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EDITORIAL

CD103$^+$ cells at the forefront of anticancer immunity

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Owing to their unprecedented success in the management of advanced or metastatic disease, immune checkpoint blockers (ICBs) are being elevated to the rank of standard-of-care for patients affected by multiple tumors, including melanoma and non-small cell lung carcinoma (NSCLC). However, a limited fraction of these patients respond to ICBs as standalone (immuno)therapeutic interventions, calling for (1) the development of combinatorial regimens, and (2) the identification of robust prognostic and predictive biomarkers.[1,2] High levels of tumor-infiltrating lymphocytes (TILs) – in particular CD8$^+$ cytotoxic T lymphocytes (CTLs) – at baseline have been associated with positive prognostic value in multiple cohorts of cancer patients receiving not only immunotherapy, but also chemotherapy, radiation therapy and targeted anticancer agents.[3-5] This implies that the effector arm of the adaptive immune system is required for solid tumors to optimally respond to virtually any form of treatment. Accordingly, considerable efforts are being dedicated at the development of a novel tumor staging system that takes into major consideration the amount, composition and localization of the immunological tumor infiltrate, the so-called "immunoscore".[6,7] However, the molecular and cellular mechanisms that underlie the activation of a therapeutically relevant anticancer immune response have just begun to emerge.

One of the processes that has attracted attention over the past decade as a potential means for cancer cells to prime an immune response upon treatment is immunogenic cell death (ICD). This functionally peculiar variant of regulated cell death (RCD) is accompanied by the timely release of danger signals, and hence is sufficient for the priming of a tumor-specific immune response associated with the establishment of immunological memory.[8] The occurrence of ICD as opposed to relatively less immunogenic forms of RCD may explain why some anticancer treatments (*e.g.*, anthracycline-based chemotherapy, hypofractionated radiation therapy) actively drive an anticancer immune response while other (*e.g.*, cisplatin-based chemotherapy; single high-dose radiation therapy) do not.[9,10] However, it does not explain why tumors of the same type and stage can exhibit an elevated variability in the abundance and composition of the immunological tumor infiltrate.

BATF3-dependent migratory CD103$^+$ dendritic cells (DCs) had previously been shown to play a critical role in the activation of CTL-mediated immunity and hence in the rejection of highly immunogenic tumors.[11] For the most part, such a critical function depends on the capacity of migratory CD103$^+$ DCs to efficiently transport antigenic material from malignant lesions to tumor-draining lymph nodes and potently cross-prime tumor-targeting CTLs, both directly and upon the hand-off of tumor-derived antigens to resident myeloid cells.[12] Two recent reports demonstrate that not only migratory but also tissue-resident CD103$^+$ cells play a major role in anticancer immune responses.[13,14]

Ganesan *et al.* set out to identify the molecular signatures defining so-called "hot" tumors (*i.e.*, tumors with an abundant immune infiltrate) in treatment-naïve NSCLC patients. To this end, an unbiased transcriptomic profiling was performed on >100 CD8$^+$ T-cell samples purified from neoplastic lesions or adjacent non-malignant tissues. Among various other biomarkers, CD103 – which identifies a population of tissue-resident memory T (T_{RM}) cells – was strongly associated with increased T-cell abundance, proliferative potential and cytotoxic activity, ultimately identifying a subset of patients with improved outcome independent of CTL density.[13]

Spranger and colleagues performed a series of experiments in a preclinical model of melanoma that recapitulates so-called "cold" tumors (*i.e.*, tumors with a limited tumor infiltrate). In this setting, the inability of CTL to infiltrate neoplastic lesions was linked to reduced amount of tissue-resident CD103$^+$ DCs and consequent lack of appropriate chemotactic signals including C-X-C motif chemokine ligand 9 (CXCL9) and CXCL10.[14]

Altogether, these findings highlight the critical role of tissue-resident CD103$^+$ cells in the establishment of an abundant CTL infiltrate in solid tumors. Importantly, because (1) type I interferon (IFN) signaling is essential for the recruitment of CD103$^+$ DCs to the tumor bed,[15] and (2) radiation therapy has recently been shown to trigger type I IFN secretion from cancer cells,[16] it will be interesting to investigate whether radiation therapy can be harnessed to recruit CD103$^+$ cells to cold tumors and hence increase the number of patients that ultimately benefit from immunotherapy with ICBs. Irrespectively,

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both migratory and tissue-resident $CD103^{+}$ cells appear to stand at the forefront of anticancer immunity.

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