The cancer stem cell family: atavistic origin and tumorigenic development

Abstract
aCLS (PGCC) is the mother cell of the atavistic cancer stem cell family. Its numerous microcell progeny starts the atavistic stem cell lineage encoded in the human dark genome. The atavistic lineage contains two antagonistic sublines: a reproductive hypoxic subline producing aCLSs by cyclic differentiation (aCLS+ subline) and a somatic oxygenic subline that proliferates without aCLS formation (aCLS- subline). In cancer development both sublines enriched their phenotypic and genomic profile (clonal evolution). In conditions of stress, both sublines may convert from one into the other. Subline interconversion assures the flow of phenotypic and genomic information between the evolving CSC family. I suspect, the cancer stem cell family has an atavistic origin and are not generated by damaged adult stem cells.

Keywords: CSC, atavistic cancer stem cell family, CSC evolution, CSC hybrids, cell fusion, microenvironment, Entamoeba

Introduction
The concept of cancer stem cells (CSCs) is the hot topic of the day and everyone is talking about them. Patients with metastases now know that their condition is due to recurrent CSCs with increased resistance to chemotherapeutics (rCSCs). However, there is confusion and controversy about the origin and development of CSCs in the scientific community. Where do CSCs come from and how do they develop during cancer progression? Even now, the origin of CSCs remains unclear. Some confusion lies in the fact that most theories have in mind tumorigenic stem cells and suspect therefore that CSCs arise in specific cancer cell niches by oncogenic reprogramming of progenitor cells, adult stem cells or dedifferentiated cells; accordingly, it would be the cancer cell niche (CSN) that control CSC development, self-renewal, proliferation and phenotypic diversification. Regarding the cellular origin of cancer, many researchers share the idea that CSCs originate from a human stem cell (hSC) that evades the normal regulation of the adult stem cell niche (CSN) and forms cancer progenitor cells (CPCs). In their opinion CSCs and CPCs are equivalent to normal stem cells and CSCs take over the stemness features of the normal hSCs. Other researchers mean CSCs come from damaged human stem cells undergoing excessive cell repair. Many terms such as cell-of-origin and non-stem-cells forming CSCs, transformed cells and mutated genes are ambiguous and less suitable. It was Nguyen that demands clarification and a more adequate terminology.

The atavistic origin of cancer stem cells
In the last twenty years more and more researchers have come to understand that the somatic mutation theory of carcinogenesis is a textbook-dogma that should be dropped and replaced. Regarding cancer cell stemness, I think it is an error to consider CSC stemness directly related to the normal hSC stemness. In a recent paper on the biology of cancer stem cell families I show that CSCs may have an atavistic origin and are outside of the regulatory control mechanisms of hSCs. The cell of origin of cancer (protoprecursor cell) is a human cell losing proliferation capacity. It gets locked into an accelerated state of premature apoptosis. To escape imminent death this mitotically blocked cell reactivates an atavistic stem & progenitor cell lineage encrypted in the human dark genome (cancer initiation). During cancer progression pre-carcinogenic CSCs evolve from the atavistic aCSC type to more complex CSC hybrid types that acquire novel phenotypic and genomic properties including metastatogenic potential.

The reproductive cancer cell cycle
The mitotically blocked protoprecursor bypasses mitosis entering a reproductive life cycle analogous to the life cycle of modern day protists. It is a re-emergence of the differentiated metazoan cell system by the reappearance of the unicellular features which makes the cell assume surviving atavistic characteristics by old gene organizations and many nuclear gene networks. The protoprecursor cell forms a reproductive cyst like structure (aCLS, PGCC) that disseminates invasive microcells (daughter cells) in host tissues. Undifferentiated microcells are the totipotent cells of the system. They form a sub-pool of primary stem cells starting the atavistic sublines. Proliferating progenitor cells, differentiating precursor cells, aCLSs mother cells and undifferentiated totipotent microcells belong to the asymmetrically dividing reproductive subline (Figure 1). aCLSs (PGCCs) are the mother cells of the atavistic stem cell family. They occur in numerous human cancers by a cycling mechanism referred to, in the case of cancer, as neosis. The undifferentiated totipotent microcells initiate an immortal self sufficient stem and progenitor cell lineage (caSPCL) controlled by regulatory mechanisms that originated from ancient single-celled eukaryotes. It is a state-in-state development extremely dangerous for the parasitized host organism, which does not have control and defense mechanisms against the atavistic intrusion. There is a significant correlation between the grade of cancer disease (well, moderately and poorly differentiated cancers).
and the type, location and number of reproductive αCLSs. Zhang et al.\(^7\) show that most PGCCs (aCLS) are located around necrotic tissue at the hypoxic boundary between normal and tumor tissue and believe that hypoxia favours PGCC formation. The progeny have increased migration capacity and lead to isolated PGCC formation that disseminates budding daughter cells in the stroma or tumor emboli. Single budding stromal PGCCs were observed in ≥ 90% of poorly differentiated tumors, 50% of moderately differentiated and 27% of well differentiated colorectal cancers.\(^7\) Single stromal PGCCs are considered to be the signal of lymph node metastasis. Usually, PGCCs are uniformly distributed but frequently hot spot PGCCs fields were observed. These hot spots fields occur more frequently in high grade malignant tumors and are rare in low grade tumors.

**Reproductive and somatic sublines**

Analogous to the ancestral SPC lineages also conserved in modern day protists, cancer stem cell populations have two basic antagonistic sublines. One is the reproductive subline (aCLS+ subline, progenitor subline) capable of forming numerous reproductive aCLSs by cyclic differentiation. Progenitor cells divide by asymmetric cell division: one of the daughter cells becomes self renewing and forms a new progenitor cell (fusogenic cell) while the second daughter cell is a committed precursor cell that forms an aCLS (Figure 1). The second subline is a fusogenic/cloneogenic somatic subline (aCLS- subline) capable of expressing its hidden differentiating potential under conditions of stress and genotoxic insults. It forms stress induced siCLS and genotoxic induced giPGCC that gives rise to more resistant and more invasive recurrence CSCs (rCSCs). Both sublines persist and evolve in cancer development, progression and recurrence. The reproductive subline is a differentiating hypoxic subline of anaerobic metabolism while the somatic/vegetative subline is more oxygenic and proliferative.

**Clonal evolution and subline inter-conversion**

While the reproductive subpopulation has a strict hierarchy, the somatic subpopulation is highly fusogenic, it forms numerous hybrids, clones and stress-induced siCLSs (Figure 2). Chronically inflamed tissues favor cell fusion events between macrophages and CSCs.\(^13\) The linear clonal development occurring by stepwise acquisition of new features and patterns (from a handful to hundreds of acquired new hallmarks) confers selective advantages. On can say the more advanced the disease the more complex the profile of the CSCs.\(^16–20\) Several researchers even assume a preferential sequence of events by inferring the prevalence of certain hallmarks at each stage\(^21\) and consider clonal evolution crucial for tumorigenesis.\(^22\) Genetic and non-genetic heterogeneity, intrinsic and adaptive modifications, cell-to-cell variations in genetic signature, gene expression and post-translational modifications are found in almost every type of cancer.\(^23\) Epigenetic changes - defined as stable or inheritable changes of genetic information without changing the DNA sequence - have a crucial contribution to differential cancer cell types. Phenotypic heterogeneity is intrinsically determined by an inherent differentiating ability. It enables stem cell to respond to various differentiation stimuli of the surrounding microenvironment (extrinsic induced heterogeneity).\(^24\) On the other side cancer cells such as the defective p53 tumor cells modulate microenvironment by exosomal transfer and reprogram macrophages to a tumor supportive anti-inflammatory state.\(^25\)

Despite of the traditional concept of stem cell diversification and plasticity the atavistic cancer stem cell model preserves the hierarchical structure of the ancestral SPC lineage (Figure 1) (Figure 2). In environmental conditions unfavorable for further proliferation and stress, atavistic sublines convert from one into the other. Subline interconversion assures the flow of phenotypic and genotypic information gained by cell fusion, reprogramming cells for pathways of increased invasiveness and resistance. Cell fusion plays a crucial role in cancer and CSC hybrids exhibit an increased differentiation capacity.\(^13–15\) Cell fusion events between CSCs and normal human cells such as fusogenic macrophages, epithelial cells and fibroblasts enhance tumorigenic capacities. Subline interconversion, also observed in the primitive protists such as invasive intestinal amoebae,\(^12\) assures on one side the somatic-reproductive transfer (SRT) and on the other the reproductive-somatic transfer (RST).

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**Figure 1** A human mitotic blocked cell (protoprecursor) escapes imminent cell death and reactivates an atavistic stem/progenitor cell lineage that bypasses mitosis and starts the reproductive cancer cell cycle.
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Figure 2 Fusogenic and clonogenic development of the tumorigenic CSC family during cancer proliferation and progression. Proliferative cells (somatic and self renewing progenitor cells) are capable of cell fusion expanding their phenotypic and genomic profile by multiple clonal expansion. The surrounding environment also modulates CSC’s. More advanced the disease more complex the CSCs. Acquired CSC properties may be propagated by both somatic and reproductive sublines.

Postgenotoxic development

Postgenotoxic reprogramming taking place in giCLSs play a pivotal role in recurrence, invasiveness and resistance to chemotherapeutics. However, it is not clear if resistance to chemotherapeutics is an acquired (adaptive) hallmark of cancer (stem) cells or an inherent atavistic property (Figure 3). In contrast to the protected cells of the inner host body, single-celled eukaryotes have been exposed over millions of years to hostile life conditions such as oxygen variation, harmful chemicals, and increased radiation. To survive they developed adaptive mechanisms for protection controlled by ancient resistance unicellular genes rUGs. It may be that some of the atavistic cancer cells express reactivated ancient rUGs. In contrast to the predominantly somatic cell fraction ~2% of the somatic cells survive genotoxic crisis. In a first step after genotoxic shock these cancer cells repair the damaged DNS regions by replication, nuclear division and “bad micronuclei” autophagy; subsequently they express their hidden reproductive differentiation potential, form giCLSs and resistant microcells, and establish a stem cell population resistant to chemotherapeutics. In other words, the genotoxic pressure exerts a selective process forming a resistant cancer stem cell population (Figure 3). Mitotically arrested p53 deficient cancer cells switch postgenotoxically into the reproductive pathway from a tetraploid G1 state that follows the mid-G2 blockage and cyclin B degradation. In our opinion the tetraploid G1 state is responsible for the epigenetic SRT that leads to formation of mother giCLSs and resistant microcells. I compare the process above with the events occurring in a printing house. In the upper floor, editors decide what will be written (reprogramming and SRT commitment). In the middle floor printing machines multiply editorial decisions (WGC by polyploidisation). On the bottom floor, cutting machines cut the individual newspapers (genome segregation, depolyploidisation, dissemination of dedifferentiated totipotent microcells). However, the pivotal decisions are coming from the editors and not from machines. The G1 phase has the determinant role both in cancer initiation and recurrence.

Concluding remarks

According to the atavistic cancer theory, cancer cell stemness cannot be simply attributed to stem cells originating from normal stem cells. Many researchers consider that cancer reactivates a “universal common gene module” (Arguello, personal communication) or “an
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atavistic unicellular gene transcription network” encrypted in the human dark genome. In our opinion cancer reactivates an atavistic stem and progenitor cell lineage inherited from the common eukaryotic ancestor that forms in humans and mammalians the cancer stem cell family. The atavistic pre-carcinogenic SPCL evolved in cancer to a more hybrid caSPCL. It remains tempting to see to what extent UGs of intestinal pathogenic amoebae resemble the pre-carcinogenic CSCs genome. The entire sequence of Entamoeba is available in the EMBL database. Similarities and differences to other cancer concepts are subjected by a separate work (see Vladimir F Niculescu: “Cancer cell of origin and cancer stem cells as they are described by the atavistic model and the cancer theories so far”).

Acknowledgement

I express my gratitude to Dr. Dennis Thomas (native English speaker) for reading the manuscript and improve my English.

Conflict of interest

The author declares no conflict of interest.

References


Citation: Niculescu VF. The cancer stem cell family: atavistic origin and tumorigenic development. MOJ Tumor Res. 2018;1(2):71–74. DOI: 10.15406/mojtr.2018.01.00015