Insights into a versatile molecular death switch

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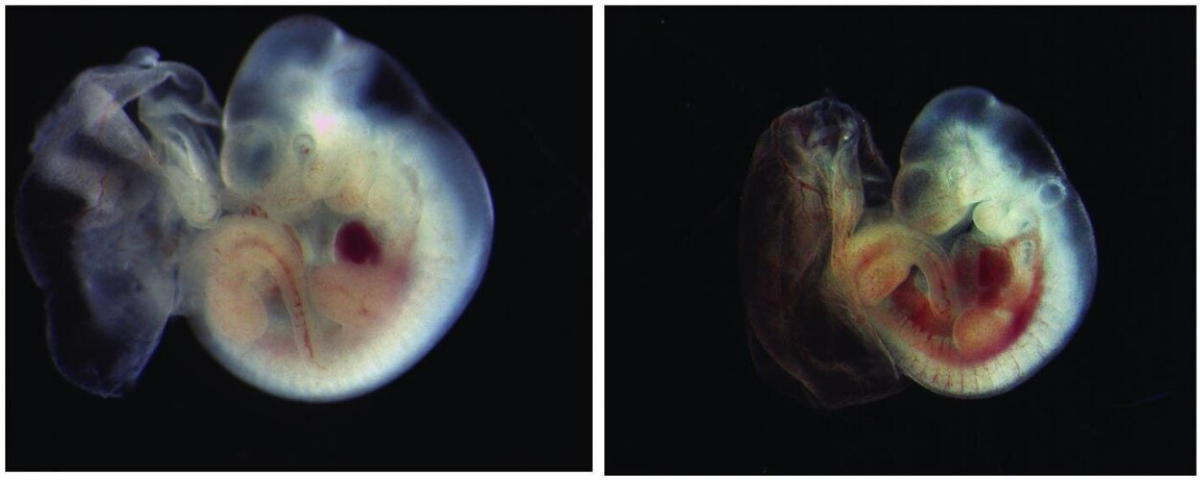

Pictures shows a wild type embryo on the left and an embryo expressing inactive Caspase-8 causing cardiovascular destruction (right) Credit: University of Cologne, CECAD

The enzyme caspase-8 induces a molecular cell death programme called pyroptosis without involving its enzymatic activity, a new study by Hamid Kashkar published in *Nature* shows. In order to safeguard healthy and functioning tissues, cells utilize different cell death mechanisms to dispose of unwanted cells (e.g. infected or aged cells). Apoptosis is a 'cellular suicide programme' that does not cause tissue injury and is induced by caspase-8.

Necroptosis is another mode of regulated cell death which causes cellular damage and is normally engaged when caspase-8 is inhibited. Pyroptosis describes an inflammatory mode of regulated cellular death process, which is normally activated in response to microbial pathogens and is central for mounting anti-microbial immunity. Hamid Kashkar and his team have now shown that caspase-8 not only controls apoptosis and necroptosis but pyroptosis as well. The study "Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis" was published in *Nature*.

The research team studied the biological roles of caspase-8 in cell cultures and mice. Kashkar's group showed that the enzymatic activity of caspase-8 is required to inhibit pyroptosis. "We found out that the expression of inactive caspase-8 causes embryonic lethality and inflammatory tissue destruction. This could only be restored when necroptosis and pyroptosis were simultaneously blocked," Hamid Kashkar explains. The lack of caspase-8 enzymatic activity primarily causes necroptotic cell death. Interestingly, when necroptosis is blocked, the inactive caspase-8 serves as a protein scaffold for the formation of a signalling protein complex called inflammasome, which ultimately induces pyroptosis. "Microbial pathogens are heavily reliant on the fate of infected cells and have evolved a number of strategies to inhibit apoptosis and necroptosis," Hamid Kashkar adds.

The current study hypothesises that these strategies may have driven the counter-evolution of pyroptosis to secure cellular death as a host defence mechanism. The caspase-8-mediated switch between different modes of cell death adds a critical layer to the plasticity of cell death-induced immunity, which is increasingly involved in aging-associated disorders.

More information: Melanie Fritsch et al, Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis, *Nature* (2019). DOI: 10.1038/s41586-019-1770-6

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