What Is “Phenoptosis” and How to Fight It?

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Abstract—Phenoptosis is the death of an organism programmed by its genome. Numerous examples of phenoptosis are described in prokaryotes, unicellular eukaryotes, and all kingdoms of multicellular eukaryotes (animals, plants, and fungi). There are very demonstrative cases of acute phenoptosis when actuation of a specific biochemical or behavioral program results in immediate death. Rapid (taking days) senescence of semelparous plants is described as phenoptosis controlled by already known genes and mediated by toxic phytohormones like abscisic acid. In soya, the death signal is transmitted from beans to leaves via xylem, inducing leaf fall and death of the plant. Mutations in two genes of Arabidopsis thaliana, required for the flowering and subsequent formation of seeds, prevent senescence, strongly prolonging the lifespan of this small semelparous grass that becomes a big bush with woody stem, and initiate substitution of vegetative for sexual reproduction. The death of Pacific salmon immediately after spawning is surely programmed. In this case, numerous typical traits of aging, including amyloid plaques in the brain, appear on the time scale of days. There are some indications that slow aging of higher animals and humans is also programmed, being the final step of ontogenesis. It is assumed that stepwise decline of many physiological functions during such aging increases pressure of natural selection on organisms stimulating in this way biological evolution. As a working hypothesis, the biochemical mechanism of slow aging is proposed. It is assumed that mitochondria-generated reactive oxygen species (ROS) is a tool to stimulate apoptosis, an effect decreasing with age the cell number (cellularity) of organs and tissues. A group of SkQ-type substances composed of plastoquinone and a penetrating cation were synthesized to target an antioxidant into mitochondria and to prevent the age-linked rise of the mitochondrial ROS level. Such targeting is due to the fact that mitochondria are the only cellular organelles that are negatively charged compared to the cytosol. SkQs are shown to strongly decrease concentration of ROS in mitochondria, prolong lifespan of fungi, invertebrates, fish, and mammals, and retard appearance of numerous traits of aging. Clinical trials of SkQ1 (plastoquinonyl decyltriphenylphosphonium) have been successfully completed so that the Ministry of Health of the Russian Federation recommends drops of very dilute (0.25 µM) solution of this antioxidant as a medicine to treat the syndrome of dry eye, which was previously considered an incurable disease developing with age. These drops are already available in drugstores. Thus, SkQ1 is the first mitochondria-targeted drug employed in medical practice.

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I once asked my old friend, the famous philologist and metrician M. L. Gasparov: “Mikhail Leonovich! How would you call the programmed death of an organism if a similar type of phenomenon with respect to a single cell is called “apoptosis”? “Phenoptosis!” — answered the academician without any hesitation.

In memory of my friend Mikhail Leonovich Gasparov

Abbreviations: \(\Delta \psi\), transmembrane difference of electric potentials; BLM, bilayer planar phospholipid membrane; C\(_7\)TPP, dodecyltriphenylphosphonium; MitoQ, ubiquinonyl decyltriphenylphosphonium; ROS, reactive oxygen species; SkQ, derivatives of plastoquinone and penetrating cations (Sk\(^+\)); SkQ1, plastoquinonyl decyltriphenylphosphonium; SkQR1, plastoquinonyl decylrhodamine 19.

That happened back in 1997, and today, 15 years later, we are releasing the first (and hopefully not the last) issue of the journal with this word on the cover. If successful, the journal will be published as a series of special editions of Biochemistry (Moscow), in both English and Russian. Since 1990, the impact factor of Biochemistry (Moscow) has grown almost an order of magnitude, so that it has already become one of the most cited Russian journals, with the largest contribution to the citations being made by special thematic issues composed mainly of review articles by leading Russian and foreign scientists [1]. In January 2012, the editorial board of the journal decided to make some such issues periodic. The title of this issue is Biochemistry (Moscow). Phenoptosis (similar,
for example, to American Journal of Physiology. Heart Circ. Physiol.). I would like to express my sincere gratitude to all those who helped me, the editor-compiler of this issue, to prepare for publication the first volume of the new edition (and I am especially grateful to those of them who also wrote articles for this issue): my deputies G. Libertini (Italy) and R. D. Ozrina (Russia), R. Lozier (USA, the editor of the English version of the journal), V. N. Anisimov (Russia), M. Blagosklonny (USA), L. A. Gavrilo (USA), T. Goldsmith (USA), D. B. Zorov (Russia), V. B. Ivanov (Russia), V. Longo (USA), K. Lewis (USA), V. N. Mansikhi (Russia), A. V. Markov (Russia), J. J. Mitteldorf (USA), F. F. Severin (Russia), and M. V. Skulachev (Russia). Excellent work of the biochemist-translator A. Brzyska should also be noted.

Phenoptosis is defined as genetically programmed death of an organism [2–4]. As a rule, the death program is encoded in the genome of the dying organism, being a chain of biochemical events that ultimately cause its suicide. That is why it is first of all biochemists that study the phenomenon of phenoptosis. More rarely, death occurs as a result of behavioral responses coded in the genome of the dying individual, its sexual partner, or a close relative of the victim [2, 3, 5].

EXAMPLES OF PHENOPTOSIS

Prokaryotes. Examples of phenoptotic phenomena can be found in all the kingdoms of living organisms. Homologs of eukaryotic genes that in higher cells participate in apoptosis, i.e. cell suicide, have been found also in prokaryotes [6]. In bacteria there exist “long-lived toxin—short-lived antitoxin” systems, when the cell slowly synthesizes a protein potentially able to kill it. Such a “murder” does not occur as long as amino acids necessary for protein synthesis are in sufficient quantity, for another protein, an antitoxin forming an inactive complex with the toxin, is rapidly synthesized. The toxin is not only slowly synthesized, it is also slowly decomposed. At the same time, the antitoxin decays faster than the toxin. It is because of these relationships that the decrease in the level of free amino acids leads to the disappearance of antitoxin, whereas the amount of toxin is only slightly reduced. The toxin released from a complex with the antitoxin is activated, and it kills the bacteria. As a result, the concentration of bacteria decreases, and therefore the consumption of amino acids by these bacteria is also reduced. In the end, the level of amino acids in the few surviving bacteria increases, reaching the amount sufficient for protein synthesis, and there appears the possibility of maintenance of an antitoxin concentration at a level higher than that of the toxin [7, 8]. It seems to be quite essential that the lack of not only amino acids, but also respiratory substrates and oxygen, as well as the appearance of pollutants — inhibitors of transcription, translation, or metabolism, and other adverse factors inhibiting the biosynthesis of proteins, can trigger the phenoptotic “toxin—antitoxin” system as the last line of defense of a bacterial population against complete extinction [8].

Yeast as an example of unicellular eukaryotes. F. F. Severin and coworkers have shown that the long-known phenomenon of the toxicity of pheromone excess for yeast should be attributed to the phenomenon of phenoptosis [9–12]. Mating partners of these unicellular organisms, marked by the letters A and B, secrete short peptides (α and β, respectively), which are specifically bound by the receptors of the cells of the opposite sex, where they cause certain biochemical and morphological changes favorable for sexual reproduction. Yeasts possess no mechanism of active movement. They follow the laws of Brownian motion in the liquid medium and, in case of random collision, stick together for the time needed for DNA transfer from the donor cell to the recipient cell. If this process is unsuccessful, the cells cannot separate, but they continue secreting pheromones into the narrow intercellular gap. In this situation, the pheromones become the killers of cells with corresponding receptors (i.e. pheromone α kills the cells of A type and pheromone β kills the cells of B type). This effect was shown to be absolutely specific (i.e. pheromone α does not affect cells of B type, and pheromone β does not affect cells of A type). Excess of pheromone α, added to a suspension of A cells, triggers the following cascade of events:

– activation of a special protein kinase necessary for the biosynthesis of some proteins that cause a sharp increase of Ca2+ level in the cytosol;
– stimulation of respiration, increase in membrane potential, and powerful generation of reactive oxygen species (ROS) in mitochondria, the process being accompanied by fragmentation of elongated mitochondria into small spherical ones;
– subsequent decrease in potential, swelling of mitochondria, and the release of cytochrome c (apparently due to the rupture of the outer mitochondrial membrane) to cytosol.

The described cascade strongly resembles the one of mechanisms of animal cells’ apoptosis [8]. The biological significance of yeast phenoptosis caused by the pheromone excess can be attributed to the stimulation of transition of these unicellular organisms from vegetative to sexual reproduction. This effect is in turn a response to deteriorating external conditions. In fact, the pheromones discard the cells that were incapable of sexual reproduction that increases the diversity of offspring and, therefore, increases the chances of the emergence of new properties that could be useful for adaptation to the changing environment [11, 13]. (For other cases of apoptosis in yeast, see review [14]).

Plants. The rapid aging of semelparous plants that reproduce only once in their life is perhaps the most frequently described example of phenoptosis, the biochemi-