ABSTRACT

REAL TIME IMMERSION INTO THE MODE OF ACTION OF ANTI-TUMOR IMMUNOTHERAPIES IN DIFFERENT ANATOMICAL SITES : SAME THERAPY DIFFERENT OUTCOMES

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The use of monoclonal antibodies (Ab) to eliminate malignant cells can be an effective strategy to treat patients with cancer. Rituximab, an anti-CD20Ab, was the first therapeutic Ab to be used in the clinic and has significantly improved the outcome of patients with B cell malignancies or autoimmune disorders. It acts by depleting normal and malignant B cells through several possible mode of action (MOA) extensively explored in vitro: Anti-CD20Ab trigger Ab-dependent cellular cytotoxicity (ADC) by natural killer (NK) cells, bind the complement cascade (CDC) or induce Ab-dependent phagocytosis (ADP) by macrophages. In vivo, target cells can invade multiple sites [eg. blood, bone marrow (BM), lymph nodes (LN)] and thus different MOA may occur depending on the effector composition of the anatomical site. There is a general assumption that anti-CD20mAb anti-tumor activity largely relies on FcR-dependent MOA further supported by patients' data, associating polymorphisms in Fc receptors with improved therapeutic response. Despite NK cells being often considered as the central players, depletion of macrophages/monocytes in mouse models has highlighted them as essential for mediating Ab therapeutic activity. Nevertheless, despite two decades of clinical use, linking the respective contribution of these MOA in different tumor sites, to the therapeutic response of anti-CD20Ab, remains a central question to optimize Ab use in the clinic.

Through 2 photon real time in vivo imaging, we investigate anti-CD20Ab in three common sites of B cell malignancies by using fluorescent mouse-models and lymphoma cells expressing a dual FRET-based reporter of apoptosis and phagocytosis. We visualized target B cells travelling through the liver sinusoids and being depleted efficiently by Kupffer cells within minutes. By contrast, tumor cells in the BM or LN appeared largely sessile highlighting the importance of evaluating local MOAs. Like in the liver, we find ADP by macrophages to be the dominant MOA but with a reduced efficacy: B cell tumor elimination in the BM was partial with ADP being no longer active after one hour. Moreover, macrophages were present at low density in tumor-rich regions and could only reach out for neighboring tumors further impeding anti-CD20Ab activity. More suprisingly, depletion in LNs seems to be spatially regulated raising important questions for the clinic as LNs are one of the primary site of lymphomagenesis. Here, we pinpoint both temporal and spatial constraints limiting ADP, raising important questions for treatment optimization. A fine understanding of MOA at different tumor sites is key for the rational design of next-generation therapies.

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