

Researchers elucidate transport pathway of immune system substances

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To transport substances from the site of their production to their destination, the body needs a sophisticated transport and sorting system. Various receptors in and on the cells recognize certain molecules, pack them and ensure that they are transported to the right place. One of these receptors is Sortilin. It is present in the cells of the nervous system, the liver, and the immune system. Studies by Stefanie Herda and Dr. Armin Rehm (Max Delbrück Center for Molecular Medicine, MDC, Berlin-Buch and Charité–Universitätsmedizin Berlin) and the immunologist Dr. Uta Höpken (MDC) have now shown that the receptor Sortilin plays an important role in the function of the immune system.

In the search for diseases, the T cells of the immune system go on patrol throughout the body. If they encounter a cell infected by viruses, they bind to it and secrete substances that ensure that the [target cell](#) dies. One of these substances is granzyme A, which penetrates the infected cell and induces programmed cell death. In addition, the immune cells secrete [interferon-gamma](#), which induces the surrounding cells to have a stronger immune response.

Interferon-gamma is produced by [cytotoxic T cells](#) (formerly: T killer cells), T [helper cells](#) and [natural killer cells](#). It enhances the activity of immune cells and induces other cells of the body to increasingly present fragments of the pathogen on their surface so that the T cells can find the affected cells more easily. To facilitate the transport of interferon-gamma from the interior of the T cell where it is produced to the [cell membrane](#) where it can be released, the cell uses its interior processing

and transport system, to which the [Golgi apparatus](#) belongs.

If one were to imagine the Golgi apparatus as a post office, Sortilin's task is to wrap the interferon-gamma cargo into these packages and navigate them to their destination. Without Sortilin, however, the packages cannot be delivered and remain in the post office, that is in the Golgi apparatus. Correspondingly, in the serum, i.e. outside of the cell, too little interferon-gamma is present. Thus, lack of interferon-gamma is not caused by diminished production, but rather by reduced or abrogated transport activity, eventually preventing the interferon-gamma from reaching its destination. This in turn leads to a weakened immune defense system since the interferon can only exert its immune-stimulating effect when it is released from the [immune cells](#).

While the transport of interferon-gamma is disturbed in the absence of Sortilin, the transport of granzyme A, which destroys diseased cells directly, is more effective. Granzyme A uses another transport pathway, which is dependent on a multi-part receptor complex. This complex includes the molecule VAMP7. Together with its binding partners, this molecule ensures that transport packages containing granzyme A as part of its cargo reach their correct address in the cell. The work of the researchers led by Dr. Rehm suggests that Sortilin has an indirect influence on VAMP7 by promoting transport routes that lead to the degradation of VAMP7. In cells lacking Sortilin the researchers were able to detect increased VAMP7. This condition allowed for a more efficient transport and therefore an increased release of granzyme A.

Accordingly, Sortilin influences two different transport pathways for key immunological effector molecules in an opposite manner. Without Sortilin, less interferon-gamma is available, instead there is an increased level of granzyme A. But the increased concentration of granzyme A cannot compensate for the interferon gamma deficiency. In the experiment, the immune system of mice in which the researchers had

deactivated Sortilin was significantly weaker and the fight against viruses and bacteria was less effective. The advantage for these animals, however, was that autoimmune diseases – that is, diseases in which one's own immune system reacts against the body – were much less pronounced.

More information: The sorting receptor Sortilin exhibits a dual function in exocytic trafficking of interferon- γ and granzyme A in T cells, *Immunity*, [doi: 10.1016/j.immuni.2012.07.012](https://doi.org/10.1016/j.immuni.2012.07.012)

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