Experiments prove 'stemness' of individual immune memory cells

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The immune system has evolved to recognize and respond to threats to health, and to provide life-long memory that prevents recurrent disease. A detailed understanding of the mechanism underlying immunologic memory, however, has remained elusive. Since 2001, various lines of research have converged to support the hypothesis that the persistence of immune memory arises from a reservoir of immune cells with stem-cell-like potential. Until now, there was no conclusive evidence, largely because experiments could only be carried out on populations of cells. This first strict test of the stem cell hypothesis of immune memory was based on mapping the fates of individual T cells and their descendants over several generations.

That experimental capability was developed through a long-term collaboration, focused on clinical cell processing and purification, between researchers based in Munich and Seattle. Since 2009, the groups of Prof. Dirk Busch at the Technische Universität München (TUM) and Prof. Stanley Riddell at the Fred Hutchinson Cancer Research Center have combined their technological and clinical expertise under the auspices of the TUM Institute for Advanced Study. The University of Heidelberg, the University of Düsseldorf, the Helmholtz Center Munich, the German Cancer Research Center (DKFZ), and the National Center for Infection Research (DZIF) also contributed to the present study.

Homing In On The "Stemness" of T Cells

After generating an immune response in laboratory animals, TUM researchers Patricia Graef and Veit Buchholz separated complex "killer" T cell populations enlisted to fight the immediate or recurring infection. Within these cell populations, they then identified subgroups and proceeded with a series of single-cell adoptive transfer experiments, in which the aftermath of immune responses could be analyzed in detail. Here the ability to identify and characterize the descendants of individual T cells through several generations was crucial.

The researchers first established that a high potential for expansion and differentiation in a defined subpopulation, called "central memory T cells," does not depend exclusively on any special source such as bone marrow, lymph nodes, or spleen. This supported but did not yet prove the idea that certain central memory T cells are, effectively, adult stem cells. Further experiments, using and comparing both memory T cells and so-called naive T cells – that is, mature immune cells that have not yet encountered their antigen – enabled the scientists to home in on stem-cell-like characteristics and eliminate other possible explanations.

Step by step, the results strengthened the case that the persistence of immune memory depends on the "stemness" of the subpopulation of T cells termed central memory T cells: Individual central memory T cells proved to be "multipotent," meaning that they can generate diverse types of offspring to fight an infection and to remember the antagonist. Further, these individual T cells self-renew into secondary memory T cells that are, again, multipotent at the single-cell level. And finally, individual descendants of secondary memory T cells are capable of fully restoring the capacity for a normal immune response.

Insights With Clinical Potential

One implication is that future immune-based therapies for cancers and other diseases might get effective results from adoptive transfer of small

numbers of individual T cells. "In principle, one individual T cell can be enough to transfer effective and long-lasting protective immunity for a defined pathogen or tumor antigen to a patient," says Prof. Dirk Busch, director of the Institute for Medicial Microbiology, Immunology and Hygiene at TUM. "Isn't that astonishing?"

"These results are extremely exciting and come at a time when immunotherapy is moving into the mainstream as a treatment for cancer and other diseases," says Prof. Stanley Riddell of the Fred Hutchinson Cancer Research Center and the University of Washington. "The results provide strong experimental support for the concept that the efficacy and durability of T cell immunotherapy for infections and cancer may be improved by utilizing specific T cell subsets."

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