Anaerobiosis and Stemness: An evolutionary paradigm

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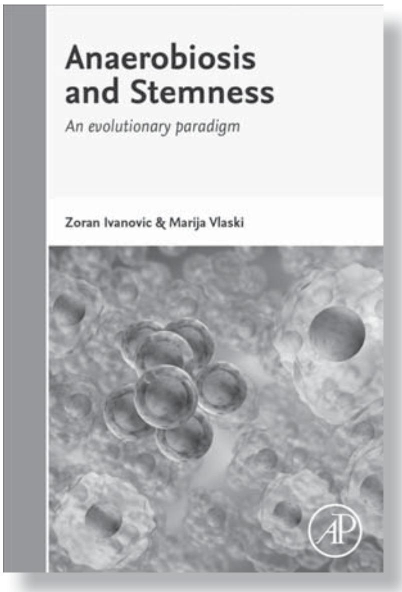
Recently, Academic Press has issued a new challenging book titled *Anaerobiosis and Stemness: An evolutionary paradigm.* Authors present the concept on the role of oxygenation in the maintenance, differentiation and proliferative properties of stem cells. The concept is based on original experimental evidence and linked to evolutionary biology. Considerable knowledge on cell biology is essential to understand complex regulation of stem cells in the scope of different oxygen availability.

After two "special remarks" chapters, in which the functional definition of stem cell was reaffirmed and the incorrect use of the terms "hypoxia" to say physiological tissue normoxia ("physioxia") corrected, the argumentation of this book is presented in two parts: the first part, composed of five chapters, is reviewing available data on the relationship between the anaerobic and facultative anaerobic conditions with stemness and the slow self-renewing proliferation. Furthermore, complete signaling associated with the stemness is also related to the anaerobic metabolic profile.

The entity called "stem cell," evidenced in hematopoiesis and other tissues of an adult organism, is defined on the basis of its capacities to produce cells of several lineages and to self-renew. The ratio of self-renewing divisions to the total number of divisions through proliferative history of a clone determines the "proliferative capacity" of the cell which initiated that clone. It is very high in stem cells. Going back to fetal and embryological development, the stem cells are more and more frequent in the tissues until the most primitive stem cells – zygote and the cells resulting directly from its division, which are



totipotent, i.e. are able to "generate" a whole organism.

The data obtained during the past two decades, including the results acquired by the authors of this book, revealed the relationship between "primitiveness" of stem cells and their anaerobic metabolic type. Back in 2000, the first one who connected the self-renewal of hematopoietic stem cells with the shortage in oxygen supply to the cells, the first author of this book started to develop a universal concept assuming that the "self-renewal" represents nothing but a simple division of non-differentiated cell, which is not accompanied by activation of molecular extensions leading to commitment and differentiation. This type of cell proliferation is compatible with low energy slow divisions reduced only to a strict replication *à l'identique*. This primitive proliferation takes on in microaerophilic and anaerobic conditions. On the contrary, commitment and differentiation processes are related to increased energetic demands. Since this behavior of stem cells reminds one of anaerobic and facultative anaerobic single-celled eukaryotes, in 2009 this author proposed the "oxygen stem cell paradigm", comparing the primitive functional state and self-renewal capacity of a stem cell with the reproduction, i.e. simple proliferation *à l'identique* that had occurred in the ancestral first single-cell eukaryotes risen in anaerobiosis more than two billion years ago.

The book *Anaerobiosis and Stemness: An evolutionary paradigm* reveals the arguments not only to support this concept but also to provide the key to understand the basic processes related to the stem cells, self-renewal and differentiation as more or less conserved archetypes of the features that appeared during the complexification of single-celled eukaryotes: while the most primitive mitotic eukaryote cell division, providing the mean for reproduction of the first eukaryotic common ancestor, can be identified as the archetype of self-renewal, the appearance of the complex life cycle of the single-celled eukaryotes represents an archetype of differentiation and, vice versa, dedifferentiation. Since the appearance of complex life cycle is related to the appearance and rise of O_2 in the Proterozoic ocean, the further rise of O_2 provoked more complex differentiation pathways leading to the improved cell cooperation, firstly in the form of colonial single cell organisms, and further to the appearance of multicellular organisms.

In the second part, also composed of five chapters, the authors provide an exclusive and original comparative analysis of the stem cell systems from humans to the first metazoans and further, extending this analysis to the single-celled eukaryotes. This analysis completed by one of metabolic ways, and molecular signaling through the evolution, confirms, in fact, their hypothesis. Furthermore, most transcripts today known as "pluripotency factors" represent the mechanisms acquired during the early evolution aimed at preventing the differentiation and, consequently, enabling self-renewal, i.e. simple reproduction. This analysis also allowed proposing the existence of a "minimal essential genome" enabling life and simple reproduction of most primitive eukaryotes lacking the capacity of differentiation, but also of primitive stem cells during their symmetrical division ("full") self-renewal in situation where the commitment and differentiation are prevented.

Having in mind this principle, the authors provide explanation for a large number of results obtained in stem cell engineering and therapy. For example, the classical "exhaustion" of stem cells in a culture ex vivo is caused mainly by a hyper-oxygenation since the atmospheric O_2 concentration is several fold higher than tissue one; to make its clone "survive" in these conditions, the anaerobic stem cell commits and differentiates to produce cells more resistant to O_2, somehow repeating, in an incredibly accelerated manner, what happened during the diversification and complexification of the first eukaryotes between 2.3 and one billion years ago. Engineering the cultures mimicking the so called "hypoxic response" can allow the preservation of the primitive cell population in parallel with the production of committed and differentiated cells, which is already used for clinical scale production of cells and their use in phases 1 and 2 of clinical trials. Respecting the same concept may revolutionize the cell transplantation in ischemic tissue zone, which is one of the major challenges of regenerative medicine today.

Finally, within the frame of the same concept, the authors provide original and logical interpretations of some features, initially and still considered to be specific cancer cell features, demonstrating that they represent a general set of basic features of stemness. Their presence and association with cancer result from the fact that highly proliferative cancer cells are stem cells. In other words, some of the most known metabolic and functional cell properties traditionally associated with cancer are nothing else but features of stemness.

The "evolutionary stem cell paradigm" of Z. Ivanović and M. Vlaški thus provides the key for understanding and predicting stem cell behavior in vivo and ex vivo, which is of paramount importance for the cell engineering and anti-cancer strategies. Furthermore, beyond these pragmatic aspects, this paradigm relates the stem cell entity and stemness with the early eukaryote evolution on the basis of the functional and molecular arguments. This way "the evolutionary stem cell paradigm" can be considered to be revisiting, from another point of view and by other means, Haeckel's "recapitulation of evolution" concept. And, finally, but by no means less important, this book points to oxygen as a factor which, due to its primary toxicity, induced major evolutionary events and enabled the diversification and complexification of eukaryotes. However, the sources of life, primitive stem cells, serving for physiological and pathological renewal of tissues, remained non-adapted to O_2, which resembles the first single-celled eukaryotes. This should be taken into consideration when manipulating these undifferentiated cells. The concept on anaerobiosis and stemness presented in this unique book implies to the epigenetic missing link in stem cells behavior. The evolutionary paradigm described, although partly hypothetical, is important for understanding developmental biology.

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