Scientists discover a tap that controls the flow of pro-inflammatory molecules

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One of the major therapeutic targets for inflammatory diseases is the inflammation-inducing molecule TNF. However, excess levels of TNF cause side effects and can lead to diseases. In a study now published in *eLIFE*, the research team led by Colin Adrain of the Gulbenkian Institute of Science (IGC, Portugal) discovered a new protein, called iTAP, that controls the levels of TNF in circulation by regulating its release from immune cells. These findings open avenues for the design of improved therapeutics for inflammatory diseases.

TNF is released from the surface of immune cells called macrophages in response to infection, and helps to coordinate the actions of the immune system to fight the pathogen. Although beneficial in clearing infection, excess or prolonged TNF release can be harmful. Elevated levels of TNF are associated with septic shock, can drive the development of some cancers, and are strongly associated with chronic inflammatory diseases (e.g. rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, ankylosing spondylitis).

Specific therapies that block the actions of TNF are in clinical use, but are not always effective on their own, and patients sometimes stop responding to the drugs during the course of treatment. A better understanding of the machinery that controls TNF release from cells is important to identify new strategies to treat inflammatory diseases."For some years now, we have focused on identifying the molecular pathways involved in TNF secretion. TNF molecules are normally attached to the cell surface, but to perform many of their functions, they have to be

released from the membrane by an enzyme called TACE. Now we have found a new part of the machinery called iTAP, whose role is to prolong the amount of time TACE spends on the cell surface to promote TNF release," says Colin Adrain, leader of the IGC Membrane Traffic Laboratory and lead author of this study.

The researchers found that when the iTAP gene is removed from human or mouse cells, the release of TNF is reduced substantially, because TACE is destabilized on the cell surface and degraded in lysosomes, the cell's garbage disposal unit.

"If we think of iTAP as a tap that controls TNF release into circulation, controlling iTAP through a drug may enable partially closing the TNF tap in a patient with an inflammatory disease. This may help reduce harmful inflammatory responses without impeding the TNF functions necessary for the normal functioning of the body," explains Ioanna Oikonomidi, a Ph.D. student at IGC and the first author of the article. But the IGC team warns that "more research and validation is needed before this discovery can translate into clinical advances."

More information: Ioanna Oikonomidi et al, iTAP, a novel iRhom interactor, controls TNF secretion by policing the stability of iRhom/TACE, *eLife* (2018). DOI: 10.7554/eLife.35032

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