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Cancer Stem Cell and its Influence in Carcinogenesis – An Update

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Abstract

For long, cancer is widely considered a heterogeneous disease. Due to recent evolution in technology, we have bypassed simple pathological analysis, immunohistochemistry evaluation and molecular genetics to characterize cancer as an individual and static disease. In fact, pathology has for long been the "gold standard" to characterize cancer within each type, in many different subtypes according to its oncological behaviour, aggressiveness and tailoring treatment. Now-a-days, rapid analysis of cancer genome at a single nucleotide level, has allowed scientists to define inter-tumour heterogeneity, at the basis of somatic alterations, which are common between tumours with the same histology (gold standard).

Keywords: Cancer stem cell; Carcinogenesis; Solid tumours; Targeted therapies; Genetic diversity

Introduction

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Not all tumors are cancerous; benign tumors do not spread to other parts of the body. Peter Nowell first described the concept of clonal cell cancer evolution in 1976 [1]. It has been applied to try to understand tumour growth, aggressiveness, and resistance to treatment, migration, proliferation and metastization. This has been confirmed, through time by many clinicians that the same cancer subtype doesn´t behave in the same way. The natural history of each cancer arises from a single "mutated" cell that acquires biological capacity to progress and bypass environmental diversity's.

Besides all the advances in target therapy, many patients still fail to survive because they develop primary and acquired resistance [2]. Much is yet to be understood. We cannot keep on thinking only on tumour heterogeneity, but also that the tumour grows up in a complex ecosystem, with many cell types such as endothelial, hematopoietic, stromal and other types that can influence the tumour main driver pathway to survival [3,4]. Genetic diversity, tumour micro-environment and epigenetics are coming together and influence the concept of maintenance of stem cell state. This revolutionary idea changed the historical concept that tumour cells may harbour stem cells, and with these active properties they may influence carcinogenesis and patient's outcome as never seen before.

Literature Review

What is the rationale for the use of cancer stem cells in solid tumours?

Normal stem cells are rare intra-organ cells with the capacity of self-renewal, which can generate all kind of different cells that make up an organ and lead to organogenesis. On the other hand, cancer stem cells (CSC) are rare intra-tumoral cells, a sub-population of cancer cells with auto-renewal capacity; generate phenotypically diverse tumour cell lineages, leading to tumorigenesis. These cells are considered highly malignant, fundamental for the growth of neoplasia, for recurrence, for drug resistance and for metastasis. Also they are considered highly resistant to chemotherapy, radiotherapy and target therapeutics. As known, the operational concept of a stem cell is maintenance of long-term clonal growth, keeping its functional properties and repopulation. On the other hand, they have been isolated in the vast majority of tumours, colon cancer, breast cancer, ductal adenocarcinoma of the pancreas, glioblastoma, and many others, becoming a potential target for the treatment of oncological diseases [5-15].

It is becoming increasingly clear that CSCs play a key role in the pathogenesis of many solid tumours. CSCs have been isolated from many solid tumours in humans using the combination of cell surface markers, including CD44, CD24, ESA 18 among others **(Table 1)** [16,17]. These CSC play a predominant role in the initial phase of tumorigenesis [18,19]. In addition, CD133, present on the cell surface of these cells, gives them great proliferative capacity [20], and the positive marker expressed in cells surface such as CD133 and CXCR4 gives them the capacity to migrate and to metastases [20]. It is also worth mentioning that CSC expressions in solid tumours are related to patient's lower survival [21]. These facts suggest

that inhibition of CSCs may be a therapeutic target for cancer **(Table 2)**.

Table 1 Biomarkers of CSC.

Tumour Type	Representative Markers
Acute myeloid leukemia	CD34+/CD38-
Breast cancer	CD44+/CD24-, ALDH1+
Colorectal cancer	CD133+/CD44+/ALDH1+, EpCAM+/CD44+, CD166+, CD44+/CD24+, Lgr5+/GPR49+
Metastatic Colon	CD133+/CD26+
Gastric cancer	CD44+
Liver cancer	CD133+/CD49f+, CD90+/CD45-, CD13+, EpCAM+
Pancreatic cancer	CD133+/CD44+/CD24+/ESA+, CXCR4+
Esophageal cancer	CD44+/ALDH1+

Table 2 Therapeutic agents targeting dysregulated signalling pathways in CSC.

CSC Target	Therapeutic Agent
STAT3	Napabucasin
LRP/FZD	Vantictmab
WNT	Ipafricept
Anti-DLL4	Demcizumab
NOTCH	Tarextumab

Many signalling pathways described, have shown to be dysregulated in CSC. The most known ones are: Wnt/β-catenin, Hedgehog (Shh), Notch, JAK/STAT3 pathways. Many new molecules are now being developed and tested in clinical trials, to block theses pathways, which are uncontrolled in cancer stem cells. Some of these new small molecules block the self-renewal and induction of apoptosis in CSCs. Although, not recognised as kinase inhibitors, they act inhibiting the Wnt/β-catenin pathway, STATE 3 pathway, the NOTCH pathway and the hedgehog pathway. The STATE 3 pathway is critical for the self-regeneration and survival of CSCs in various neoplasms. Inhibition of this pathway inhibits cell proliferation *in vitro* and reduces tumour growth *in vivo* [22,23]. The STATE 3 pathway is connected to β-catenin pathway activity, which is also very important in the early stage of carcinogenesis and progression of disease in many cancers.

Some of these pathways, which are dysregulated, are more common in some types of cancers. The Wnt/β-catenin pathway is mostly dysregulated in colorectal cancer and epidermal cancer; the hedgehog pathway is dysregulated in colorectal cancer, gastric cancer, pancreatic cancer, basal cell carcinoma and medulloblastoma; the NOTCH pathway in colorectal cancer, pancreatic cancer, breast cancer and leukemia and finally, the JAK/STAT3 pathway in colorectal cancer, gastric cancer, breast cancer and glioblastoma [16,17].

Another query is how to identify these subclones which express dysregulation of these crucial pathways ? Science has advanced and identified sub-populations, which are eventually responsive to the blockage of these new molecules. This sub-population of clones of patients with tumor-positive biomarkers are those which are stained by (fixed paraffin-block and formalin-fixed) immunohistochemistry (IHC) for β-catenin and phosphate-STAT3.

New and Future Perspectives

In the last years, many gigantic steps were taken in understanding how cancer survives multifactorial mechanisms of cell control. Besides the already mentioned, incredible advances in genome sequencing to identification of specific somatic mutations, may targets can be aimed by new agents, also in constant evolution due to primary or secondary resistance. Nevertheless, the concept that a tumour is a family of distinct sub-clones, still finds many resistance in clinical practice. In fact, it has become clearer that a tumour does not have a single genome, but multiple genomes, which belong to different sub-clones. These different sub-clones will contribute to tumour intra-tumoural heterogeneity. Nevertheless, these different sub-clones don't all behave in the same way: some are active and maintain their capacity of auto-renewal and are pluripotent, others remain dormant in a quiescent form and others are in a post-mitotic condition and run into apoptosis.

The new revolutionary concept that one or more of these clones may harbour CSC, redefines the driver clone "the harmful cancer clone" that attributes the growth and survival potential. These cells in fact maintain the embryological potential to maintain its primary capacity to stimulate their own oncogenes and inhibit the tumour suppressor genes, favouring carcinogenesis. These clones are the hierarchy of tumour survival, and should be the main aim to personalize medicine in the near future. In first place, tumour genetics, epigenetics and carcinogenic pathways as well as the microenvironment should be highly considered and not neglected into backstage. Secondly, in the new era of personalized medicine we must open our minds to the new the concept of existing CSC in tumour clones **(Figure 1)**. Comprehending the diversity of these sub-clones will allow us to understand, how each of them orchestrate their own functions, their place in hierarchy chain of sub-clones, allowing tumour maintenance and survival.

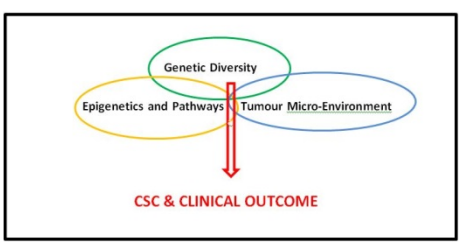

Figure 1 CSC and it's implication in clinical outcomes.

Combination of CSC inhibitors with cytotoxic therapy may likely improve and maximize therapeutic efficiency. Thus, the concept that all subclones in the host tumour, with their own CSC must be targeted in order to eliminate the cancer successfully. Many phase I and II trials are on way namely in pancreatic cancer as shown in **Table 3.**

Table 3 CSC- Targeted therapies in pancreatic cancer.

Phase	N	Treatment
Ib	37	Napabucasin + gemcitabine + nab-paclitaxel
Ib/II	41	Napabucasin + paclitaxel
Ib	24	Frontline Vantictmab + gemcitabine + nab-paclitaxel
Ib	22	Frontline Ipafricept + gemcitabine + nab-paclitaxel
Ib	56	Frontline Demcizumab + gemcitabine +/- nab-paclitaxel
II	207	Frontline Demcizumab + gemcitabine + nab-paclitaxel vs placebo + gemcitabine + nab-paclitaxel (ongoing not recruiting)
Ib/II	217	Frontline Tarextumab + gemcitabine + nab-paclitaxel vs placebo + gemcitabine + nab-paclitaxel

Conclusion

Ongoing clinical trials have to be analysed to conclude unanswered questions, such as which is the best way to target tumours with CSC? Science progression has to be awaited to answer the question “how?” but it gets very confusing when you ask “why?”. But certainly, the winner will be the best combination in the right sequence and in the right timing.

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