On the Origin of Stemness and Ancient Cell Lineages in Single-Celled Eukaryotes

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Abstract

The appearance of stem cells was a major evolutionary advance. It remains however unknown which ancestral biosystem evolved first for stemness and under what conditions. The purpose of this report is to provide an overview of the evolutionary origin of stem cells. It summarizes the current knowledge and dogmas on the origin of stem cell evolution. Understanding stemness in metazoans illustrates the basic principles of lineage organization and stem cell hierarchy in ancient single-celled eukaryotes.

Keywords: Entamoeba; Ancient stem cells (AnSC); Cell differentiation; Physiological hypoxia; Quiescent cells

Abbreviations

LUCA: Last Universal Common Ancestor; LECA: Last Eukaryotic Common Ancestor; HSC: Human Stem Cells; AnSC: Ancient Stem Cells; OCB: Oxygen Consuming Bacteria; TD6^{LT} and QD24^{LT}; Stem cell lines in long term cultures; MYA: Million Years Ago

The appearance of stem cells was a major evolutionary advance. It remains however unknown which ancestral biosystem first evolved the characteristics of stemness, when it evolved and under what environmental pressures. Experimental models capable of self renewal and differentiation, older than Spongia and Cnidaria (Hydra), would need to be identified to clarify these issues. It is with such models that it should be possible to clarify the questions of whether ancient stem cells lines were multipotent or unipotent? Did ancient stem cell systems function by potency restriction and totipotency recovery? Where these cell lines in fact lineage-structured systems appearing first with by later metazoan evolution [1]? At this time there is little research addressing these issues [2,3] and other opinions as well.

Regulatory mechanisms leading to cell differentiation and functional multicellularity are fundamental steps for understanding the origin and evolution of eukaryotic stem cells as the very significant development in the history of biology. Cell differentiation operates by asymmetric division and there is evidence that mechanisms implicated in the regulation of asymmetric division are ancestral, existing in common ancestors of the LUCA- (Last Universal Common Ancestor) and LECA (Last

Eukaryotic Common Ancestor) -families. Asymmetric division is recognized today in both bacterial sporulation and eukaryotic cell differentiation, substantiating the common ancestor hypothesis. Investigations on the nature of the last universal common ancestor take LUCA as a most eukaryotic-like ancestor, although it is unclear whether LUCA was a single species or whether there were extensive lateral transfers between divergent life forms [4]. The main conclusion of Penny and Poole [4] is that Eukarya retain the greatest similarities with LUCA while prokaryotes have been through a long period of reductive evolution. If this is correct, the LUCA family was the origin of both symmetric and asymmetric cell division patterns. On the evolutionary path to the last eukaryotic common ancestors (LECA) the molecular mechanism for asymmetric divisions, stem cell differentiation and multicellularity were refined and adjusted. LECA evolved from a redox syntrophy in anoxic and micro-oxic proterozoic habitats [5]. Most of the prominent features present in all eukaryotes appear to have been already present and well developed in LECA [6]. Thus, key gene families used in metazoan development had already diversified in early unicellular ancestors [7]. Obviously there were differences between LECA's gene family and the functionally genes of ancient protists and choano-flagellates [7-9]. Single- and multi-celled organisms today have lost many ancestral genes during evolution (developmental loss).

Key steps in the transition to functional multicellularity occurred quickly and were highly adaptive [10]. In all of evolution, multicellularity has evolved repeatedly in unrelated phylogenetic groups [11] and the potential of multicellularity may be less constrained than is frequently postulated [10].

It is clear the emergence of stem cells and their development was the prerequisite for the evolution of multicellularity [12], but the evolutionary origin of stem cells and their evolutionary history remain obscure and poorly understood [13]. Unfortunately, microbial eukaryotes remained virtually unstudied. It was Ernst Haeckel 145 years ago who first considered single-celled organisms as the phylogenetic ancestors of multicellular organisms [14]. However, protist researchers in the past could not develop adequate experimental systems, with which to study and elucidate the evolutionary history of stem cells and functional multicellularity at the level of a single-celled organism.

Many hoped therefore that these evolutionary developments could be identified by comparative genomics studies.

The lack of available data for the realm of protists led several authors to hypothesize that the phylogenetic evolution of multicellularity originated from metazoan ancestors [13,15,16,]. They excluded the possible existence of primitive stem cells in the LECA and protists today. As a result some developmental biologists considered populations of single-celled organisms (protist) as homogenous communities, where each individual was self sustaining and all cells are identical [17]. Until recently, the emergence of stem cells was considered as happened in basal metazoans such sponges and hydras. The earliest cell lineages and stem cell differentiation patterns known to date were described in basal Metazoa such as Spongia and Cnidaria (Hydra).

One of the best arguments towards the metazoan dogma is the “oxygen stem cell paradigm” and the *physiological hypoxia* needed by stem cells systems of aerobes. The physiologic activity of many mammalian and humans stem cells is often better at hypoxic ranges and low pO₂ values (1-5% O₂) than in atmospheric oxygen concentrations (21% O₂). Stem cells in humans reflect an early evolutionary environmental niche where availability of O₂ was limited, in other words similar to the environments of anaerobes and facultative anaerobic single-celled organisms [18,19]. Following this hypothesis, stem cells of the upper metazoa, are reminiscent of those single celled-ancestors that did not completely adapt to atmospheric oxygen, thus retaining the hypoxic metabolism of their ancestors. The concept of specialized microenvironments (niches) governing stem cell behaviour is now commonly accepted [20]. While most regulatory relationships between stem cells and environment are based on metazoan models, meaningful progress in our understanding depends on the development of relevant single-celled protozoan models which retain features of the Ur-protozoan ancestor [7].

Recently, paleozoologists found in rocks from 570 MYA in South China a single-celled hermaphroditic fossil, considered to be both an amoeba-like protist and an ancestral “animal embryo”. The mechanisms of cell differentiation and multicellularity appear, preserved in the developmental pattern of its life-cycle. This includes cell divisions not accompanied by cytoplasmic growth (palintomy), followed by differentiation of asexual propagulae as endospores indicating differentiation during the maturation of the cyst [21].

Eukaryotic cells evolved to divide by asymmetric division, giving rise to non-identical daughter cells. This was the origin of the ancient stem cells. According to the baseline definition, a stem cell is a cell that is capable of both self-renewal and differentiation. One of the daughter cells is determined for self renewal and the other embarks a pathway of differentiation, according to their individual development potential and differentiation potency. Stem cells act as reserves to regenerate systems and reside in hypoxic niches where they may remain mitotic arrested (quiescent) waiting dormant in the G₀ phase of the cell cycle [22], until they are activated by a need to generate new cells. Any long term subpopulations such as adult human stem cells (HSC) are

predominantly quiescent or in slow cell cycle progression (slow cycling). These cells provide a self renewing reserve to support survival by an efficient reconstitution processes [23].

The inability of the stem cells to carry out phagocytosis is a different issue. Quiescent HSC are unable to perform receptor mediated phagocytosis since the appropriate receptors are not expressed and are lacking on their surface [24]. Subsequently differentiated HSC stem cell stages and cycling stem cells express receptors for pinocytosis and opsono-phagocytosis. Many stem cell types showed a dependence on hypoxic conditions for many of their properties such as maintenance in the G₀ phase, self renewal, differentiation, pluripotency and lineage commitment. These properties are regulated by hypoxia which control signaling mechanisms derived from the ancestor. Most stem cells are still unipotent, giving rise to a single differentiated cell type, as probably as did the ancestral LECA family.

All these data suggest that modern-day intermediate range protists should carry more clues about stem cell evolution than previously thought. Ancient stem cell types were found in protist pathogens as *Entamoeba invadens* grown under changing hypoxic conditions [25,26]. Hypoxic bottom sediments with oxygen consuming bacteria (OCB) brought *E. invadens* as close as possible to its natural environment and allowed two ancient stem cell lines to be identified in long term cultures (TD6^{LT} and QD24^{LT}). Parallels were drawn to the previously described magna and minuta cell types of *E. histolytica*. These results have been reinterpreted with respect to the modern understanding of the stem cell biology. A subsequent paper Niculescu VF [27] describe the particularities of the protist stem cell system in detail.

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