UCL research

UCL study identifies mechanism responsible for immunotherapy failure

While immunotherapy generated undreamt-of results in the treatment of aggressive and advanced metastatic cancer, they occurred in only one-fourth to one-third of patients, leaving a large majority that didn’t respond. Explaining why and increasing immunotherapy’s efficiency was the research objectives of Benoît Van den Eynde, a researcher at UCL’s de Duve Institute and director of the Brussels Branch of the Ludwig Cancer Research Institute. This 10 November 2017, his study, which revealed a mechanism responsible for the failure of immunotherapy, was published in the journal Nature Communications.

To study tumour immunotherapy, researchers usually transplant tumours into mice, starting from tumour cells grown in vitro. The problem is that transplanted tumours do not mimic the natural development of a tumour as it occurs in humans. For human cells to grow into a tumour, they must endure months, sometimes years, of thwarting traps set by the immune system. To recreate a human-like tumour environment, UCL de Duve Institute researchers established a model of an ‘induced’ tumour in mice, in which they can turn cells from the mouse into a tumour by genetically activating oncogenic pathways. They also designed the model so that the induced tumours express P1A, a tumour antigen that serves as a marker that can be detected by the immune system.

Immunotherapy functions by activating millions of lymphocytes, which function like tiny ‘soldiers’ that locate, target and kill abnormal cells. In the case of a transplanted tumour, lymphocytes work perfectly and eliminate the tumour. In the case of an induced tumour, which better mimics clinical situations, researchers were surprised to find that three weeks after the lymphocytes were deployed, they disappeared and the tumour’s size remained unchanged, even though they had been specific to the P1A antigen. Did they desert? Were they killed?

To understand what happened, the researchers injected millions of anti-P1A lymphocytes into mice bearing each tumour – transplanted and induced – and compared their fate. At the start, lymphocytes seemed to storm both tumours. But in the induced tumour model, after only four days, half of the lymphocytes seemed to be victims of programmed cell death, or apoptosis. The cancer cells of each tumour environment were identical, so the researchers also compared the tumours’ non-cancerous cells to understand what could have eliminated the lymphocytes. In the induced tumour, and only in the induced tumour, Prof. Van den Eynde and his team detected the presence of a type of cell called PMN-MDSC (polymorphonuclear myeloid-derived suppressor cell). This belongs to the family of immune cells known to help tumours elude the immune system. Induced tumour molecular analysis revealed that PMN-MDSCs produce a protein called FAS ligand, which acts directly on lymphocytes and provokes their death by apoptosis.

By identifying the FAS ligand protein as the source of one of the mechanisms responsible for the inefficiency of immunotherapy in some patients, the researchers found a target for neutralising attempts to provoke lymphocyte programmed death. In parallel, treatments are in development. The next steps for Prof. Van den Eynde’s team: a clinical human trial, and identifying other immune suppression mechanisms in the induced tumour model.

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MORE INFORMATION: https://www.nature.com/articles/s41467-017-00784-1

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