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editorial article

# Cancer stem cells in surgery

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SUMMARY: **Cancer stem cells in surgery.**

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*The Cancer Stem Cells (CSC) hypothesis is based on three fundamental ideas: 1) the similarities in the mechanisms that regulate self-renewal of normal stem cells and cancer cells; 2) the possibility that tumour cells might arise from normal stem cells; 3) the notion that tumours might contain 'cancer stem cells' - rare cells with indefinite proliferative potential that drive the formation and growth of tumours.*

*The roles for cancer stem cells have been demonstrated for some cancers, such as cancers of the hematopoietic system, breast, brain, prostate, pancreas and liver.*

*The attractive idea about cancer stem cell hypothesis is that it could partially explain the concept of minimal residual disease. After surgical macroscopically zero residual (R0) resections, even the persistence of one single cell nestling in one of the so called "CSCs niches" could give rise to distant relapse.*

*Furthermore the metastatic cells can remain in a "dormant status" and give rise to disease after long period of apparent disease free. These cells in many cases have acquired resistance traits to chemo and radiotherapy making adjuvant treatment vain.*

*Clarifying the role of the cancer stem cells and their implications in the oncogenesis will play an important role in the management of cancer patient by identifying new prospective for drugs and specific markers to prevent and monitoring relapse and metastasis.*

*The identification of the niche where the CSCs reside in a dormant status might represent a valid instrument to follow-up patients also after having obtained a R0 surgical resection. What we believe is that if new diagnostic instruments were developed specifically to identify the localization and status of activity of the CSCs during tumor dormancy, this would lead to impressive improvement in the early detection and management of relapse and metastasis.*

KEY WORDS: Cancer stem cells (CSC) - Relapse - Metastasis - CSCs niches - R0 surgical resection.

More than 150 years ago, the German pathologist Virchow proposed the theory according to which cancers might originate from immature cells (1). Later, Cohnheim (2) and Durante (3) introduced the concept that adult tissues still contain dormant embryonic remnants that in particular conditions could be activated and give rise to a tumor. Only in the 1959 Makino (4) was the first author to introduce the term "tumour stem cell" defining them as "a small subpopulation of cells that were insensitive to chemotherapy and had chromosomal features different from the bulk of cells". Experiments proved these cells are potentially able to reiterate all cell types within an individual tumorand establish immortal cell lines (5-7).

Normal stem cells defined by their long term replicative potential, their ability to give rise to more differentiated subtype of cells in a particular organ and by their capability of self-renewal and perpetuate themselves giving rise to daughter cells which are identical to themselves with the same proliferation, expansion, and differentiation potentials. Thus maintaining intact the stem cells pool.

The Cancer Stem Cells (CSC) hypothesis is based on three fundamental ideas: 1) the similari-

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ties in the mechanisms that regulate self-renewal of normal stem cells and cancer cells; 2) the possibility that tumour cells might arise from normal stem cells; 3) the notion that tumours might contain 'cancer stem cells' - rare cells with indefinite proliferative potential that drive the formation and growth of tumours (8).

Because normal stem cells and cancer cells share the ability to self-renew, it seems reasonable to propose that newly arising cancer cells appropriate the machinery for self-renewing cell division that is normally expressed in stem cells (8). The idea that CSC could be at the base of the carcinogenesis is supported by the fact that CSC proliferate throughout life and therefore are more likely to accumulate genetic mutations compared to the more differentiated cells with shorter life span (9, 10). Normal stem cells are notable for the vigilance with which their proliferation is controlled and for the care withwhich their genomic integrity in maintained. Tumorgenic cells are frequently distinguished by their lack of control of such processes (11). A consistent observation supporting the CSC theory is that the de-regulation of normal stem cells function could be linked to carcinogenesis. Many genes that promote self-renewal are also oncogenesand many genes that inhibit self-renewal are also tumor suppressor genes (11). The roles for cancer stem cells have been demonstrated for some cancers, such as cancers of the hematopoietic system, breast, brain, prostate, pancreas and liver.

Studies have proved that normal stem cells and cancer stem cells express different surface markers. This would allow bio-molecular techniques to identify and differentiate the two types of cells. For example CD133 surface markers also known Prominin 1 is a transmembrane glycol-protein considered as an indicator but not as a reliable markers for CSC since its expression has been proved by CSC but also by other subpopulation of cells (12). Another technique proposed for the identification of CSC is the Hoechst-dye exclusion assay (13).

The attractive idea about cancer stem cell hypothesis is that it could partially explain the concept of minimal residual disease. After surgical macroscopically zero residual (R0) resections, even the persistence of one single cell nestling in one of the so called "CSCs niches" could give rise to distant relapse. Furthermore these cells might acquire genetic traits enablingmechanisms of resistance to chemotherapies.

With the development of new and cutting-edge technologies for the detection of cancer in their early stages and surgical techniques to achieve residual zero resections, cancer treatments nowadays have curative intents in many cases. Neo-adjuvant and adjuvant radiation and chemotherapy aim to reduce the relapse and metastasis rate. Despite all these advances, the global mortality rate for many tumors remains stable. This disappointing data can be explained with some observations. Metastasizing potential is acquired in the very early stage of the cancer life, therefore even the early detection and treatment sometimes cannot prevent the cancer cell systemic seeding. Furthermore the metastatic cells can remain in a "dormant status" and give rise to disease after long period of apparent disease free. These cells in many cases have acquired resistance traits to chemo and radiotherapy making adjuvant treatment vain.

Clarifying the role of the cancer stem cells and their implications in the oncogenesis will play an important role in the management of cancer patient by identifying new prospective for drugs and specific markers to prevent and monitoring relapse and metastasis.

The identification of the niche where the CSCs reside in a dormant status might represent a valid instrument to follow-up patients also after having obtained a R0 surgical resection. What we believe is that if new diagnostic instruments were developed specifically to identify the localization and status of activity of the CSCs during tumor dormancy, this would lead to impressive improvement in the early detection and management of relapse and metastasis.

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