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State of the art

Stem cell evolutionary paradigm and cell engineering

Paradigme évolutionnaire de la cellule souche et ingénierie cellulaire

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Abstract

Studying hematopoietic and mesenchymal stem cells for almost three decades revealed some similarities between the stem cell entity and the single-celled eukaryotes exhibiting the anaerobic/facultative aerobic metabolic features. A careful analysis of nowadays knowledge concerning the early eukaryotic evolution allowed us to reveal some analogies between stem cells in the metazoan tissues and the single-celled eukaryotes which existed during the first phase of eukaryotes evolution in mid-Proterozoic era. In fact, it is possible to trace the principle of the self-renewal back to the first eukaryotic common ancestor, the first undifferentiated nucleated cell possessing the primitive, mostly anaerobically-respiring mitochondria and a capacity to reproduction by a simple cell division "à l'identique". Similarly, the diversification of these single-cell eukaryotes and acquiring of complex life cycle allowed/conditioned by the increase of O_2 in atmosphere (and consequently in the water environment) represents a prototype for the phenomenon of commitment/differentiation. This point of view allowed to predict the ex-vivo behavior of stem cells with respect to the O_2 availability and metabolic profile which enabled to conceive the successful protocols of stem cell expansion and ex vivo conditioning based on "respecting" this relationship between the anaerobiosis and stemness. In this review, the basic elements of this paradigm and a possible application in cell engineering were discussed.

Keywords: Stem cells; Evolution; Anaerobiosis; Self-renewal; Proliferative capacity; Ex vivo engineering

Résumé

Quasiment trois décennies d'études des cellules souches hématopoïétiques et mésenchymateuses nous ont amené à constater les similitudes entre l'entité appelée « cellule souche » et les premiers eucaryotes ayant des propriétés métaboliques anaérobies ou aérobies facultatives. Une analyse approfondie, basée sur les connaissances actuelles concernant l'évolution des premiers eucaryotes permet de reconnaître quelques analogies entre les cellules souches dans les tissus métazoaires et les eucaryotes unicellulaires primitifs datant de la période mi-protérozoïque. Il est possible de tracer le principe de l'autorenouvellement jusqu'au premier ancêtre commun des eucaryotes, la première cellule nucléée non différenciée possédant les mitochondries primitives capables de respiration anaérobie et ayant une capacité de reproduction limitée à une simple division cellulaire « à l'identique ». De façon similaire, la diversification des eucaryotes unicellulaires et l'acquisition du cycle de vie complexe permises/conditionnées par l'augmentation du taux d'O_2 dans l'atmosphère (et par conséquent dans le milieu aquatique) représentent le prototype du phénomène d'engagement/différenciation. Cette façon de voir les choses a permis de prévoir le comportement des cellules souches ex-vivo par rapport à la disponibilité d'O_2 et à leur profil métabolique et ainsi concevoir des protocoles efficaces de leur expansion ex vivo ou de leur conditionnement avant la greffe. Dans cette revue générale ont été discutés des éléments majeurs de ce paradigme, ainsi que leur application possible dans l'ingénierie tissulaire.

Mots clés : Cellules souches ; Évolution ; Anaérobiose ; Autorenouvellement ; Capacité proliférative ; Ingénierie ex-vivo

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1. Stem cells "memorize" early single-cell eukaryote evolution

On the basis of results published in the second half of 20th century and the beginning of 21st century, we revealed a parallel between anaerobic single-cell organisms and stem cells [1]. As a matter of fact, the primitive stem cells are able to self-renew at extremely low O_2 concentrations, a behavior similar to the reproduction of non-differentiated forms of single-cell protists. Analyzing the evolution of eukaryotes revealed an interesting feature: the first common eukaryote ancestor appeared in conditions of almost total anoxia in the environment of the "primitive ocean" [2,3 (Chapter 8)]. In the same time, in some ecologic niches of this ocean, oxygen was present in extremely low concentrations. This first eukaryote already integrated an alpha-proteo bacteria as a symbiont, i.e., possessed mitochondria. These mitochondria, although capable of both anaerobic and aerobic respiration performed mostly anaerobic one [2,3] (Chapter 9)]. This first single-celled eukaryote had a simple life-cycle. In fact, it was capable to perpetuate the simple-cell divisions "à l'identique" without a capacity to differentiate and give rise to different cell variants. These simple-cell divisions "à l'identique" are recognized in metazoa as self-renewal of non-differentiated cells, also called "primitive cells" or "stem cells". Starting from the last common eukaryote ancestor, through the diversification of single-cell eukaryotes including those with complex life cycles and colonial organization, until the metazoa and their diversification, a multitude of functional extensions was accumulated [3; Chapter 10]. This accumulation of functional extensions goes in parallel with the increase of O_2 in atmosphere and consequently in the ocean. This is nothing else than accumulation of the "capital" for differentiation that is usually called "differentiation potential". Execution of this differentiation potential is related with higher energy demands and is enabled by oxidative phosphorylation which is, however, conditioned by sufficient oxygen availability. From this viewpoint, commitment and differentiation in metazoan stem cell systems somehow reproduced acquiring the new functional extensions during the single-cell eukaryote evolution which occurred in parallel with the increase of O_2 availability. This notion allows us to understand the evolutionary origin of self-renewal and commitment/differentiation, which are the main properties of the metazoan stem cell systems including higher organisms and men himself [3; Chapter 10]. This concept allows to understand why stem cell self-renewal is associated with either low O_2 availability, or anaerobic metabolic energetic profile, or both. However, in order to enable a cell to perform a simple cell division without differentiation, in the presence of a very big number of differentiation programs activated spontaneously, if oxygen is available, the evolution provided the genes, which activation results in effective transcription factors able to inhibit and silence these spontaneous pro-differentiation signals. Most of these genes are known today as "pluripotency factors", "factors of stemness", "factors of primitiveness", etc. If they are expressed in parallel with the expression of genes regulating cell cycle and elementary cell metabolic functions enabling survival, the result will be divisions "à l'identique" of non-differentiated cells, i.e. self-renewal [3; Chapter 10, 11]. Of course, this result can be obtained if the primitive, non-differentiated cells were exposed to extremely low O_2 concentrations, and even to anoxia. How anoxia/extreme hypoxia regulates self-renewal remains to be elucidated: both genetic and epigenetic regulation of "pluripotency factors" is considered.

2. Oxygenation as a critical factor

Oxygen is one of the most powerful poisons on the planet. When its atmospheric concentration reached a critical level, a big part of living organisms disappeared (reviewed in [4]). Only those who exhibited a possibility to reduce oxygen, hence to neutralize its toxicity, survived. This detoxification took different ways. Some of them improved its efficiency during the evolution and complexified, leading to the synthesis of high-energy phosphates. This way, based on a chain of redox reactions, the oxidative phosphorylation (oxphos) finally became the main energetic source for eukaryotic cells. In metazoan organism, tissue homeostasis (especially oxygenation) is maintained constant by a complex cardiorespiratory regulation. The oxygen concentration in the tissue is maintained in a range between 3 and 5% whatever its environment concentration is. This optimal oxygenation allows the aerobic metabolism and prevents the negative effects of hyper-oxygenation. As stipulated by French scientist Massabuau, this "standard" was established in Paleozoic era (400 to 450 million years ago) and the development of complex cardiorespiratory regulation afterwards is aimed to maintain this oxygenation homeostasis [5]. In mammals, the intracellular O_2 concentration is in the range of 5 to 25 μM (4 to 20 mmHg or 0.5 to 3%) and the critical concentration below which respiration becomes anaerobic is in the range of 2 to 6 μM (1.6 to 4.8 mm Hg or 0.2 to 0.63%). This limit corresponds well to the "Pasteur point" at which facultative anaerobic eukaryote starts to perform aerobic respiration [6]. The value of "Pasteur point" 2 μM O_2 or 0.21% corresponds to 0.01 of the present atmospheric oxygen level (PAL) marking the level of oxygen in the early atmosphere of the Earth that is believed to have led to major evolutionary changes. It also corresponds with recently estimated O_2 concentration in Proterozoic atmosphere [7]. Thus, if the mean tissue oxygenation in mammals still keeps the Paleozoic standards, then the extremely low O_2 concentrations (probably in some cases complete anoxia) correspond to much older, Proterozoic standard, in the middle of which era the single-celled eukaryotes evolved and diversified (1.8–1.3 billion years ago) [3; Chapter 10].

3. Atmospheric O_2 concentration considered as "normoxia"–a misleading concept

The atmospheric O_2 concentration (20 to 21%) depending on the temperature, results in 200 to 250 μM dissolved O_2 concentration, which is at least 10-fold more than in tissues in vivo and more than 100-fold above the "Pasteur point". Thus, the ex vivo cultures exposed to the atmospheric O_2 concentration represent