Cancer immunotherapy

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T_H17 cells boosted by nanoparticle-bound fungal motifs

Mihai G. Netea & Willem J. M. Mulder

Antitumour responses mediated by T helper 17 cells can be induced by intratumourally injected hollow nanoparticles displaying the polysaccharide mannan.

At the end of the nineteenth century, William Coley, a surgeon at New York Memorial Hospital, observed the remission of a spontaneous tumour in one sarcoma patient who had a concurrent *Streptococcus* infection. Inspired by this observation, Coley prepared a combination of the bacteria *Streptococcus pyogenes* and *Serratia marcescens*, and used it in patients as an anticancer therapy[1]. Although the method was never tested in large randomized trials, and septic complications sometimes overshadowed antitumour activity, substantial evidence had accumulated for the effects of the so-called Coley's toxins, and the therapy was systematically used to treat patients with cancer until the 1960s. Today, interest in the use of comparable approaches to elicit antitumour immune responses remains high. Coley's pioneering work was an important indication that the activation of the immune system has a role in the eradication of cancer. Although at the time the mechanisms of action of Coley's toxins were unknown, it is now clear that the immune responses are triggered by the activation of pattern-recognition receptors (PRRs) by conserved bacterial motifs known as pathogen-associated molecular patterns (PAMPs). By leveraging nanotechnology, materials can now be designed to display PAMPs to induce an immune response without the risk of severe sepsis. This is exemplified by a study by James Moon and colleagues[2], published in *Nature Biomedical Engineering*, reporting the design and development of a nanoparticle incorporating structures of the polysaccharide mannan derived from the fungus *Saccharomyces cerevisiae*. By engaging the well-known PRRs dectin-2 and Toll-like receptor 4 (TLR4) on dendritic cells, the nanoparticles decorated with mannan motifs acting as PAMPs potently induced the activation of responses from the innate and adaptive immune system and did not cause overt toxicity.

Fungal mannans are potent inducers of T helper 17 (T_H17) responses[3]. Moon and co-authors now show that the mannan-displaying nanoparticles strongly induce T_H17-mediated lymphocyte differentiation, skewing the balance between T_H17 and regulatory T (T_{reg}) cells towards the activation of cellular immune responses and away from the inhibitory effects of T_{reg} cells. Notably, the capacity of the nanoparticles to activate both T_H17 and innate immune cells led to the intratumoural stimulation of CD8 cells and natural killer cells, and to potent antitumoural effects, as the authors demonstrate in mice treated intratumourally with the nanoparticles. The authors also show, in mouse models of colon carcinomas and melanoma, that the antitumoural effects of the nanoparticles were further strengthened by combining the nanoparticles with agonistic antibodies for the OX40 co-stimulatory receptor.

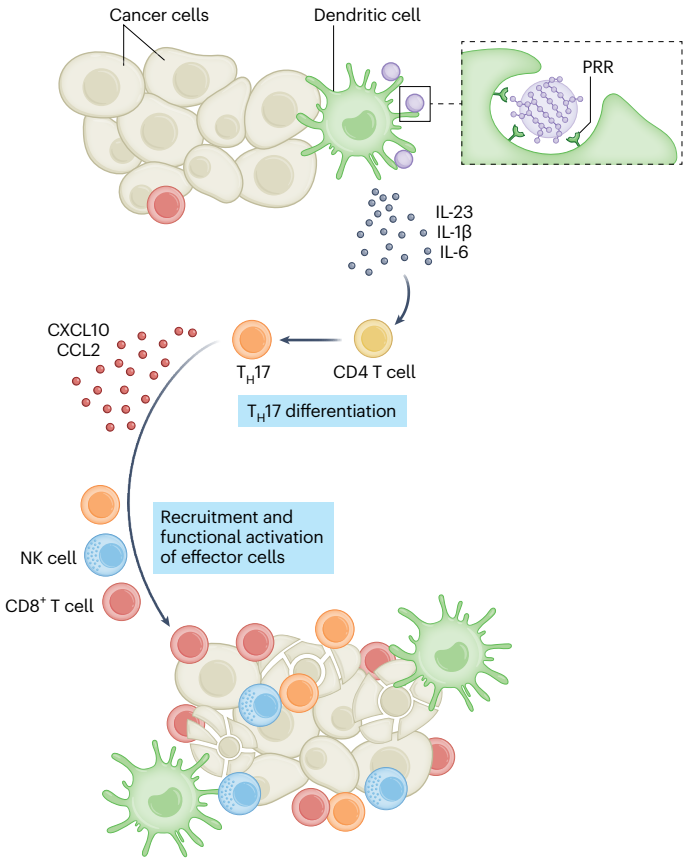

Fig. 1 | Nanoparticles decorated with pathogen-associated molecular motifs induce the activation of T_H17 cells. Nanoparticles displaying the fungal polysaccharide mannan delivered intratumourally engage PRRs on dendritic cells, inducing T_H17-mediated lymphocyte differentiation via the interleukins IL-23, IL-1β and IL-6. T_H17 cells favour the intratumoural recruitment of $CD8^+$ T cells and natural killer (NK) cells by releasing pro-inflammatory chemokines (such as CXCL10 and CCL2). Figure adapted with permission from ref. 2, Springer Nature Ltd.

The infiltration of tumours by various populations of immune cells is a hallmark of cancer. Depending on their type and function, immune cells in the tumour differentially influence disease progression[4], and their function is impacted by the tumour microenvironment[5,6]. In fact, cancer drives an increase in myelopoiesis, in particular in the production of monocytes, macrophages and neutrophils, and these cells can accumulate in the tumour periphery and shift their phenotype to boosting tumour growth[6,7]. Such immunosuppressive myeloid cells are also a major obstacle to the beneficial effects of checkpoint inhibitors on

CD8 activation and tumour elimination[8]. Moreover, CD4 lymphocyte populations (T_H1, T_H2 and T_H17) release endogenous mediators (such as cytokines) that influence antitumoural immune effects. The role of T_H1 CD4 lymphocytes is closely associated with immunosurveillance programmes, yet much less is known about the role of T_H17 lymphocytes in cancer and about their potential as immunotherapeutic target. It has been recently shown that adoptively transferred T_H17 cells reduce tumour growth and that tumour-associated interleukin-17 (IL-17) correlates with the survival of patients with cancer[9,10]. But how to induce such antitumour effects in vivo was unclear.

Moon and co-authors' findings bring new insights at several levels. At the pathophysiological level, they validate the importance of T_H17 responses in the induction of antitumoural mechanisms through the activation of CD8 and natural killer cells (Fig. 1); this opens the door to future immunotherapeutic approaches. The authors also report the role of dectin-2 and TLR4 in this process; this may facilitate the development of modulatory therapies acting at the level of these receptors, to be used either in conditions characterized by immune suppression (via stimulatory agents), or by inflammation and autoimmunity (via inhibitory approaches). At the technological level, the authors have shown the possibility to engineer nanoparticles containing complex microbial glycans (in their case, *Saccharomyces* mannans), and that the nanoparticles displayed important antitumoural effects. Other fungal glycans, especially beta-glucan, have been shown to exert potent antitumoural effects in experimental models of cancer, but these effects have been ascribed to arise from the induction of trained innate immunity[11]. The induction of innate immune activation by mannan nanoparticles may well lead to long-term trained-immunity induction (in addition to T_H17 differentiation); whether this is the case would need to be investigated in follow-up studies. And, at the therapeutic level, the authors show the strong synergism of T_H17 differentiation induced by the mannan-decorated nanoparticles and of OX40 activation by agonistic antibodies. This supports the notion that, in general, combination cancer immunotherapies are likely to be much more effective than monotherapies.

Mannans are complex structures that interact with multiple PRRs on various innate and adaptive immune cells. The relevance of any additional potential mechanisms through which mannan-decorated nanoparticles exert their effects, including effects at the level of the innate immune system such as the induction of trained immunity (which can also induce antitumour responses[12]), needs further study. Also, a distinction needs to be made between the immune stimulatory and antitumoural effects of the nanoparticles themselves. Other nanoparticle systems, such as the lipid nanoparticles used in the COVID-19 vaccines[13], can elicit strong inflammatory effects. Hence, any inflammation-mediated adverse effects would thus need to be investigated. The combination of mannan-decorated nanoparticles and anti-OX40 agonistic antibodies seems translationally promising, and hence it would be worth optimizing the nanoparticles for intravenous administration. In addition, it would be important to study whether the nanoparticles could also potentiate the effects of antibodies against immune checkpoints (such as the programmed cell death receptor 1 or the cytotoxic T-lymphocyte-associated protein 4), as well as the effects of other types of immunotherapy. Nanoparticles bearing PAMPS that activate PRRs could lead to new immunotherapies.

Mihai G. Netea [1,2] ✉ **& Willem J. M. Mulder** [1,3] ✉

[1]Department of Internal Medicine and Radboud Center for Infectious Diseases (RCI), Radboud University Medical Center, Nijmegen, The Netherlands. [2]Department for Genomics and Immunoregulation, Life and Medical Sciences Institute (LIMES), University of Bonn, Bonn, Germany. [3]Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands.
✉e-mail: mihai.netea@radboudumc.nl; W.J.M.Mulder@tue.nl

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Competing interests

The authors are scientific founders of BioTRIP and TTxD.