BACKGROUND (THE CHAOS): An Attempt towards Naming and Family Naming of Cancer Stem Cells and Their Descendants.

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Short Communication:

The Cancer Stem Cell [CSC] hypothesis envisages cancers to be made up of a variable sized population of cells with self renewal and differentiation properties. CSCs multiply through symmetric and asymmetric divisions to regenerate their own kind or generate transit amplifying cells [TAPs] which self-renew a certain number of times before differentiating into fully differentiated cells [DFC]. CSCs have tumorogenous properties, are relatively more resistant to various forms of therapy and are considered to be the seedbeds of recurrence following therapy. Targeting them bore the promise of the “elusive cure” in many cancers [1]. With time it has been found that the currently apparent truth is far more complex. A tumor can and usually contains different types of CSCs throwing up the seemingly insurmountable challenge of CSC heterogeneity [2,3]. These CSCs have different dynamic properties which imply that their derivative TAPs and DFCs are also likely to be heterogeneous, implying the presence of dynamically distinct compartments, based on their parent CSCs. [Figure1]

To add to the woes, the paradigm of “Stem cell plasticity” has revealed that, when exposed to appropriate conditions, non-CSCs may Trans-differentiate back into CSC state, potentially adding to the heterogeneity and the chaos [2]. This implies that it is possible to derive a cancer stem cell [thus initiating a new compartment] from a transit amplifying cell or differentiated cell of an earlier compartment as a result of dedifferentiation. Although some markers have demonstrated the heterogeneity in CSCs [CD133 positive and negative CSCs in Glioblastomas [for example], it is still not possible to identify all the different CSCs and their derivatives [3] by currently available markers alone. However in the future it might be possible to devise ways to identify these cells as being members of particular compartments.

In that case there should be a theoretical framework which will take into account not only the heterogeneity but the generation of new compartments from pre-existing ones to better define intra-compartmental and inter-compartmental feedback mechanisms. Heterogeneity is assumed to be due to the generation of new CSCs from CSCs or their progeny from previously established compartments. They may be referred to as parent compartments and derived compartments respectively as shown in [Figure 2]. The possible familial relationships between the compartments have been shown in [Figure 3] and they have been numbered successively based on the parents and derivative compartments.

The Proposed Method: An Attempt Towards Order [Genealogy Of Cancer Cells] [Figure 4]

A cell is identified as a combination of letters and numbers. The general format is \( C_{KLMN} \).

i) \( C \) identifies the cell type and takes values of S, T or D based on whether they are “Cancers stem cells” CSCs, Transit Amplifying cells [TAP]s or DFCs.

ii) \( K \) identifies the compartment number and takes values of 1 to n.

iii) \( L \) identifies the compartment from which the parent CSC of this compartment was derived and takes values from 1 to n-1.

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ii) \( K \) identifies the compartment number and takes values of 1 to n.

iii) \( L \) identifies the compartment from which the parent CSC of this compartment was derived and takes values from 1 to n-1.
iv) $M$ takes the values of 1, 2, 3 depending upon the level of the previous compartment from which that CSC was derived in the following way such that it takes the value of 1 if it was derived from a CSC, 2 if it was a TAP and 3 if it was a DFC.

v) $N$ denotes the generation number i.e. number of times the cell has divided.

**Two Illustrative Examples**

Example 1: Cell identified as S[2,3,4,5] denotes

I) S- CSC
II) 5- Compartment 5
III) [2,3] Derived from a TAP [value2] of Compartment 3
IV) 5- Undergone 5 cell divisions

Example 2: Cell identified as T[2,3,6,7] denotes

I) T- TAP
II) 6- Compartment 6
III) [2,3] Parent CSC was derived from compartment 2, through dedifferentiation of a DFC
IV) 7- Undergone 7 divisions

**Comments**

The method takes into account cellular hierarchy, CSC heterogeneity related multi compartmentalization and cellular plasticity to impart some order to the ever-evolving chaos in cancer biological concepts. It could be of relevance in the future when it might be possible to clearly identify CSCs and their derivatives as distinct entities based on their compartmental membership and study the effects of the microenvironment and therapy on them individually.

**References:**

3. Piccirillo SFM: Fluorescence guided sampling of Glioblastomas identifies phenotypically distinct tumor initiating cell populations in tumor mass and margins. BJC (2012); 107; 462-468