

Metabolic sensor causes granulomas to form

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Granulomas are tissue nodules of immune cells that occur in diseases such as tuberculosis and sarcoidosis and can damage many organs. For the first time, a team of researchers at the Center for Pathobiochemistry and Genetics at MedUni Vienna has identified what causes them to form. It is the chronic activation of the metabolic sensor mTOR (mammalian Target Of Rapamycin) that is responsible for the formation of granulomas. The scientists also discovered that, in sarcoidosis (in which granulomas cause damage to the lungs), this mechanism leads to a course that is chronic and difficult to treat. Since mTOR inhibitors belong to a group of drugs already licensed for clinical use, these findings, which have now been published in *Nature Immunology*, offer new and quickly testable treatment options.

Granulomas are clusters of [macrophages](#) in inflammatory diseases, which occur as nodules of tissue in many different types of organ and can drastically impair the tissue function. Normally, macrophages are important immune defence cells, eating and disposing of bacteria or old endogenous cells. For reasons that have hitherto been unknown, macrophages swell up in granulomatous inflammations and cluster together – forming the basic structure of the granuloma. Up until now, it was not known which molecular switches in the macrophages are responsible for this change. A team led by Thomas Weichhart, research group leader at the Institute of Medical Genetics of the Medical University of Vienna, has now been able to prove that the chronic activation of a single molecule is enough to trigger granulomas.

"We discovered that the chronic activation of the mTOR protein directly

in macrophages is enough to form spontaneous granulomas in many tissues in the [animal model](#)," explains Monika Linke, PhD student at MedUni Vienna and lead author of the study. mTOR is a central sensor of the cells that measures the availability of nutrition and energy and regulates cell metabolism accordingly, which in turn has a great influence upon the immune response. The activation of mTOR leads to uncontrolled cell replication, prevents cell death and leads to the swelling of the macrophages. "To a certain extent, granulomas can be compared to benign tumours," explains Linke. The activation of mTOR regulates metabolism in the macrophages and makes for increased glucose dependence, a feature that also occurs in tumour cells, and is currently the subject of intensive research with a view to identifying a therapeutic vulnerability.

Sarcoidosis: active mTOR protein leads to progression of the disease

The research group was also able to transfer these extremely interesting basic scientific study findings directly to patients: sarcoidosis is a disease that affects approximately 1 in 3,000 people and in which the granulomas primarily damage the lungs. The author Thomas Bernhard was probably the most well-known sarcoidosis patient in Austria, having written about his disease in his book "Die Kälte. Eine Isolation" [The cold. An isolation]. In many cases the disease has a favourable outcome, for which no treatment is needed. However, in approximately 20 – 30% of cases the disease takes a chronic, progressive form, which is often very difficult to treat and can result in death.

Weichhart: "We discovered that, especially in the progressive form of sarcoidosis, mTOR is also active and leads to progression of the disease." These findings are of immediate practical significance: mTOR inhibitors are licensed drugs, which are already being successfully used

in transplant medicine and cancer treatment.

The results indicate that mTOR inhibitors could also have a therapeutic effect in progressive sarcoidosis. In the animal model, these drugs caused the granulomas to disappear very quickly. The researchers are now performing tests using a larger patient group to see whether the inhibition of mTOR can indeed cure [sarcoidosis](#). For Thomas Weichhart, who has been investigating mTOR for many years, these results are also an important statement: "This once again underscores the importance of basic research and shows how quickly some findings can be transferred to patients." The researchers believe that, in future, the animal model will also provide new information about the formation of [granulomas](#) in other diseases such as tuberculosis, which affects many millions of people throughout the world.

More information: "Chronic mTORC1 signaling induces macrophage granuloma formation and marks sarcoidosis progression." M. Linke, H. T. Thanh Pham, K. Katholnig, T. Schnöller, A. Miller, F. Demel, B. Schütz, M. Rosner, B. Kovacic, N. Sukhbaatar, B. Niederreiter, S. Blüml, Peter Kuess, Veronika Sexl, M. Müller, M. Mikula, W. Weckwerth, A. Haschemi, M. Susani, M. Hengstschläger, M. J. Gambello, T. Weichhart; *Nature Immunology*, [DOI: 10.1038/ni.3655](https://doi.org/10.1038/ni.3655)

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