TUMOUR IMMUNOLOGY

To be (immunosuppressive) or not to be

“ potential existence of species discrepancies in the biology of tumour-associated myeloid cells ”

Myeloid cells of the monocyte and macrophage lineage (MMLCs) accumulate in many tumours and are thought to have pro-tumoural and immunosuppressive functions. In a recently published article, Singhal et al. characterized tumour-infiltrating MMLCs in patients with early stage lung cancer and found that their accumulation does not correlate with any clinical parameters and that their function might not be primarily immunosuppressive, as mice studies had previously suggested. Additionally, they found that the expression of the T cell inhibitory receptor programmed cell death 1 ligand 1 (PDL1) by MMLCs within the tumour microenvironment may not be involved in inhibiting the activity of cancer-specific T cells.

In most murine models, tumour-infiltrating MMLCs consist mainly of monocytic myeloid-derived suppressor cells (Mo-MDSCs) and tumour-associated macrophages (TAMs). TAMs have predominantly been described as having a tumour-promoting, immunosuppressive M2 polarized phenotype in contrast to an M1, pro-inflammatory and antitumoural phenotype. However, in human tumours there is still a lack of conclusive information regarding the composition and function of MMLCs, particularly in early stages of tumour development. The role of PDL1 expression in the tumour micro-environment remains controversial in both species.

Singhal et al. reported the phenotypic profiling of tumour-infiltrating myeloid cells from 93 patients with stage I and stage II non-small-cell lung cancer. They found a similar number of MMLCs in tumour tissue when compared with non-cancerous lung tissue, suggesting no active accumulation. However, they observed a marked increase in the proportion of TAMs in the tumour tissue. Interestingly, contrary to what had been observed in late-stage human cancers, these patients had a very low frequency of Mo-MDSCs cells.

The proportion of TAMs across individual patients varied from 15% to 90% of all MMLCs. Patients who were not enriched for TAMs were enriched for an MMLC population resembling monocytes that was defined as tissue-tumour monocytes (T-Mo). Neither the number of TAMs nor of T-Mos correlated with patients' overall survival or with the functional status of tumour-infiltrating CD8⁺ T cells. A more detailed analysis revealed that TAMs had a hybrid phenotype and simultaneously expressed both M1 and M2 differentiation markers and also both T cell inhibitory and co-stimulatory receptors.

To further investigate the immunosuppressive function of the MMLCs, the authors used an ex vivo cell-based assay. Tumour-derived MMLCs from 55 patients were incubated in co-culture with cancer antigen-specific T cells and cancer cells and tested for their ability to modulate T cell function. MMLCs were divided into those suppressing, those stimulating and those having a neutral effect on T cell function. Most MMLCs showed minimal or

no effect on T cell response. No correlation was observed between the functional effect of MMLCs and clinical parameters. MMLCs with stimulatory activity had a general higher abundance of TAMs whereas suppressive and neutral activity was mostly observed in T-Mo-enriched tumours. To assess the functional relevance of PDL1 expression, the authors compared the functionality of matched PDL1^{high} TAMs with that of PDL1^{low} TAMs isolated from 24 patients. They observed no effect induced by PDL1 expression on TAMs, although they could clearly see an impairment of T cell function when PDL1 was expressed by the cancer cells.

Despite the limitations of the use of ex vivo functional assays, the results of this study suggest the potential existence of species discrepancies in the biology of tumour-associated myeloid cells that might hinder the translation of preclinical findings to the clinic. However, such differences might only reflect an early stage tumour-development situation, rarely modelled in mice, in which the myeloid cells have not yet acquired a fully committed phenotype. In either case, these data advocate for further assessments of myeloid cell functions in human tumours at different stages of development in order to establish the utility and applicability of therapeutic protocols aimed at targeting the presumed immunosuppressive myeloid cells.

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