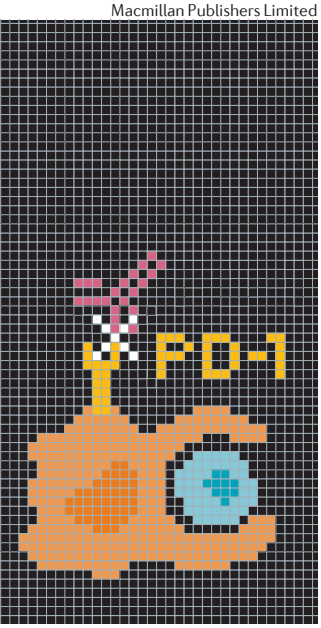
Nature Reviews Clinical Oncology | Published online 13 Jun 2017; doi:10.1038/nrclinonc.2017.87

IMMUNOTHERAPY

Exploiting PD-1 on TAMs for tumour cell kill

Macmillan Publishers Limited



In patients with cancer, the presence of tumour-associated macrophages (TAMs) portends a poor prognosis. Macrophages have been shown to express PD-1 in the context of pathogen infection; thus, the possibility that TAMs might also express PD-1 in the tumour microenvironment was explored in a new study. The results show that mouse and human TAMs express high levels of PD-1, and that PD-1 expression on TAMs is correlated with reduced phagocytosis. The researchers used HAC, a unique high-affinity protein that binds both human and mouse PD-L1, "to block PD-L1 on tumours in immunocompromised mice to determine if the inhibitory break on macrophages could be released", explains Sydney Gordon, lead author of the study.

Previous research by Irving Weissman, Gordon, and colleagues showed that macrophages express SIRPα — a 'don't eat me' receptor for CD47 expressed on the surface of some cancer cells — and wondered if macrophage PD-1 could transmit a similar signal. Their new fndings showed that, indeed, PD-L1 binding to macrophage PD-1 acts as a 'don't eat me' signal, which can be blocked by HAC or anti-PD-L1 antibodies. Thus, binding of CD47 and PD-L1 to SIRPα and PD-1, respectively, on TAMs independently deliver antiphagocytic signals. Blocking both PD-L1 and CD47 was shown to have additive effects in promoting tumour-cell phagocytosis *in vitro* and *in vivo*. "PD-1 expression inhibits the phagocytic ability of TAMs; PD-1 blockade can partially restore the ability of TAMs to phagocytose cancer cells", adds Gordon.

PD-1/PD-L1 inhibitors have been demonstrated to help reverse T-cell exhaustion. "There is probably an unrealized interplay between PD-1$^+$ TAMs and PD-1$^+$ T cells that patients in the clinic are already benefiting from. It shall be important to decipher the exact signals tranduced by PD-1 in T cells versus TAMs, and similarly, if the same or different signals are transduced in macrophages and perhaps in T cells by SIRPα."

"Now that we realize that PD-1/PD-L1 blockade activates macrophages as well as T cells, we can design macrophage-targeted therapies that could synergize with PD-1/PD-L1 inhibitors", Gordon concludes.

Lisa Hutchinson

ORIGINAL ARTICLE Gordon, S. R. *et al.* PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. *Nature* **545**, 495–499 (2017)
FURTHER READING Mantovani, A. *et al.* Tumour-associated macrophages as treatment targets in oncology. *Nat. Rev. Clin. Oncol.* http://dx.doi.org/10.1038/nrclinonc.2016.217 (2017)