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DISCUSSIONS

If Cancer Is a Special Case of Phenoptosis, How Can We Conquer It?

(The Editor-in-Chief Commentary to the Discussion Initiated by the A. V. Lichtenstein's Paper Published in 2005 in *Biochemistry (Moscow)*, 70, 1055-1064)

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First of all, I would like to express my gratitude to the participants of the discussion, A. V. Lichtenstein and L. M. Berstein, for their trouble of exchanging very profound notes concerning the essence of the problem: whether cancer can be a special case of phenoptosis (programmed organism's death). I am pleased just to see in the pages of our Journal materials published in a new (and really unprecedented for scientific magazines) section of "Speculative Hypotheses". In this case, the Editorial Board of the *Biochemistry (Moscow)* had in mind to revitalize the tradition of scientific discussions, which is, unfortunately, lost by our journals.

The theme excited by A. V. Lichtenstein [1] is derived from the concept of August Weismann [2] that in some cases the death of an individual is favorable for the population, hence, suicide mechanisms can emerge and be fastened during the evolution by the natural selection. Because of this idea, Weismann was accused of anti-darwinism, although in Darwin's works a similar viewpoint can be found. In his book *The Descent of Man*, Darwin wrote: "the community of many individuals, which included those ready to help one another and sacrifice oneself for the common wealth, would gain a victory over many other communities, and just this would be a natural selection" [3]. Nevertheless, the consideration of the death as an evolutionary invention was rejected by the overwhelming majority of biologists based on some theoretical assumptions (e.g., [4]).

Only in the end of the XXth century, such concepts again became a subject of discussion in connection with the discovery of apoptosis, or programmed cell death [5]. It has been found that similar phenomena of self-elimination of a biological system exist on both sub- and supercellular levels [6-8], and the suicide mechanism of the yeast cell, which is really an organism, is strikingly like apoptosis of cells in multicellular organisms [6, 8, 9]. Different suicide mechanisms have been described for bacteria, which are another type of unicellular organisms [6, 10]. It has been also found that a chronological aging of yeast has all features of apoptosis, and the death of the Pacific salmon after spawning is a hormone-controlled accelerated aging (progeria): the gonadectomy or adrenalectomy prevents the death (reviews [6, 8]).

It is reasonable to think that the usual ("normal") aging of multicellular organisms is also programmed and controlled by the senescent organism itself. It seems that aging was invented by evolution as a mechanism for selecting small positive variations, which are not essential for a strong young organism but become important for the weakening aged one. I like an example of a fox and two hares, one clever and another silly. When the hares are young, they both will escape from the fox simply because they run faster than the carnivore. But with age, on decreasing the muscular strength because of sarcopenia (reduction of the myocyte number), a moment comes when the hare's advantage in speed comes to nothing, and only a clever hare will save himself from the fox. And he will procreate leverets, whereas a silly hare will perish. As a result, the hares' population will grow wiser.

The phenomena of programmed death of organisms were proposed to unite under the term "phenoptosis", by analogy with apoptosis and mitoptosis (the self-liquidation of cells and mitochondria, respectively) [11, 12]. At least, in unicellular organisms, phenoptosis is responsible

for defense of the population's genofond. According to K. Lewis, neither competition, pathogens, nor food insufficiency is the main danger for unicellular organisms, but their own clone which has generated "hopeless monsters" leading to the death of a population [10]. It is reasonable to think that such "monsters" are similarly dangerous for multicellular organisms. In 1999, Muir and Howard published a paper, which discussed "The Trojan Gene Hypothesis" [13]. They studied a population of aquarium fishes some of which had received the gene of the human growth hormone. The transgenic fishes grew faster, and this made the transgenic males advantageous in the competition for the females which preferred the bigger partners. But the life cycle of the transgenic fishes was so accelerated that only two-thirds of them entered the age of reproduction. And according to calculation, the transgenic animals had to be only 0.1% of the total number of individuals in the population to result after 40 generations in a complete disappearance of the population.

If the organism's genome were absolutely stable, the evolution would be impossible. On the other hand, an excessive instability of the genome is dangerous for the population because of appearance of "Trojan genes" which themselves are not lethal for an individual, but are disastrous for the fate of the population and species as a whole. On the cell level, the defense against such events consists of three lines which are activated successively in response to damage of DNA: (i) the intensification of DNA repair processes, (ii) arresting the cell divisions, and (iii) the cell suicide (phenoptosis of unicellular beings or apoptosis of cells of multicellular organisms) [12]. According to Lichtenstein's hypothesis [1], cancer is phenoptosis of a multicellular organism, which purifies the population of individuals with an unstable genome. And a direct conclusion from this postulate will be prevention of cancer by genome-stabilizing agents.

Reactive oxygen species (ROS) generated during life activity play a fundamental role among agents responsible for damaging DNA. As they are, DNA and O_2 can peacefully coexist for a thousand years, at least, at the temperature of Antarctica ice: on thawing, ancient microorganisms successfully come to life and multiply. But ROS, produced from O_2 in a functioning cell, uninterruptedly attack and oxidize DNA of the cell. The aging program strategy as a slow phenoptosis presents a gradual weakening of the organism's antioxidant defense. And I think that just this causes with age an increase in the genome instability associated with activation of cancer which seems to be a program aimed to purify the population from this trouble. It seemed that antioxidants should possess a powerful prophylactic effect and prevent the emergence of cancer. However, *natural* antioxidants are unlikely to be a great success, because the organism treated with them will respond by attempts to activate the aging program, and this will additionally decrease the level of endogenous antioxidants. To overcome this difficulty, it seems promising to use *artificial* antioxidants selectively affecting mitochondria. Such antioxidants are shown to be accumulated in mitochondria in thousandfold excess as compared to their level outside the mitochondria [14, 15]. And it is hardly probable that the organism will be able to withstand their effect. This approach seems promising also because mitochondria are the main source of ROS and mitochondrial DNA is the most vulnerable element of the genome [8, 15].

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Closing Remark

Shortly after this note was written, I received from Tomsk a monograph *Essays on Evolutionary Oncology* by V. N. Manskikh. A chapter of this book printed in 2004 by the Siberian Medical University (SMU) Publishers is entitled "Tumor Growth as a Regulatory Mechanism of Mutational Burden in Populations". In this chapter, V. N. Manskikh develops an idea very similar to that published by A. V. Lichtenstein in 2005 in our journal. For justice, it should be emphasized that A. V. Lichtenstein had set forth his hypothesis at my seminar in 2004, thus, the two authors came independently to the same conclusion. Considering this situation, I proposed to V. N. Manskikh, with the permission of SMU, to reprint his chapter in *Biochemistry (Moscow)*.

The permission was obtained, and the reader will have an opportunity to make acquaintance with it. One cannot but mention about the author's personality. Vasilii Nikolaevich Manskikh is only 23 years old. He is a V course student of SMU. While still a pupil of school classes V-VI, Manskikh had studied without assistance full courses of histology and microbiology, and was indulged in the Chairs of Microbiology and Clinical Pathology, Novokuznetsk Institute of Advanced Training for Physicians under the direction of Ass. Prof. V. A. Rykov. His first scientific work was made when he was a VIIth class pupil. He engaged in oncology 7 years ago. He has published more than ten papers, including those printed in the *Voprosy Onkologii* journal. From the bottom of the heart, we wish the young author to have the greatest achievements in his future work in science.