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Alternative oxidase from a marine animal works in mammals and combats bacterial sepsis

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Mitochondrial alternative oxidase from a sea-squirt works as a safety valve for stressed mitochondria. This property enables it to stop the runaway inflammatory process that leads to multiple organ failure and eventual death in bacterial sepsis.

Mitochondria are the generators of cellular energy. Based on work just published, in which Marten Szibor and Howard 'Howy' Jacobs from the Institute of Biotechnology, University of Helsinki, are key contributors, it is becoming clear that mitochondria also participate in the signalling process that leads to the activation of macrophages.

Macrophages are one of the front-line components of the immune system. When stimulated by lipopolysaccharide, a common chemical constituent of the outer envelope of bacteria, they undergo a reprogramming of metabolism. Mitochondria switch to the production of oxygen radicals, alerting the body to the threat. Sepsis occurs when the process spins out of control.

"The mitochondrial switch initiates a cascade of pro-inflammatory signals. But the process can be counteracted by various different treatments which limit oxygen radical production," says Howy Jacobs.

For a number of years, Jacobs' group has been studying the properties of the mitochondrial "alternative oxidase", AOX. AOX can buffer many

pathological stresses in mitochondria, including the excessive production of oxygen radicals. Together with collaborators, they have now demonstrated its potential to combat the runaway inflammatory process that leads to multiple organ failure and eventual death, in bacterial sepsis.

AOX is not found naturally in mammals, so the group have turned to the sea-squirt Ciona as a source. Remarkably, the AOX gene from this species is fully functional when expressed in human cells or model organisms like fruit-flies or mice.

AOX by-passes the mitochondrial energy system when it isn't fully functional due to chemical damage, toxins, genetic errors or overload. Under normal conditions, it seems to have no effect on cellular processes, yet it acts as a kind of safety valve when the mitochondria become stressed. So AOX is effective in blocking sepsis, because it relieves the build-up of metabolic intermediates that otherwise lead to excessive oxygen radical production.

"More people die of sepsis than of cancer. So anything that improves our understanding of how it develops and how to fight it, should have dramatic life-saving implications. It's obviously far too soon to say whether AOX could be used as an actual therapy for sepsis, and if so, how best to deliver it. But equally, using the knowledge obtained in this project may lead to simpler, 'chemical' ways of producing a similar outcome and saving many lives," Howy Jacobs says.

More information: Evanna L. Mills et al. Succinate Dehydrogenase Supports Metabolic Repurposing of Mitochondria to Drive Inflammatory Macrophages, *Cell* (2016). DOI: 10.1016/j.cell.2016.08.064