltrates quantified in the core and invasive margin of the tumor are summarized in the Immunoscore (CD3 and CD8) of all resected metastases of stage IV colorectal cancer patients. Immunoscore and adaptive immune cells evaluation have prognostic and predictive information with important clinical impact.

infiltrated metastases, but the overall intra-metastatic immune infiltrate might be better estimated with multiple biopsies or sampling of larger tumor areas.[5] The use of a single, randomly selected tumor-biopsy could thus limit and bias the discovery of new biomarkers for targeted treatments. Immunoscore (CD3 and CD8) and TB score (CD8 and CD20) evaluated as the mean of all metastases or on a random selected metastasis were informative and statistically associated with relapse and survival, in contrast to the most infiltrated metastasis.[5] Immunoscore and TB score evaluated within the least infiltrated metastasis were best predicting clinical outcome. Immunoscore remained the only statistically significant parameter for disease-free and overall survival during multivariable analysis involving relevant clinico-pathological factors after metastasis resection (Figure 1). To predict patients' survival, Cox multivariable analysis supports the advantage of Immunoscore and TB-score compared with histopathologic features, including TRG.

The impact of T- and B-cells on response to treatment

The response of metastases to preoperative chemotherapy ± targeted therapy has been described as a prognostic factor.[1] The histological data could affect the prognostic and predictive significance of the TRG through its quality and heterogeneity. The immune infiltrate and Immunoscore of metastases are associated with the rate of the response to treatment, and with the survival of the patients. Strikingly, a strong infiltrate with adaptive immune cells was prolonging the survival of the patients, independent if they responded or not to the treatment. Furthermore, patients who had a pathological response as evidenced with a low TRG-score, but who also had a weak adaptive immune cell infiltration had short survival times. These findings underline the importance of immunological markers in determining the prognosis and response to therapy.

The adaptive immune response plays an important role in preventing tumor recurrence in metastatic CRC. Evidence for immunoediting, and the role of cytokines were also previously highlighted as mechanisms of increase intratumoral T-cell densities.[3] The natural immunity and long-lasting capacity of memory T-cells could play a central role for patients' survival. Disease free and overall survival in stage IV patients are largely governed by the state of the local adaptive immune response within the metastases, and particularly within the least immune-infiltrated metastasis. This provides further support for immunotherapy, aiming at modulating the preexisting immunity, as a foundation of cancer treatment.

To guide treatment strategies, the consensus Immunoscore has been developed as an in vitro diagnostic test (CE-IVD), and is available for routine use in FDA-CLIA-certified laboratories. Immunoscore identifies patients at risk of recurrence and death independently of the level of the tumoral development. This efficient classification method can be applied for early stage patients (stages I–II), stage III patients, and also for metastatic (stage IV) patients, within resected metastases or metastatic biopsy specimens. Immunoscore underscores limitations of the classical TNM staging and provides a refined prognostic of colon cancer patients. Indeed, the current standard classification system for colon cancer, the American-Joint -Committee-on-Cancer/Union-Internationale-Contre-le-Cancer (AJCC/UICC) TNM staging system, has recently introduced in its guidelines the immune response as essential and desirable diagnostic criteria for colorectal cancer.

Declaration of interests

JG and BM have patents associated with the immune prognostic biomarkers. JG is co-founder of HalioDx biotech company. Immunoscore® a registered trademark from the National Institute of Health and Medical Research (INSERM) licensed to HalioDx.

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