Editorial

Back into focus: tumour-associated macrophages and their role in immune checkpoint inhibition

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The onset of immune checkpoint inhibition in clinical oncology has shed light on new and promising treatment options for various types of cancer including melanoma (1,2), non-small cell lung cancer (NSCLC) (3,4), renal cell carcinoma (5) as well as kidney cancer (6) leading to unexpected high tumour responses and shifting the focus of current research attention on the host´s immune response.

Early studies on programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) and their role during viral infections placed the major mode of action on $CD8^+$ T-cells (7,8). However, it has become clear over the time that beside the adaptive arm of the immune system, the innate immune system does also play a role in the interplay of immune checkpoint molecules (9) but only very recently a connection was found of PD-1 on tumour-associated macrophages (TAMs) and cancer.

Gordon *et al*. (10) investigated the expression of PD-1 in the context of colon cancer and found PD-1 to be expressed on approximately 50% of all TAMs in contrast to its total absence on circulating monocytes and splenic macrophages in a syngenic tumour cell model in mice.

The authors were furthermore intrigued about the differentiation state of the macrophages and flow cytometry analyses revealed that almost all $PD\text{-}1^+$ TAMs expressed M2-like markers in contrast to $PD\text{-}1^-$ TAMs which were more prone to be of M1 phenotype. Moreover, the $PD\text{-}1^+$ TAMs population increased over time, starting after 2 weeks, in the mouse model and correlate with time after engraftment and tumour volume. The results from the animal model were validated in human colorectal cancer tissues showing a "high but variable" PD-1 expression on human TAMs with more $PD\text{-}1^+$ TAMs of M2 phenotype than M1 phenotype. When the authors took a detailed look on the cellular behaviour of these cells, they hypothesized that the phagocytic effector activity of PD-1 expressing macrophages could be impaired, as it inhibits the effector function of T cells. They were able to answer this question using either $PD\text{-}1^+$ or $PD\text{-}1^-$ TAMs from murine CT26 tumours and *S. aureus* bio-particles by observing that $PD\text{-}1^+$ TAMs exhibit a diminished phagocytic activity.

Further studies employing either PD-L1 over-expressing or $PD\text{-}L1^{-/-}$ knockout cells provided more insight into PD-1/PD-L1 antagonism in myeloid cells. In fact, knockout of PD-L1 had no effect on phagocytic activity of $PD\text{-}1^-$ TAMs which was opposed by elevated phagocytosis in $PD\text{-}1^+$ TAMs while leaving the overall abundance of $PD\text{-}1^+$ TAMs unaltered by PD-L1 knockout and hinting that the PD-1/PD-L1 axis can specifically modulate TAM effector function. The authors finally concluded that the tumour-battling mode of TAMs in their model is highly influenced by the PD-1/PD-L1 axis and that anti-tumour functions of TAMs could be restored by PD-1 or PD-L1 blockade, thereby highlighting that the immune checkpoint regulatory circuitry needs to be expanded to these cells as well.

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Since the authors observed that the majority of PD-1$^+$ TAMs were of tumour-promoting M2 phenotype, special consideration of ways to re-polarize these cells might be of clinical interest (11).

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Footnote

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