Reprogramming immune system cells to produce natural killer cells for cancer

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A team of researchers has developed a method to produce cells that kill tumour cells in the lab and prevent tumours forming in mouse models of cancer. Although the current work is in cells and mouse, if the research transfers to human biology, the new type of cell could be a new source for cell-based anticancer therapies.

The cells were produced by knocking out a single gene essential in the pathways of development of immune cells: the modified cells become a novel type, which the authors call Induced T to Natural Killer Cells (ITNK cells).

Many cell types cooperate in the immune system to battle invaders, such as bacteria and viruses, and to remove abnormal or dead cells. T lymphocytes/T cells play an important part in defending against pathogens and abnormal self cells. They are thought also to play a role in autoimmune disease.

In this research, T cells were transformed into cells similar to another type, Natural Killer (NK) cells, which commonly act against viruses and cancer cells.

"We have been examining ways to produce clinically useful immune system cells," explains Peng Li, PhD student and first author on the publication, from the Wellcome Trust Sanger Institute. "We had shown that a gene called Bcl11b was essential for normal development of immune system cells - and of particular interest in the development of T

cells.

"Here we can see the fruits of that work: we show, for the first time, that we can modify the developmental fate of immune system cells to produce a novel type that - if we can see the same effect in humans - could be of enormous value in cancer treatment."

The Bcl11b protein is a master switch that works by regulating the activity of other genes and it was known to be important in the immune system. However, this role in T lymphocyte development is entirely novel.

In the careful research, the team first showed that the Bcl11b gene was active only in T cells in the immune system and that its activity was needed at the earliest stages of production of T cells. When the team knocked out the Bcl11b gene, the mice produced no T cells.

"Remarkably, the mice lacking the Bcl11b gene produced a new type of immune system cell - the Induced T to Natural Killer cells," explains Dr Pentao Liu, senior author on the project from the Wellcome Trust Sanger Institute. "This is the first time we have seen these cells and the first time a gene regulator like Bcl11b has been shown to carry out such an important role in T cells.

"Even more important, we can see that these reprogrammed killer cells can attack cancer cells, whether in test tubes or in mouse models."

The ITNK cells killed melanoma and lymphoma cells in experiment in test tubes and were much more efficient than unmodified Natural Killer cells in the mouse and in human.

But they worked also on cancers. When tumour cells were injected into mice they produced at least tenfold fewer tumour foci in the Bcl11b-

deficient than in Bcl11b-competent mice.

"The reprogrammed killer cells were effective in preventing metastasis - spread of the tumour in mice," explains Dr Francesco Colucci, from the University of Cambridge School of Clinical Medicine Dept of Obstetrics & Gynaecology. "The killing seems to be specific to the tumour cells and the normal cells seem to be spared.

"This is a really exciting development that could, if it can be transferred to humans, lead to development of new effective anticancer treatments. The results are stunning. One problem with cellular therapies is that one needs to produce large number of cells, something this work suggests could be done fairly easily with reprogrammed killer cells"

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The team also looked at the effects of the cells in the medium term and showed that the ITNK cells continued to survive for at least three months. Equally important, they could find no evidence of abnormality in the mice carrying ITNK cells. This suggests that ITNK cells do not indiscriminately kill normal cells or cause other damage, leading to optimism that ITNK cells might perform well in future therapies.

More information: Li P et al. (2010) Reprogramming of T cells to Natural Killer-like cells upon Bcl11b deletion. *Science*. Published online before print.

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