

By impounding iron, FHC foils cell suicide, fuels inflammation

12 Nov 2004

A research team based at the University of Chicago may have found a way to manipulate cell suicide, also known as programmed cell death, a normal process that regulates cell number but that goes awry in chronic inflammatory disorders, cancer and other diseases.

In the 12 Nov. 2004 issue of the journal *Cell*, the scientists show that a key step in the process of preventing cell suicide is the induction of ferritin heavy chain (FHC), a protein that collects and hoards iron. By sequestering iron -- which cells with suicidal tendencies need to make the harmful substances that induce death -- FHC prevents cellular suicide.

This finding suggests that drugs that modulate FHC or iron metabolism could provide a new and effective approach to anti-inflammatory therapy without the side effects, such as weakening the immune system, that come with current treatments.

"In a long and complicated biochemical chain, this is one of the final links, which is exactly what we want," said study author Guido Franzoso, M.D., Ph.D., associate professor in the Ben May Institute for Cancer Research at the University of Chicago. "If we tamper with the front end, it changes everything, but boosting or blocking a downstream component allows us to select for a specific response."

Programmed cell death, also known as apoptosis, is the mechanism all multi-cellular organisms use to eliminate excess or damaged cells. Each year, through a balance of cell death and cell division, humans lose and regain a mass of cells roughly equal to their weight.

When a virus attacks an organism, for example, infected cells commit suicide to protect their healthy neighbors. At the same time, white blood cells multiply rapidly to battle the invader. Once the virus is eliminated, however, most of those virus-chasing white blood cells orchestrate their own demise. If they fail to thin their ranks sufficiently, they keep accumulating, infection after infection, which can lead to autoimmune diseases, such as arthritis, in which left-over warrior cells that no longer have an enemy turn on the self.

The researchers focused on NF-kB, a family of transcription factors -- proteins that turn on or off specific genes. The NF-kB family plays a crucial role in regulating immune and inflammatory responses to microbial invasion. During the early stages of an infection, for instance, NF-kB prevents white blood cells from dying off, allowing them to multiply quickly to fight off infection.

The problem of chronic inflammation begins when these lymphocytes evade cell death after winning the battle. In diseases like Crohn's or arthritis they can turn their weaponry on healthy cells, which they misidentify as invaders, causing lasting disease and tissue damage. A similar process, when dysfunctional cells fail to die, plays a key role in the accumulation of cancerous cells and then protects those cells from radiation and chemotherapies designed to provoke tumor cell suicide.

Drugs that inhibit NF-kB are already in use for inflammatory bowel disease and certain cancers, such as Hodgkin's lymphoma and multiple myeloma. But the tasks controlled by NF-kB are so wide ranging that blocking them globally can have serious side effects, such as reduced ability to fight off an infection.

"The goal has been to find new compounds that disrupt unwanted cell survival, but that act downstream from NF-kB so that they won't harm the immune system," Franzoso said. For a long time that concept was a fantasy, he added, but "as we learn more about this pathway, it has become realistic." NF-kB acts through one subset of genes to influence immunity and a different subset to cause programmed cell death.

To map out those genes, Franzoso and colleagues used a "death-trap" screen. They exposed cells to TNF- α , a biochemical signal that can trigger cell death, then collected DNA from cells that survived. Several rounds of this process produced a library of potential protective genes. Next, they used microarrays to detect the genes that were boosted most though this selective process.

"This system told us which genes were most enriched by selection," Franzoso said, which provided "a semiquantitative indication of protective efficacy."

When they looked closer at each gene associated with survival after exposure to TNF- α , they found that FHC was the "pivotal mediator" preventing cell death.

Next, they tracked down the mechanism FHC uses to block apoptosis. They found that by hiding iron, FHC prevented the accumulation of oxygen radicals $\cdot V$ extremely unstable molecules that can damage other molecules and cell structures. Without an accumulation of oxygen radicals, cells are unable to take the final steps toward programmed cell death.

"The data indicate that the antioxidant activity of FHC involves iron sequestration and that this sequestration is crucial for suppression of death of white blood cells induced by proinflammatory factors," the authors note. These findings identify FHC as the mechanism "by which NF-kB controls the cascade of intracellular events that ultimately lead to cell suicide."

The next step is to develop drugs that can reduce or raise FHC levels. Lower levels could prevent inflammation and may also enhance the effects of anti-cancer therapies. Higher levels may prevent the unwanted cell death that occurs in neuro-degenerative disorders such as Parkinson's and Alzheimer's disease.

"Not all that long ago, the NF-kB family, despite its crucial role in so many processes, was a complete puzzle," said Franzoso. "Now we have most of the pieces in place; we know how they fit together. The goal is to use this knowledge to make better therapies."

The National Institutes of Health and the Daymon Runyan Foundation supported this research. Additional authors include Can Pham, Concetta Bubici, Francesca Zazzeroni, Salvatore Papa, Joy Jones, Kelleen Alvarez, Shanti Jayawardena, Enrico De Smaele and Rong Cong of the University of Chicago; Carole Beaumont of INSERM, Paris; and Frank Torti and Susan Torti of Wake Forest University, Winston Salem, North Carolina.

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Source: <http://www.medicalnewstoday.com/medicalnews.php?newsid=16267>