Inflammatory responses in flies give insights into human diseases

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Small male Drosophila melanogaster fly. Credit: André Karwath

Francis Crick Institute scientists have discovered that fruit flies and humans have much in common when it comes to inflammatory responses to stress or injury. Their research gives insights into human diseases and possible new treatments.

Drosophila fruit flies were used as a model for the response to actin due the powerful genetics in that organism as well as their lack of redundant genes. However the findings will lead the way for future investigations into if and how extracellular actin drives inflammation in mammals, including humans.

Things like trauma, burns or strenuous exercise all cause an inflammatory response. But unlike inflammation caused by infection, no microbes need to enter the body - which is why this is called a sterile inflammatory response. While sterile inflammation generally serves an important purpose, if uncontrolled, it's thought to contribute to many diseases, from cancer to neurodegeneration. All animals need to be able to detect injuries so they can set in motion the inflammatory responses that pave the way for tissue repair.

Sterile inflammatory responses are initiated by signals from damaged cells. These signals include molecules from inside cells that become exposed when the cells' membranes become leaky. The signals are known as damage-associated molecular patterns (DAMPs).

Work led by Francis Crick Institute scientists studying Drosophila fruit flies has revealed that actin, an abundant protein that makes up part of the cell cytoskeleton, can act as a DAMP and can induce sterile inflammatory responses. The findings have implications for human diseases where actin has been found in places where it shouldn't be - indicating that in some cases the protein might be prompting harmful inflammatory responses and worsening disease.

Naren Srinivasan and Oliver Gordon in Caetano Reis e Sousa's group at the Crick carried out much of the work. They explain: "Sterile inflammation can be initiated when molecules that are kept inside cells are released when cells die and their plasma membranes become leaky. Our lab previously found that, in mammals, one such molecule is actin. As actin has been highly conserved throughout evolution, we wanted to know whether it can serve as a signal for tissue damage in simpler organisms such as Drosophila and whether the latter is a useful model to study sterile inflammation."

The researchers injected Drosophila with purified actin and saw signs of

systemic inflammation. They showed that this response depends on activation of a signaling pathway called JAK/STAT, which was already known to be induced in response to a range of different stresses, all of which are likely to result in cell death.

Although some parts of the actin-sensing machinery are different in flies and mammals, there seems to be a common need to detect extracellular actin, which indicates that this pathway is important. The research also showed that other parts of the signaling machinery are essentially the same in flies and mammals.

Professor Reis e Sousa says: "Extracellular actin has been observed in clinical settings including acute respiratory distress syndrome, Alzheimer's, rheumatoid arthritis, cystic fibrosis, among others. Our data indicate that extracellular actin could instigate inflammatory responses in these situations and exacerbate disease. Therefore limiting the availability of actin in circulation might help alleviate these damaging immune responses. This is an idea that we are now investigating."

Another next step is identifying the receptor that detects actin in Drosophila. This will allow scientists to assess the contribution of released actin to various diseases and to find orthologues, or genes with the same function, in mammals, including humans.

More information: Naren Srinivasan et al. Actin is an evolutionarily-conserved damage-associated molecular pattern that signals tissue injury in, *eLife* (2016). DOI: 10.7554/eLife.19662

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