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Trophoblastic-like transdifferentiation: A key to oncogenesis

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ABSTRACT

The epigenetic plasticity of cancer stem-like cells allows them to reprogram multifaceted properties. Being determined by an oncogene driving force, the reprogrammed properties are suitable for extensive, non-homeostatic clone expansion rather than controlled tissue generation. They belong to physiological phenotypes, under strict control in normal cells but illicitly expressed in malignant cells. Comparing the embryo nidation implemented by trophoblast with tumor progression, it clearly appears that trophoblastic and cancerous cells share strongly similar behavior and logistical properties, likely making the trophoblastic phenotype a core component of the malignant phenotype. By reprogramming it, malignant cells acquire a coordinated set of functions very efficient for survival, protection, expansion and migration. This phenotype seems to have not yet been experimentally studied in depth as to its contribution to oncogenesis. We suggest opening a specific field of research on malignant cells and host tissue receptivity, guided by the relationship between nidation and tumor implantation.

1. Introduction

Cancer cells present various anomalies, mainly oncogenic and adventitious mutations, genomic instability and an overall non-homeostatic behavior (Hanahan and Weinberg, 2000, 2011). The mutations present in cancer cells are a motley collection of gene or chromosome alterations resulting from in principle stochastic events. The ones are strictly oncogenic, participating in starting and development of the process. They cause constitutively hyper-functioning proto-oncogenes (genes driving cell proliferation) or defective tumor suppressor genes (genes involved in the cell cycle control, senescence and apoptosis, and DNA reparation). The others contribute to the genomic disorder and may have a favorable or conversely a null or negative influence on the tumor progression. Furthermore, oncogenic effects may result from a sustained cell multiplication within an inadequate local environment. This is for instance the case of aberrant proliferation due to a defective differentiation or of long-term tissue regenerating in the poor conditions having to do with chronic inflammation and atrophy. However, in contrast to the above both numerous and miscellaneous ways of entering into the malignant process, the development and the progression of cancer, as well as the host reaction, have rather constant features irrespective of the tumor type. The overall uniqueness of cancer evolution appears to be not explicable through only stochastic accumulating of various mutations or related cell malfunctioning. In particular, cancer cells consistently develop properties favorable to lasting cell survival, protection, expansion and migration. Concretely, they implement essential functions like telomere regeneration, metabolic adaptation, protection against xenobiotics and host immune reaction, induction of angiogenesis, and ability to expansion and migration. Our purpose

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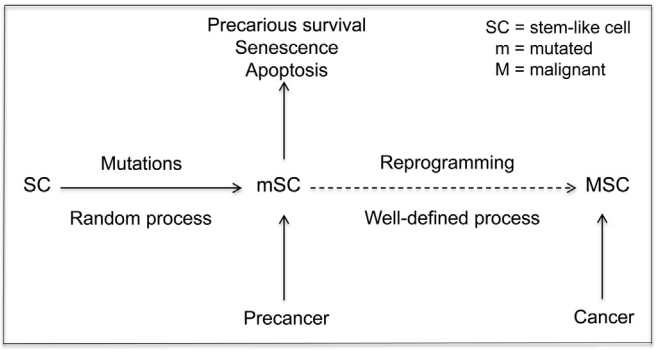

Fig. 1. The steps of malignant transformation.
Oncogene-mutated cells that have a stem profile are assumed to undertake a life-saving reprogramming. Those achieving it (infinitesimal probability) would become truly malignant stem cells maintaining and spreading the disease.

will be to discuss the rationale of this well-defined set of functional attributes and accordingly to suggest some relevant research proposals.

2. The malignant reprogramming of cancer cells

We support the idea that any cell being aggressed or having its vital status impaired does not remain passive. It responds according to the means at its disposal, certain cells having a high potential from this point of view. Thus, the epigenetic plasticity of both stem cells and progenitor cells allow them to respond through a wide and multifaceted genome reprogramming (Lunyak and Rosenfeld, 2008). Moreover, hypoxia-inducible factor (HIF) seems to enhance the undifferentiated state of stem cells (Mathieu et al., 2013).

It has been amply demonstrated that oncogenes induce cell malfunction conducive to a precarious survival with the risk of senescence or apoptosis (Hanahan and Weinberg, 2011; Halazonetis et al., 2008; Collado and Serrano, 2010).[1] However, the senescence and apoptosis foci observed in precancerous tissues have a tendency to virtually disappear after transition to actual cancer. To explain this change, we hypothesize that the precancerous cells that have a stem profile undertake an epigenetic life-saving reprogramming and that, unlike random mutations, this reprogramming is a well-defined process. Being determined by an oncogene driving force, the reprogrammed properties are a priori suitable for extensive, non-homeostatic clone expansion instead of controlled tissue generation. Thus, through their deregulating effects on proliferation, oncogenic mutations do blaze a trail for a genome-wide reprogramming associated with a deep functional corruption. Cells fully achieving it are assumed to become truly malignant cells in the sense of being equipped for immortality, vital needs sustainable fulfilling and ability to generate a continuously expanding tumor (Fig. 1). The reprogramming has nevertheless a very rare chance to succeed or otherwise the resulting cancer rate would be disproportionate to the observed one. For instance, concerning the continuous telomere regeneration implemented by the constitutive activation of telomerase or homologous recombination ALT, which is the immortality component of the malignant reprogramming, the probability is of the order of 10^{-6} or less (Shay et al., 1993). Assuming that the reprogramming probabilities of the various components are of this order of magnitude, then the global reprogramming probability, formally equal to their product, would be infinitely small, even in case of a link between some of the components.

Cell reprogramming still remains a topic of investigation getting to grips with deciphering the mechanics of that process (Cyranoski, 2014). Here we consider transdifferentiation, i.e., direct reprogramming, avoiding the pluripotent state. Such a phenomenon is currently being studied and research is in full expansion with various cocktails of transcription factors being used according to the starting and the desired final cell types (Kelaini et al., 2014; Nizzardo et al., 2013; Kagias et al., 2012; Zuryn et al., 2014; Graf, 2011). Our purpose is to consider the particular situation of oncogene-mutated cells becoming malignant cells through transdifferentiation. Such a transdifferentiation, that could be called malignant transdifferentiation, would in fact consist of a reprogramming of normally silent physiological functions aimed at cell survival and expanding. From the mechanistic point of view, it is supposed not to directly result from action of the oncogene products but to be a sort of adaptive cell transformation induced by the proliferative deregulation. The biological underlying process remains to be elucidated. Such an approach is more consistent to explain the rather overall uniqueness of cancer development than would be a model only based on various random mutations. Nevertheless, this is a very unusual situation like is the paradox of cancer cells displaying major anomalies in parallel to supplanting normal tissues.

The phenotypes contributing to malignancy, listed by Hanahan and Weinberg (2011), can be considered as plagiarizing physiological functions that are normally dormant but illegitimately expressed in cancer cells. The endogenous transcription factors of these reprogrammed phenotypes are presumed to be similar to those acting in physiological processes. According to the proposed hypothesis, the reprogrammed phenotypes are simply added to the own phenotype of the cell and do not interfere with the genetic footprint of the clone. They are exclusively functional (epigenetic) in nature and do not modify the mutational (genetic) pathway of the tumor. The identity of the tumor is respected and all the reprogrammed cells remain traceable to the original stem cell. In fact, it seems reasonable to consider that malignant tumors do present a dual heterogeneity:

- a structural, genetic heterogeneity related to random mutations understood in the broad sense of gene and chromosome alterations. The over-time added mutations lead to sub-clones containing their own mutations besides those of the primitive clone (clonal filiation) (Turajlic et al., 2015);
- and a functional, epigenetic heterogeneity related to a more or less completed, planned reprogramming aimed at cell survival and expanding. Knowing the nature of the reprogrammed cell functions would help to develop a therapy targeting the products of the associated master genes.

The obviously critical condition for the malignant reprogramming to be achieved is the unlocking of the master genes controlling the relevant phenotypes (Fig. 2). This would clearly be a key-point of susceptibility to cancer. Thus, considering the numerous putative cancer-causing factors, it finally appears that both the risk and the severity of cancer would ultimately depend on the issue regarding two factors:

- on the one hand the level and quality of both oncogenic and adventitious mutations, de facto depending on genome control-and-repair efficiency;
- and on the other hand the more or less easiness of unlocking the master genes involved in the malignant reprogramming.

[1] A cell may become unable to produce a progeny through either senescence (non lethal persistent post-mitotic status) or apoptosis (controlled cell self-destruction). For instance, benign melanocytic nevi are visible clusters of senescent cells.