Programmed destruction

EurekAlert!

Stroke, heart attacks and numerous other common disorders result in a massive destruction of cells and tissues called necrosis. It's a violent event: As each cell dies, its membrane ruptures, releasing substances that trigger inflammation, which in turn can cause more cellular necrosis. A new Weizmann Institute study may help develop targeted therapies for controlling the tissue destruction resulting from inflammation and necrosis.

The study, conducted in the laboratory of Prof. David Wallach of the Biological Chemistry Department, focused on a group of signaling enzymes, including caspase 8, which was discovered by Wallach nearly two decades ago. Earlier studies by scientists in the United States, China and Europe had shown that this group of proteins induces "programmed," or deliberate, necrosis intended to kill off damaged or infected cells. This revelation had generated the hope that by blocking the induction of necrotic cell death by these proteins, it might be possible to prevent excessive tissue damage in various diseases.

But in the new study, reported in *Immunity*, Wallach's team sounds a warning. The researchers have revealed that under conditions favoring inflammation – that is, in the presence of certain bacterial components or other irritants – the same group of signaling enzymes can trigger an entirely different process in certain cells. It can activate a previously unknown cascade of biochemical reactions that causes inflammation more directly, without inducing necrosis, by stimulating the production of hormone-like regulatory proteins called cytokines. The research, mainly based on experiments in transgenic mice lacking caspase 8 in certain immune cells, was spearheaded by postdoctoral fellow Dr. Tae-Bong Kang. Team members Seung-Hoon Yang, Dr. Beata Toth and Dr. Andrew Kovalenko made important contributions to the study.

These findings suggest that prior to developing targeted necrosis-controlling therapies, researchers need to learn more about the signals transmitted by caspase 8 and its molecular partners: Since this signaling can lead to several entirely different outcomes, the scientists need to determine when exactly it results directly in necrosis and when it does not. Clarifying this matter is of enormous importance: Tissue necrosis occurs in a variety of disorders affecting billions of people, from the above-mentioned stroke and heart attack to viral infections and alcoholism-related degeneration of the liver.

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