QUADERNO

IL CANCRO E LA SUA COMPLESSITÀ: SPIEGARE E CURARE IL CANCRO: TEORIE SULLA CARCINOGENESI E APPROCCI TERAPEUTICI

CANCER AND ITS COMPLEXITY: EXPLAINING AND CURING CANCER: THEORIES ON CARCINOGENESIS AND THERAPEUTIC APPROACHES

Cancer is ontogenetically pre-programmed

Il cancro è ontogeneticamente pre-programmato

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Currently we experience crisis of the concept on the origin of cancer. The reductionistic theory of cancer origin from stochastic somatic mutations is stagnating and the best witness of its failure are the patients, which continue to die from advanced cancer. The concept of cancer stem cell (CSC), which appeared relatively recently as a complementation to somatic mutation theory needs to be put into the evolutionary biological context. This commentary is an attempt to return through CSC bridge to the most old embryological theory of cancer origin proposed in the 19th century. This theory postulates that immortality of cancer cells is achieved through the ontogenetic cycle of reproduction. It may represent the evolutionary primitive life-cycle which remained preserved in the genome memory of higher organisms and is recapitulated in their early embryogenesis and cancer.

Keywords: Cancer, immortality, embryonality, life-cycle, stem cells

Attualmente sperimentiamo la crisi del concetto sull'origine del cancro. La teoria riduzionista sull'origine del cancro da mutazioni somatiche stocastiche è stagnante e la migliore testimonianza del suo fallimento sono i pazienti, che continuano a morire di cancro avanzato. Il concetto di cellule staminali tumorali (CSC), che è apparso in tempi relativamente recenti come complemento alla teoria della mutazione somatica ha bisogno di essere messa in un contesto biologico evolutivo. Questo elaborato è un tentativo di ritornare attraverso il ponte CSC alla più vecchia teoria embriologica sull'origine del cancro proposta nel 19° secolo. Questa teoria postula che l'immortalità delle cellule tumorali è ottenuta attraverso il ciclo ontogenetico della riproduzione. Essa può rappresentare l'evoluzione del primitivo ciclo di vita che è rimasto conservato nella memoria del genoma di organismi superiori ed è ricapitolato nella loro precoce embriogenesi e nel cancro.

Parole chiave: *Cancro, immortalità, embrionalità, ciclo di vita, cellule staminali*

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Background

When President Nixon signed in 1971 the National Cancer Act and huge financial resource was directed for the war against cancer many expected quick results. After more than 40 years the progress in cure of cancer patients is still poor. The world leader of cancer research Robert Weinberg recognised in his article Cell March number 2014 (Weinberg, 2014) the current lack of conceptual paradigm for dealing with the complexity of cancer. The title of the article "Coming Full Circle – From Endless Complexity to Simplicity and Back Again" points to the epistemological cause of the cancer research failure – reductionism. The latter was inspired by the discovery of the genetic code and quick success of molecular biology and biotechnology since the middle of the 20th century, which put in shadow for long decades the achievements of the preceding period of cancer research started in the end of 18th and flourished in the19th century. Central of them was the embryological theory of cancer recognising a certain analogy between development of fertilized egg and fetality of cancer cells (rev. Erenpreiss 1993; Vinnitsky 2014). However, in light of the molecular-biological animation of the 20th century the nature of cancer was thought to be purely molecular as induced by stochastic somatic mutation of one or a few genes regulating cell proliferation. Such oncogenes were discovered in early 70ths and the involved pathways were enthusiastically explored. However, further the avalanche of the genes and proteins involved in cancer and their potential targets for therapy grew in a geometric progression. Now we are in the paradoxical situation when so many ways lead to cancer, the therapy of advanced cancer (*except of definitive surgical cure of localized cancers)* is largely ineffective (does not prevent in most cases the eventual death of patients from relapse of cancer), thus the money spent for research performed under the' molecular lantern', was largely wasted. "We fought cancer… and cancer won" was concluded by an observer of the Newsweek journal (Begley 2008).

Description

Cancer genome sequencing project paradoxically discovered some proportion of tumours with no cancer *census* genes or no mutations at all (Wheeler and Wang, 2013). As well paradoxically, cancer can be phenotypically normalized by only putting the tumour into normal 3D stroma context (Weaver V et al., 1997) or in the embryological morphogenic field (rev. Bizzari et al., 2011). Cancer cell nucleus can be reprogrammed by nuclear transfer into enucleated egg and go on to direct early development (McKinnel et al., 1969). Normal genetically mosaic mice can be produced from malignant teratocarcinoma cells injected in blastocyst (Minz and Ilmensee 1975). On the contrary, the embryonic tissue put in adult converts into tumour (Stevens 1970). These and similar data were opposed to the views based on somatic mutation theory (SMT) as generalized by the phrase: "cancer is development gone awry" (Sonnenschein and Soto, 2013). The most paradoxical from the point of SMT seems the fact that less genes are needed for cancer reverse – only 300 (Telerman and Amson 2009) than found in its progression – more than 13,000 mutated genes as registered in different tumours by Cosmic database 2010 (Forbes et al., 2010).

It seems that time has come to put the things from head on feet. These paradoxes mean that cancer does not result from breakage of anything (although somatic mutations certainly favour cancer), which can be just repaired or substituted and in this sense it is not a common disease, like heart failure. The accumulated data rather evidence that cancer is a developmental programmed response to disturbance (which can be generally described as DNA damage) with a certain purpose.

The key to this purpose is the immortality of cancer cells (Ērenpreisa and Cragg, 2007, 2010). When normal somatic cells are put in culture they divide for a limited number of times and then die – soma is mortal when the Hayflick' limit is exhausted (Hayflick and Moorhead, 1961). In contrast, when cancer cells are put in culture – they can live and divide indefinitely long. Cancer patients of whom cell cultures were obtained and used for decades in laboratories have died long ago. Each of us will also die. But what is immortal in us? It is the germline. It is transfer of genetic material by sexual cells from one generation to the other, from parents to children and their children and their children… This biological law of the germ immortality was discovered by August Weismann (1892). And the very first researchers of cancer advanced the embryological theory of cancer suggesting that cancer cells repeat something similar to this life-cycle, which thus explains their immortality. At that time this theory was suggested in different variants by several scientists, among them such prominent as David Hansemann and Rudolf Virchow (rev. Erenpreiss 1993). However historically the Breslau pathologist Julius Conheim (1877) was recognized as a founder of the embryological theory of cancer, because he formulated it in the most general form. In particular, he postulated that cancer develops from the embryonic rudiments retained in adult tissues. One of the contemporary variants is the Oncogerminative theory of cancer recently published in the up-dated variant by Vladimir Vinnitsky (2014). Therefore, it seems now useful to look at the current twist of the embryological theory of cancer.

This new twist is associated with revelation of special properties (which generally mean self-renewal and multi-potentiality) of a proportion of cancer cells found in each malignant tumour consequently called cancer stem cells (CSC). These cells can divide asymmetrically promoting both self-renewing and differentiating cancer cells with a limited life span (rev. Reya et al., 2001). This new situation shows

us at once several consequences: (1) The multi-potentiality and plasticity of CSC can explain us why these cells are so almighty for inducing malignancies and why the targeted therapies fail – if we hit one pathway, they can shift to another one and rescue vital functions; (2) It shows that stem cell properties of cancer cells are of the epigenetic origin and might be potentially reversible if CSC could be preferentially directed onto the differentiation pathway; (3) On the contrary, it was recently discovered that so called differentiated tumour cells possess epigenetic plasticity and can be reversed to CSC or their close progenitors by genotoxic treatments (Salmina et al., 2010) or micro-environmental signals (Chaffer et al., 2013) – so revealing a 'dark side' of the general chemo-radiotherapy schemes (rev. Vlashi and Pajonk 2014). Moreover, it was found that although CSC likely arise from adult stem cells residing in normal tissues, the aggressive tumours acquire the toti-multi-potent gene expression signature of the early embryo cleavage and embryonic stem cells stage (Ben Porath et al 2008). So, here we arrive again to the embryological roots of cancer and namely to its very early ontogenetic stage – the embryonic cleavage. At this stage, the blastomers generated by the first divisions of fertilized or parthenogenetically activated egg retain the toti-potency and very early in the blastula epiblast they segregate a group of the germline-determined cells, which will bring the relay of immortality to next generations.

To understand how these seemingly 'impossible' events can happen with a somatic cell of a higher multi-cellular organism and why cancer is so almighty, we should turn to phylogeny – to the evolutionary origin of sexual reproduction. Sexual reproduction has two fundamental aspects: (1) repair of the DNA breakage by recombination; (2) outcrossing (Bernstein et al., 1985). It was preceded by asexual reproduction that does not need fertilization, a kind of reproduction providing immortality transfer and still widely present in various, even high organisms. Two events emerged simultaneously during evolution: multi-cellularity dividing labour between cells (differentiation) and sexual reproduction with embryonic cleavage and gastrulation. However the first event was the asymmetric division in only two basic cell lines – precursors of soma and germ, which is a minimum requirement for any multi-cellularity (Monroy, 1985). The early evolution of germ cells (with no distinction of male and female) and multi-cellularity is illustrated by the algae Volvovales (Bell, 1985). In hostile environment, these unicellular organisms began to divide without completing cell division, so forming a multinucleated karyoplast, which allowed decrease of cell surface per mass, masked lethal mutations and developed energy-saving metabolic and detoxication pathways. When the environment conditions improved, the subnuclei cellularised again and again the unicellular members of the colony were free to go on themselves. In addition, there appeared organisms with facultative sex which, in inappropriate environment, switched from the asexual to sexual reproduction (meaning fusion between male and female gametes), which allows more genetic variability. It is thought that such adaptations finally lead to the origin of multicellularity and segregation of specialized reproductive cells from somatic cells, the latter served for a certain time and eventually died. And so on, increasing the complexity of differentiation function to more than 200 different kinds of tissues in mammals. But the primitive life-cycle is likely still imprinted in the early embryonic development, in which the organisms apparently recapitulate evolution of this process (Ērenpreisa and Cragg, 2008, 2011), where initially being totipotent like unicellurians, the blastomers first segregate the immortal germline.

Under challenge to their vitality usually signaled through DNA damage (as a result of mutations, chronic inflammation, trauma, and other reasons aggravating with aging) the normal mammalian cells (including adult stem cells and may be any cell of the organism) can illegitimately recapitulate the evolutionary life-cycle, which produce immortal germ-like descendants and become cancerous. Curiously, for that they likely use the most ancestral variant of reversible endopolyploidy described above for *Volvox*, which served an ancestor of meiosis and sex (briefly rev. Ērenpreisa et al., 2005). It can be suggested that this shortened ontogenetic cycle is coded in the genome memory of multi-cellularian somatic cells and becomes available in stressed conditions, mostly after overcoming the barrier of tumour suppressors. Thus, it represents adaptation to DNA damage by a programmed life-cycle-like process. In fact, cancer is a tribute to evolution and a consequence of costly complexity of higher organisms.

One may ask on the place of aneuploidy, somatic mutations, and genetic drift in this process. Certainly, they are the players in carcinogenesis. However, aneuploidy creating most of genetic mutations is in principle anti-proliferative by purely mechanic reasons. The chromosomal (aneuploidy) theory of cancer as such (Duesberg et al., 2006) and similar reasonings (based on the experimental settings which may be not adequate from the holistic point of view) that rearrangements of some chromosomes drive tumour growth while of the other impede or counterbalance it (Weaver and Cleveland 2008) as well as the reasoning on tumour progression by means of only mutations and clonal selection do not provide a simple and satisfactory explanation of immortality acting invariantly as a biological law, while the embryological theory of cancer does. In addition, it is interesting to note that the genome instability is a characteristic feature not only of cancer but also of the early embryo cells (Vanneste et al., 2009). Comprehension of this fact urges to think on the genome instability as a necessary chaotic component of embryogenesis and carcinogenesis by pre-programmed self-organisation and attraction (Prigogine and Stengers, 1984; Kauffman, 1993; Huang et al., 2009).

Conclusion

Although cancer is largely initiated by stochastic gene mutations, they are not responsible for immortality of cancer cells. It is hypothesized that cancer is driven by a programmed adaptive response to genotoxic stress (DNA damage) which was developed in evolution of protists during their transition to multi-cellular organisms as a life-cycle with segregation of germ. Just this process through which tumour cells obtain and transfer their immortality assigns them the embryonic (CSC) features. This view allows integrate somatic mutational, chromosomal, CSC, as well as tissue-based theories with the oldest concept – the embryological theory of cancer.

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