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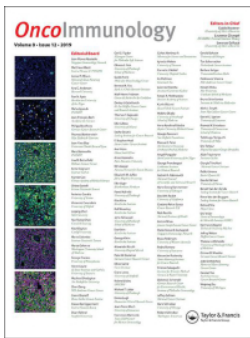
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Tumor spread or siege immunity: dissemination to distant metastasis or not

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ABSTRACT

Metastasis is the leading cause of cancer mortality. We have investigated the tumor microenvironment at all metastatic cascade steps (early-metastatic dissemination, synchronous metastasis, metachronous metastasis) to delineate the impact of tumor and immune parameters to this process. Tumors with and without signs of early metastasis invasion (venous-emboli, lymphatic-invasion, perineural-invasion, collectively, VELIPI) had similar levels of inflammatory and immunosuppressive molecules. Cancer mutations, gene expression levels or chromosomal instability did not significantly differ in primary tumors from patients with or without metastasis. In contrast, tumors without early metastasis invasion were highly infiltrated with Th1 and memory T cells and were associated with a good outcome. A cytotoxic immune signature, Immunoscore and increased lymphatic vessels at the invasive margin of tumors, protected against the generation of distant metastases. The metastatic landscape was highly heterogeneous, each of the metastases of a patient bearing diverse tumor-cell clones and diverse immune-microenvironments. The Immunoscore within a random metastasis significantly predicted major differences in patient's survival, and Immunoscore from the least immune-infiltrated metastasis was the most associated with patient long-term survival. We proposed an alternative theory of tumor evolution, where an immune selection model best-described tumor evolution in humans. Metachronous metastasis revealed that immunoedited tumor clones are eliminated, while the immune privileged clones progress underlines relationships between clonal seeding and immune surveillance and advances the understanding of cancer evolution. A strong intratumoral immune infiltrate and Immunoscore prevent the metastatic invasion at all its steps and it is associated with prolonged survival.

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Importance of the immune contexture against metastatic spread

Despite the major clinical importance of metastasis, the metastatic process remains by large unclear. The tumor develops in a complex microenvironment comprising fibroblasts, blood-vessels, lymph-vessels, and many immune cell types. The astounding complexity of multifactorial diseases such as cancer poses significant challenges to the development of precision therapies.

We previously performed a clinical study on human colorectal cancer showing that intratumoral effector-memory T-cells may control the early steps of the metastatic process. We further developed an analysis of the *in situ* immune reaction based on the location of memory T cells within distinct tumor regions. We showed that tumor recurrence and overall survival times were dependent on the presence of cytotoxic and memory T cells within the tumor.¹ The type, density, quality and location of immune cell within the tumor site predicted patients' survival better than the classical TNM system.¹⁻⁴ This led to the novel concept of cancer immune contexture^{1,3} and to the development of a consensus assay to measure the anti-tumor adaptive immune response, called "Immunoscore."⁴⁻⁶ We highlighted the continuum of cancer immunosurveillance,¹ from pre-cancer lesion,⁷ to locally advanced,^{4,6} to metastasis.⁸

Genomic data, using whole-genome sequencing of tumors, did not reveal the selective pressures within the primary carcinoma that has led to the formation of mutations associated with progression into metastasis. Therefore, an appealing hypothesis was that the selective pressure was related to the microenvironment, especially to the immune response.

We addressed three major questions. First, which primary tumor-related genes affect distant metastasis? Second, which factors among blood and lymphatic vascularization and immune reaction are associated with distant metastasis? And third, is distant metastasis a cause or a consequence of an alteration of such factors?

Integrative cancer immunology approaches allowed us to have a comprehensive view of the tumor chromosomal instability, gene expression pattern and of the immune system's evolution along with tumor dissemination to distant metastasis. We perform a comprehensive analysis of both tumors and microenvironment factors, including angiogenesis (blood and lymphatic vessels) and many immune cell subpopulations, in relation with synchronous distant metastasis. This represents the most complete analysis of the tumor microenvironment in human cancer.⁹

We analyzed three large independent cohorts of patients with colorectal carcinoma (total of 570 patients). Our analysis of the tumor-related gene expression and of chromosomal

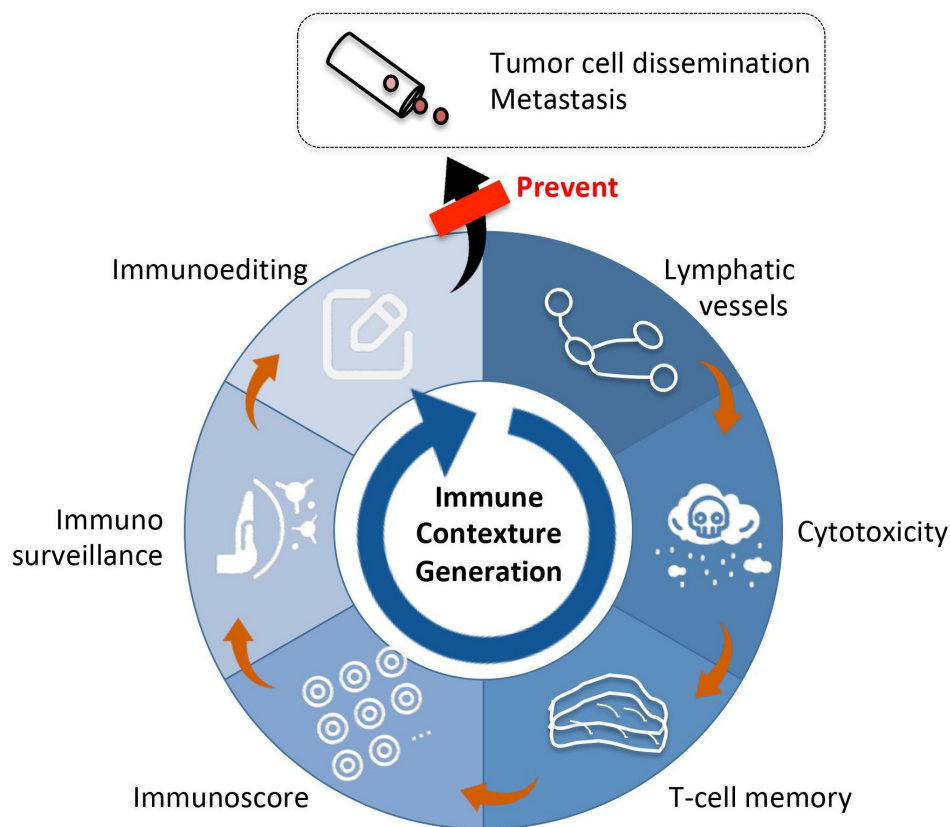


Figure 1. Prevention of metastasis circle. Parameters associated with an absence of dissemination and absence of metastatic spread. Lymphatic vessels at the invasive margin of the tumors, cytotoxicity within the core of the tumor, generation of a memory T-cell response, and high Immunoscore were associated with the generation of a productive immune contexture preventing the dissemination of tumor clones through immunosurveillance and immunoediting process.

instability did not reveal factors over-expressed or amplified implicated in tumor spread. In fact, each tumor had a unique, different set of amplifications, deletions and a particular tumor-related gene expression profile. No mutation in cancer-associated genes or pathways were associated with M-stage. Instead, mutations of FBXW7 gene were associated with the absence of metastasis (M0) and correlated with increased expression antigen presentation related-genes and of T cell proliferation.

In contrast, our comprehensive analysis of the tumor micro-environment revealed the importance of the immune contexture, lymphocyte cytotoxicity and of the lymphatic vessel densities on the metastatic process. Our data show that distant metastasis is a consequence rather than a cause of the decrease of lymphatic vessels and lymphocyte cytotoxicity in colorectal tumors, and that the immune response might be a major determinant preventing the synchronous spread of tumor cells to distant organs (Figure 1). Our comprehensive study on large cohorts of patients provides a totally novel understanding of the metastatic process in human.

Parameters associated with early-metastatic dissemination

Integrative analyses of the tumor microenvironment at all the steps of the metastatic cascade, starting with the local tumor cell invasion, the vasculature invasion, followed by the colonization at the distal sites allowed us to draw a comprehensive view the metastatic spread and to delineate the contribution of tumor and

immune parameters to this process. The early metastatic invasion is recognized by the presence of the vascular emboli (VE), lymphatic invasion (LI), and perineural invasion (PI). The VELIPI-negative tumors were characterized by increased levels of Th1 effector cells, memory T cells and Immunoscore and were associated with a good outcome. Such strong intratumoral immune presence prevents the metastatic invasion, and it is associated with prolonged survival. The main parameters associated with dissemination to distant metastases are in fact immune and not tumor-related. Any of the known cancer-associated genes or pathways were associated with the metastasis and no significant differences in known cancer gene expression levels, chromosomal instability, or key cancer-associated mutations were observed. In contrast, the Immunoscore, a cytotoxic immune signature, and increased marginal lymphatic vessels, protected against the generation of distant metastases, regardless of genomic instability.⁹ The *in situ* T cell infiltrate can now be quantified with the 'Immunoscore,' an immune-based assay that is superior to the AJCC/UICC TNM classification for colorectal cancer patients.³

The heterogeneous metastatic landscape, described as the number and size of metastatic lesions, their mutational pattern as well as their immune cell infiltrate, evolves under the immune pressure that sculpts the evolution of its clones. During metastatic progression, the immunoedited clones are eliminated, while the immune privileged clones persist and progress underlining relationships between clonal seeding and immune surveillance. The immunoediting score was associated with an active immune response, implying a predictive

potential for immunotherapy. Based on the evolvogram, we have proposed a tumor clone development model, called parallel immune selection model, that, in contrast with existing tumor-cell centric models, is linked to the intra-metastatic immune microenvironment via the immunoediting process (Figure 1).⁸

An evolutionary maps of metastasis that guides clinical decisions require the investigation of primary tumors and matched metastatic lesions, as well as of the immune microenvironment, which sculpture their evolution.⁸ The successes of immunotherapies boosting natural T-cell response against cancer have generated tremendous enthusiasm and combination immunotherapies will likely become in the future the standard for cancer treatment.¹⁰

Disclosure of potential conflicts of interest

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

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References

1. Galon J, Bruni D. Tumor immunology and tumor evolution: intertwined histories. *Immunity*. 2020;52:55–81. PMID: 31940273. doi:10.1016/j.immuni.2019.12.018.

2. Bindea G, Mlecnik B, Fridman WH, Galon J. The prognostic impact of anti-cancer immune response: a novel classification of cancer patients. *Semin Immunopathol*. 2011;33:335–340. PMID: 21461991. doi:10.1007/s00281-011-0264-x.
3. Bruni D, Angell HK, Galon J. The immune contexture and Immunoscope in cancer prognosis and therapeutic efficacy. *Nat Rev Cancer*. 2020. PMID: 32753728. doi:10.1038/s41568-020-0285-7.
4. Mlecnik B, Bifulco C, Bindea G, Marliot F, Lugli A, Lee JJ, Zlobec I, Rau TT, Berger MD, Nagtegaal ID, et al. Multicenter International Society for Immunotherapy of Cancer Study of the Consensus Immunoscope for the prediction of survival and response to chemotherapy in stage III colon cancer. *J Clin Oncol*. 2020;38(31):JCO1903205. PMID: 32897827. doi:10.1200/jco.19.03205.
5. Angell HK, Bruni D, Barrett JC, Herbst R, Galon J. The Immunoscope: colon cancer and beyond. *Clin Cancer Res*. 2020;26:332–339. PMID: 31413009. doi:10.1158/1078-0432.ccr-18-1851.
6. Pagès F, André T, Taieb J, Vernerey D, Henriques J, Borg C, Marliot F, Ben Jannet R, Louvet C, Mineur L, et al. Prognostic and predictive value of the Immunoscope in stage III colon cancer patients treated with oxaliplatin in the prospective IDEA France PRODIGE-GERCOR cohort study. *Ann Oncol*. 2020;31:921–929. PMID: 32294529. doi:10.1016/j.annonc.2020.03.310.
7. Mascaux C, Angelova M, Vasaturo A, Beane J, Hijazi K, Anthoine G, Buttard B, Rothe F, Willard-gallo K, Haller A, et al. Immune evasion before tumour invasion in early lung squamous carcinogenesis. *Nature*. 2019;571:570–575. PMID: 31243362. doi:10.1038/s41586-019-1330-0.
8. Angelova M, Mlecnik B, Vasaturo A, Bindea G, Fredriksen T, Lafontaine L, Buttard B, Morgand E, Bruni D, Jouret-Mourin A, et al. Evolution of metastases in space and time under immune selection. *Cell*. 2018;175:751–765 e716. PMID: 30318143. doi:10.1016/j.cell.2018.09.018.
9. Mlecnik B, Bindea G, Kirilovsky A, Angell HK, Obenauf AC, Tosolini M, Church SE, Maby P, Vasaturo A, Angelova M, et al. The tumor microenvironment and Immunoscope are critical determinants of dissemination to distant metastasis. *Sci Transl Med*. 2016;8:327ra326. PMID: 26912905. doi:10.1126/scitranslmed.aad6352.
10. Bindea G, Mlecnik B, Angell HK, Galon J. The immune landscape of human tumors: implications for cancer immunotherapy. *Oncoimmunology*. 2014;3:e27456. PMID: 24800163. doi:10.4161/onci.27456.