Metabolite from pomegranates improves the function of immune cells in their fight against cancer

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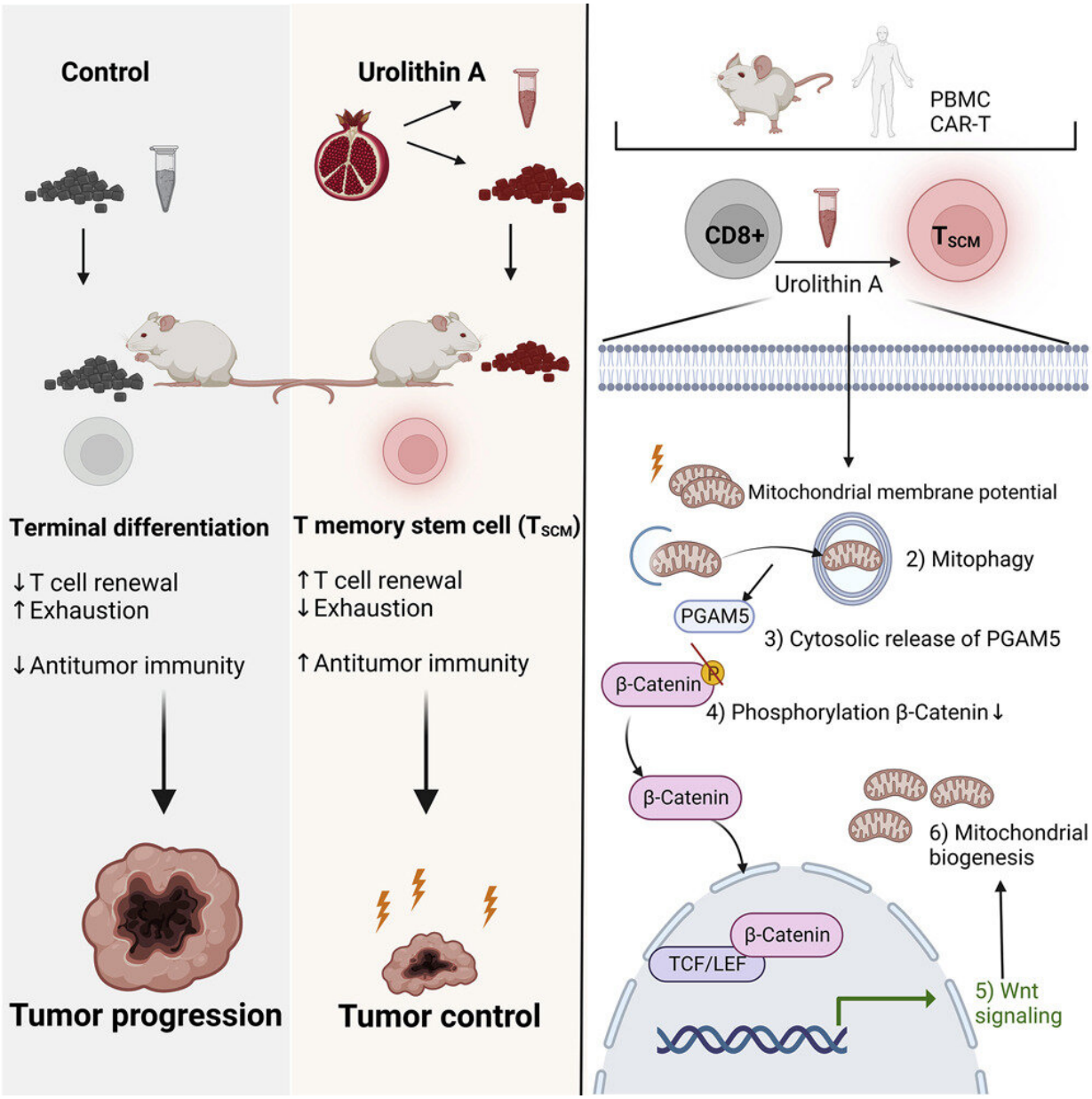

Graphical abstract. Credit: *Immunity* (2022). DOI: 10.1016/j.immuni.2022.09.014

Researchers from the Georg-Speyer-Haus in Frankfurt am Main, Germany, were able to identify a new approach for the therapy of colorectal cancer (CRC) as part of an interdisciplinary project of the LOEWE Center Frankfurt Cancer Institute (FCI). In preclinical models as well as in studies on human immune cells, they found that urolithin A, a metabolite product of the pomegranate, sustainably improves the function of immune cells in their combat against cancer.

After treatment with urolithin A, tumor-fighting immune cells, so-called cytotoxic T cells, become T memory stem cells: Potent immune stem cells that, due to their ability to divide, constantly supply the immune system with rejuvenated, non-exhausted T cells. This inhibits cancer growth by directly modulating the immune system. The results were published today in the journal *Immunity*.

Colorectal cancer remains a disease with high mortality rates in advanced stages. In recent years, numerous research findings have improved early diagnosis and therapy, although unfortunately not all patients respond adequately to novel therapeutic approaches. Current research suggests that one characteristic of tumor diseases is immune dysfunction: Immune cells that are supposed to fight the tumor are specifically suppressed by the surrounding tissue of the tumor, the tumor microenvironment. As a result, T cells, which are the natural immune response against cancer, are restricted in their function, allowing the tumor to grow and spread uncontrollably.

The research team led by Prof. Florian Greten has now come a significant step closer to a possible solution to the problem. The researchers showed that urolithin A induces a biological pathway that recycles and renews mitochondria, the "power plants" of the cell in T cells, through a process known as mitophagy. Aged and damaged mitochondria in the T cells are thereby removed and replaced by new, functional ones.

This changes the genetic program of the T cells, which are thus more capable to fight the tumor. The researchers demonstrated the therapeutic potential of urolithin A in two ways: On the one hand, urolithin A can be used as a food in the preclinical model, which limits tumor growth and even acts synergistically with existing immunotherapy. On the other hand, the benefits of urolithin A were also observed on human T cells. In vitro treatment with urolithin A rejuvenates human T cells, producing memory T memory stem cells in the laboratory.

Dominic Denk, MD, physician at Frankfurt University Hospital and first author of the study explains, "Our findings are particularly exciting because the focus is not on the tumor cell but on the immune system, the natural defense against cancer. This is where reliable therapeutic approaches are still lacking in the reality of colorectal cancer patients. By possibly improving the combination therapy with existing immunotherapies, the study opens up meaningful possibilities for further application in the clinic. We hope to use this to sustainably improve the therapy of colorectal cancer, but also of other cancers."

Building on these findings, the researchers plan to continue the successful collaboration. In future clinical trials, the application of urolithin A will be investigated in individuals with colorectal cancer.

Prof. Greten, director of the Georg-Speyer-Haus and spokesperson of the Frankfurt Cancer Institute, says, "This work proves once again how

successful the interdisciplinary concepts of the FCI are. We are very pleased that we can now quickly transfer our results to the clinic and look forward with excitement to the upcoming clinical trials."

More information: Dominic Denk et al, Expansion of T memory stem cells with superior anti-tumor immunity by Urolithin A-induced mitophagy, *Immunity* (2022). DOI: 10.1016/j.immuni.2022.09.014

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