Newly-discovered link between biological processes reveals a novel way to control inflammation

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Group pic of Malhotra's research team at CRG. Credit: CRG 2018. All rights reserved.

Scientists at the Centre for Genomic Regulation (CRG), part of the

Barcelona Institute of Science and Technology (BIST), in Barcelona, Spain, have uncovered the biological details of how cells produce a crucial molecule involved in inflammation, pointing toward a new avenue for the development of anti-inflammatory drugs. The findings are published this month in the journal *Developmental Cell*.

The team's research, led by Vivek Malhotra, head of the Intracellular Compartmentation group at the CRG, focuses on IL-1β, a protein released by immune cells in response to danger signals such as bacterial infection or tissue damage, triggering inflammation to fight off infection and aid healing.

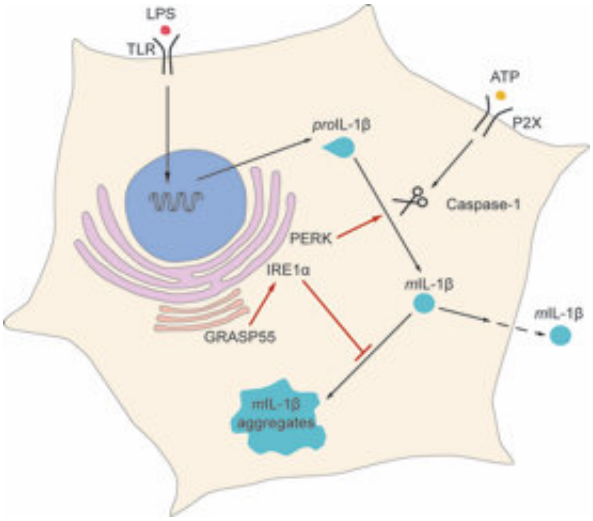
Excessive production of IL-1β leads to unwanted inflammation, which has been implicated in a wide range of illnesses including auto-immune, neurodegenerative and cardiovascular diseases. Making sure that IL-1β is produced at the right time and in the right place is therefore vital for health.

Despite its important role in inflammation, there is still a lot of mystery around how much IL-1β is made and how it is released from immune cells. For example, IL-1β lacks the usual molecular "identity badge" found on many other proteins that are exported out of cells, which directs them through the usual processing pathway.

Recent reports have suggested that IL-1β production might be dependent on something known as the unfolded protein response (UPR), a failsafe that prevents abnormal proteins building up inside cells when they are in stressful conditions such as low nutrient levels. But growing evidence points to a role for the UPR in producing proteins under normal conditions, too.

In search of the connection between the UPR and IL-1β production, Malhotra and Marioara Chiritoiu, first author of the study, took a clue

from simple slime moulds and yeast that use similar pathways to secrete proteins when they are stressed. One of the key players in this process is known as GrpA, which is very similar to a protein called GRASP55 in humans and mice.



Activation by danger molecules causes production of pro interleukin 1(IL)-1ß. ProIL-1ß is cleaved by caspase 1 to generate mature (m) IL-1ß, which is secreted by macrophages to control inflammation. Our new findings reveal that PERK arm of unfolded protein response (UPR) controls caspase 1 mediated production to mIL-1ß. Inhibition of the IRE1 arm of UPR causes intracellular aggregates of mIL-1ß, which is not secreted. The Golgi associated protein GRASP55 appears to control the activity of IRE1. So PERK and IRE1 act sequentially to produce the right quantity and form mIL-1ß for its secretion. These newly identified proteins can be targeted to control secreted mIL-ß dependent inflammatory response. Credit: Malhotra lab.

Using genetic engineering techniques, the CRG team created mice lacking the GRASP55 gene and took a close look at their immune cells. Straight away, they noticed that IL-1β was building up in clumps (aggregates) inside the cells instead of being released, meaning that it

was no longer able to trigger inflammation. These aggregates are bad news, as they mean that neither IL-1β nor the immune cells in which it is produced can respond properly to inflammation triggers.

The researchers also found that another protein playing an important role in activating the UPR under times of stress, known as IRE1α, was no longer working properly in these cells.

Discovering this crucial connection between the UPR, GRASP55 and IL-1β suggests that interfering with these pathways could be a potential way to control the production and release of this inflammatory molecule.

Drugs that block the UPR are currently being developed as treatments for neurodegenerative diseases involving abnormal proteins, including Alzheimer's, Parkinson's and Huntington's, so it will be interesting to see whether this approach could also be applied for finding new anti-inflammatory therapies.

"These findings are very important for understanding how proteins like IL-1β, which are not secreted using the standard pathway, are released from cells," says Malhotra.

"It will be very interesting to find out whether GRASP55 and UPR prevent other secreted molecules from aggregating inside cells and play a more general role in controlling the quantities of proteins that are destined to be exported," concludes Chiritoiu.

More information: Marioara Chiritoiu et al, GRASP55 and UPR Control Interleukin-1β Aggregation and Secretion, *Developmental Cell* (2019). DOI: 10.1016/j.devcel.2019.02.011

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