Researchers discover the origins of key immune cells

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Chronic inflammatory conditions are extremely common diseases in humans and in the entire animal kingdom. Both in autoimmune diseases and pathogen-caused diseases, the inflamed areas are rapidly colonized by antibody producing B lymphocytes – which organize themselves in highly structured areas called "lymphoid follicles". The scaffold of such follicles is provided by follicular dendritic cells (FDCs). FDCs have important roles in the development of immune responses, since they trap antigens for protracted periods of, thereby training B lymphocytes to recognize the invaders. However, FDCs can also play deleterious roles in disease, because they can provide sanctuaries for infectious pathogens such as the human immunodeficiency virus and prions.

But where do FDCs come from? Because they can arise so quickly, it has been discussed that FDCs might arise from circulating blood cells. Conversely, if FDCs are immobile cells, they would have to be ubiquitous in order to support formation of lymphoid follicles in any given place of the body.

In a paper which is being published in the journal *Cell*, Dr. Nike Kräutler in the team of Professor Adriano Aguzzi at the University of Zurich went after the latter question. Using novel markers identified in the Aguzzi laboratory in the past several years, they have identified clues suggesting that FDC precursor cells exist in the wall of blood vessels. This would explain many of the properties of FDCs, including the broad range of organs in which lymphoid follicles can arise during inflammatory conditions – because blood vessels are present in most

organs of the body.

The specific morphology of the putative FDC precursor cells suggested that they be identical with mural cells, pluripotent cells which decorate vessel walls. One typical marker of mural cells is platelet derived growth factor receptor β (PDGFR-β). However, FDCs do not express PDGFR-β. Aguzzi and colleagues reasoned that this may be due to mural cells losing expression of PDGFR-β during their maturation into FDCs. In order to test this hypothesis, they used a sophisticated cell-lineage tracing approach. "Reporter" mice were generated whose FDCs would be stained by a blue marker if they had expressed PDGFR-β at any point in their life, even if PDGFR-β expression was suppressed at the time of analysis. Under these conditions, Kräutler and Aguzzi found that FDCs express the blue marker, indicating that they stem from another cell type which had previously expressed PDGFR-β.

The final piece of evidence nailing the origin of FDCs came from a transplantation experiment. Kräutler and colleagues isolated pure vascular mural cell populations from fat tissue of mice, which were then introduced into collagen sponges. The sponges were then transplanted into a special mouse strain that cannot develop FDCs. Upon induction of an inflammatory state, FDCs and lymphoid follicles were found to arise within the collagen sponges. Because the FDCs could not possibly have developed from the host animals, this experiment positively demonstrates that mural cells can give rise to FDCs.

The work that is currently being published in *Cell* clarifies a question that has been controversially discussed for the last 25 years. The recognition that FDCs derive from pluripotent mural cells helps understanding autoimmune and pathogen-driven chronic inflammatory conditions, the generation of FDC-derived tumors, and certain aspects of the pathogenesis of acquired immunodeficiency syndrome (AIDS) and of prion infections. Because FDCs are an important site of prion-

replication outside the brain, there is reason to hope that interfering with the differentiation of vascular FDC precursors may play a positive role in preventing prion infections.

More information: Nike Julia Krautler, Veronika Kana, Jan Kranich, Yinghua Tian, Dushan Perera, Doreen Lemm, Petra Schwarz, Annika Armulik, Jeffrey L. Browning, Michelle Tallquist, Thorsten Buch, José B. Oliveira-Martins, Caihong Zhu, Mario Hermann, Ulrich Wagner, Robert Brink, Mathias Heikenwalder, and Adriano Aguzzi. Follicular Dendritic Cells Emerge from Ubiquitous Perivascular Precursors. *Cell*, 5 July, 2012. dx.doi.org/10.1016/j.cell.2012.05.032

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