Is our immune system mistaking tumours for foetuses?

Tumours are abnormal growths of tissue where cells produced by the body get out of control and divide at a rapid and unregulated pace. And - when you think about it – embryos too are masses of dividing cells, deeply engrafted and invasive, growing in the mother's body. There are striking similarities between foetal and tumour development. They both rely on intense cell division, invasion of host tissues, and sustained vascularisation. Also, from an immunological standpoint, both foetus and tumour express foreign antigens and are still not rejected by the immune system. For decades, scientists have been intrigued by these similarities, but there was, until recently, no robust evidence of common mechanisms at work in both settings.

Our team hypothesized that similar immune tolerance mechanisms are in play to prevent both foetus and tumour rejection and that tumours hijack mechanisms of tolerance initially selected during evolution of the mammalian immune system to protect foetuses.

Numerous innate and adaptive immune cell types and mechanisms appear to participate in the tolerant environment that protects foetuses and the success of pregnancy but also antigen-expressing tumour cells from immune destruction. Previous studies have mainly focused on individual molecules or cells so our understanding of foetal and cancer tolerance remains fragmented. We decided to investigate foetal and tumour microenvironments using whole transcriptome microarray analysis and enrichment analyses with ontology gene sets in mice to capture the complexity of the immune system at play and better understand the global nature of immune responses at work in the tumour microenvironment and uterine tissues. The gene sets tested in our analyses cover all the gene ontology biological processes, which notably include developmental, cellular, metabolic, and immune system processes.

Besides upregulated signatures related to cell proliferation, the global comparison revealed that the only significant signatures shared by the two conditions across all biological processes and from the very first days after tumour or embryo implantation were downmodulated immune response signatures. It is quite remarkable that, besides genes related to intense cell proliferation, the only genes revealed by our studies to be robustly commonly modulated are immune response–associated genes which were all downregulated in both settings. Many more functions other than immune responses, such as cellular adhesion or cellular mobility, were also downmodulated in the cancer setting only, suggesting that tumour cells may enlist further pathways to license their development.

Our study highlighted that antigen presentation, lymphocyte activation are the central downmodulated pathways. In contrast, regulatory T-cell (Treg) related pathways are upregulated. We also showed that Tregs are not only important players, but are the conductors of the immune orchestra that plays a similar score leading to tolerance to foetuses and to tumours. Treg depletion completely reverses this immune downmodulation to an immune upregulation, which leads to foetal or tumour immune rejection.

The American writer Susan Sontag had the prescience to describe her tumour as a “demonic pregnancy.” “This lump is alive,” “a foetus with its own will” she wrote in Illness as Metaphor. Thirty-eight years later, her literary vision has been validated by systems biology. We now think that the protection of cancer cells by Tregs became the price paid for the evolution of an efficient protection of embryos and that evolutionarily selected mechanisms that protect mammalian foetuses from immune attack are hijacked to license tumour development.

Further study of these signatures could help discover targets for immune intervention to improve or to break immune tolerance. As Tregs are central to both cancer and maternal–foetal tolerance, their manipulation could have therapeutic potential, to improve the efficacy of immunotherapies on one side or help control spontaneous abortion on the other.

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