

PAUL EHRLICH-FOUNDATION

The Chairman of the Scientific Council

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THE YEAR 2000 (MILLENNIUM) PAUL EHRLICH AND LUDWIG DARMSTAEDTER PRIZE IS GIVEN TO THE DISCOVERY OF NORMAL (PHYSIOLOGICAL) CELL DEATH

When in 1972 J.F.R. Kerr used the word “apoptosis“ for the first time to describe a physiological cell death necessary for normal animal development, little could he imagine that more than 20.000 scientific papers were going to mention his phenomenon between 1995 and 1999 (6700 of which only in 1998). The great popularity of this phenomenon was, however, slow to achieve: initially described as a morphological event involved in cell turnover in healthy adult tissues and responsible for focal cell elimination during development, it took almost a decade to enter into the molecular world. This happened when H.R. Horvitz, while studying the nematode *Caenorhabditis elegans*, identified genes dedicated to apoptosis and showed that cell death is the outcome of a programmed intracellular cascade of genetically determined steps. The two genes named *ced3* and *ced4* (*ced* stands for cell death) were shown to be essential for the death of the 131 cells, that usually happens during the normal development of the 1000-cells worm. The above two observations provided the rationale for the ascent of apoptosis, that happened when similar genes with similar function were discovered in humans: the protein encoded by the *ced3* gene was found to be similar to the human protein ICE (interleukin-1 converting enzyme), a protease with a cysteine in the active site that cleaves target proteins at specific aspartic acids, and that today belongs to a large family of proteases known as caspases.

Today there is no aspect of life that does not require apoptotic death for normal functioning. Apoptosis is necessary during animal and organ development to sculpt parts of the body, or to eliminate structures that are no longer needed, such as the tail of the tadpole when this turns into a frog. Immunity relies mostly on apoptosis to get rid of self-reacting lymphocytes, to induce suicide in virus-infected cells, and to eliminate normal activated lymphocytes after they have done their job and terminate an immune response. Damaged cells are often eliminated by apoptosis: cells can somehow recognize when one of its part is damaged and commit suicide. For instance, when mitochondria are damaged they release cytochrome c, a protein that normally functions in the electron-transport process to generate ATP. Once in the cytoplasm, the protein activates the caspase-proteases inducing apoptosis. Tumor development requires apoptosis escape. This usually happens by inactivating the cancer suppressing protein p53 that induces apoptosis in abnormally dividing cells. Plant resistance genes control local cell death and limit the spread of pathogen infection. Human bacterial pathogens induce apoptosis by secreting proteins that specifically bind caspases (*ipaB*) and induce massive tissue apoptosis.

Viruses have evolved apoptosis-blocking factors that allow survival of the infected cells.

In summary apoptosis is strictly linked to normal development and to most of the physiological aspects of life both in animals and plants. Hence any unbalance in this process may lead to diseases such as tumors, degenerative diseases, infections. The precise molecular knowledge of the fundamental events involved in apoptosis are today subject of intensive studies aiming at the development of drugs that may prevent or induce apoptosis to treat many diseases. A first demonstration that preventing apoptosis may cure an infectious diseases by preventing neuronal death in meningitis has been reported. This is the first of many social applications that will derive from the discovery of apoptosis.

The Paul Ehrlich Foundation is a result of Paul Ehrlich's co-operation with industry which provided him with additional means for his research. On July 13, 1929, fourteen years after Paul Ehrlich's death, his widow Hedwig Ehrlich transformed the fund into the Paul Ehrlich Foundation. Since then, the capital of the foundation has been held in trust by the Association of Friends and Supporters of Johann Wolfgang Goethe University at Frankfurt. The award-winners are chosen by the scientific council of the Paul Ehrlich-Foundation which consists of twelve internationally renowned scientists and is chaired by the President of Goethe-University, Professor Dr. Werner Meißner. The honorary president of the foundation is the president of the Federal Republic of Germany.

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