# Lineage Origins and Precursors of Cancer Stem Cells

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## Abstract:

Mutations of the somatic oncogenes have been known to cause cancers. However it has been cast aside as to how the stem cells and at which stage(s) of their differentiation processes get "afflicted" by the activation of oncogenes, unless the origins of mutated oncogenes lie in the stem cells themselves. If the latter is the case, then what is suggested as "affliction" refers in our thinking to possible recombination between a cancer cell carrying an activated oncogene and a benign stem cell. This is even more so when the cancer stem cell (CSC) has been proposed to be largely, if not totally, therapy resistant and the cancer cell (CC) consists solely of the markers of malignancies despite loss or absence of the stem cell phenotypes. However it is the chicken and egg issue between the CC and CSC, for the acquisition of the tumorigenic antigens. Herein is described through evaluation of the available studies, the logical deduction of the emergence of CSC in conjunction with a malignancy as is implied.

**Keywords:** Cancer, ESC, MSC, HSC

**Activation of oncogenes**

The advent of Next-Generation Sequencing (NGS) enables rapid detection of single nucleotide polymorphism (SNP) mutations not only in DNA of somatic cells but also in differentiated stem cells, notwithstanding, in the yet to begin to differentiate embryonic stem cells (ESCs) as well [1,2]. Detection of such mutations in these different types of cells can well be predictors of pre-existing SNPs of oncogenes for an early onset of malignancy [3]. In addition, advanced knowledge on the susceptibility to activation at a later date may well be lying within the extended upstream and/or downstream sequences of the known tumor antigens, should multiple SNPs of the oncogene are an individual genome specific requisite.

**CSCs versus CCs**

It is more plausible for a CSC to be the precursor than a CC for acquirement of the malignant phenotypic characteristics, should it happen during differentiation of the stem cells prior to their terminal lineage formation. In a preceding manner, CCs may develop due to environmental factors including pollution, diet and lifestyle, independent of stem cell involvement. For a CC to transfer its mutated oncogenes to a CSC likely requires CC – CSC recombination, which could well be a part of metastasis post-mutational events of oncogenes [4]. However hereditary mutations within the ESCs could be a malignancy process carrying early predisposition to onset of the disease.

**Candidates for CSC**

Genetically "defective" ESCs carrying SNPs or other mutations within the oncogenes presumably are prone to earlier activation and thus are susceptible to generate CSCs during their differentiation pathways [6, 7]. As generally perceived, apart from the differentiation of ESCs into cardiomyocytes, all other lineages of stem cells are known to become cancerous. This could happen at the stem cell level but then also after losing expression of their stem cell markers and thus as terminally differentiated cells, through transformation followed by their uncontrolled proliferation as CCs. Leukemias are attributed to malignancy of the hematopoietic stem cells (HSCs) [8]. It is not clear if precursors for the other cancers lie

within the HSCs and get embedded into, or fused with cells of initially selective organs of the body, if hematopoietic cancer stem cell (HCSC) to CC (tumor) is generated. If not, do the pervasive and reportedly multi-purpose-beneficial mesenchymal stem cells (MSCs) turn adversaries in several other types of tumour formation? Vascularisation of differentiated malignant MSCs into HSCs followed by their multi-lineage formation is a plausible explanation for the migration of CCs during the metastasis which occurs at later stages [9].

In our previously reported generation of HCSCs in humanized mice using intra-implant injections of Melanoma-624 cancer cells into human fetal thymus/liver conjoint hematopoietic organ, solid tumors were seen as well as excessive bleeding post-sacrifice and excision of the tumours for their cell cultures ex vivo [10]. Thus, fusion of CCs with human HSCs evidently had occurred in vivo, as well as expected malignant transformation wherein the transfer of phenotypes from melanoma CCs to HSCs via fusion to generate hHCSCs [11]. At that time, post-fusion ploidy was not determined. So also, pathological examination of the surgically opened tumour sites was not conducted to determine if the bleeding emanated from any leukemic disorders other than from the animals' systemic blood circulation.

**Brain Tumors and BBB**

Blood-brain barrier (BBB) is considered an obstruction to spread of circulating metastatic cancer cells and treatment methods including conventional chemotherapy [12-14]. Besides the targeting of specific drug nanoparticles, MSCs have been shown to cross the BBB for alleviation of brain tumours [15, 16]. However whether the expectedly beneficial effects of MSCs will become susceptible to form mesenchymal cancer stem cells (MCSCs) at some stage also requires to be considered, if such a study is to be undertaken. NGS of the generally allogeneic MSCs prior to their use for such therapies is to be considered for presence of predisposition to mutational events leading to subsequent oncogene activation and ensuing development of cancers. Also whether the gliomas are self-generative within the brain, or arise from systemically circulating cancer cells crossing the BBB, is also to be evaluated. This would draw our attention to the earlier stated SNPs and subsequent activation of oncogenes when defective ESCs differentiate into neural cell lineages and their post-homing into the brain.

**Conclusions**

In the absence of genetic information on stem or somatic cells to foretell / predict the lineage origin and onset of malignancies, we will have to conclude that as evident, cancer is on the rapid rise in modern civilisation due to changes in diet, lifestyles and environment (Figure 1). Circumventing this argument that better diagnostic tools for disease detection are increasingly available is not a consoling argument, as material development of previously under or less developed countries' populace is statistically now more vulnerable to cancers. On the better side and in support, eschewing of smoking and tobacco are examples of increased awareness and precautionary measures. At the same time, ancient civilisations using herbal and plant products besides cleaner air and physical labour were better equipped with counter-active healthy habits at home and type of work for cancer prevention. Needless to state that intake of highly processed foods and also injections of hormones (more so if chemically synthesized) into making animals fatter at a quicker pace, to gorge up their meat, eggs and animal products are examples of greatest threat for acquirement of cancers.

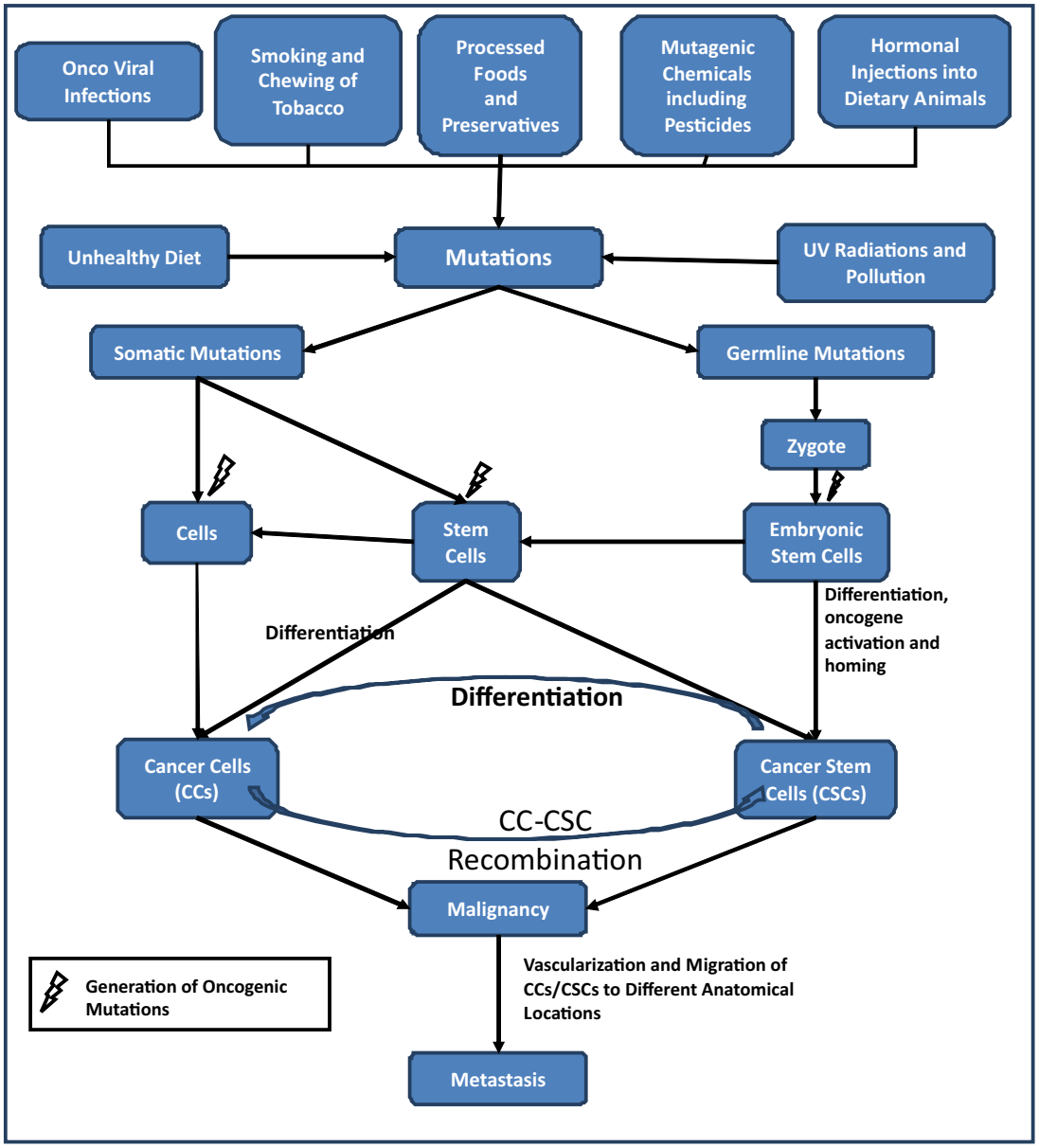


Figure 1: There are certain factors like onco-viral infections, smoking and chewing of tobacco, chemical mutagens including pesticides, UV radiation, pollution, processed foods, food preservatives, hormonal injections into dietary animals and unhealthy diet can cause mutations in the genes. Somatic and germline mutations are the two main categories of mutations. Somatic mutations affect only a particular individual in which they are present but germline mutations can be inherited. In addition to these mutations, those occurring during differentiation arise due to unfavourable changes in the cells'/stem cells' chemical or physical environment. Such changes can transform the stem or somatic cells into cancer, or cancer stem cells, respectively. Inherited oncogenes which are present in the embryonic stem cells can get activated by the differentiation cascade and give rise to cancer stem cells which then migrate into different organs depending upon their homing characteristics. These transformed cells together form tumours. The rapidly proliferating tumors can efficiently obtain their metabolic needs by generating signals for vascularization. Due to altered morphology and adhesion properties of the transformed cells they can easily detach from its tumour mass and migrate into different anatomical locations of the body through newly formed vascular network which eventually leads to metastasis.

Increase in average life span does not necessarily correlate with being healthy but implies that availability of newer generation medicines are keeping the patients alive for longer periods of time. Infant

mortality is one significant beneficiary in an increasingly densely populated under developed areas of the world that contributes to increased average life span of a country. Genetic predisposition to malignancy is on the rise along with longevity as the "dormant" oncogene gives in (becomes susceptible to activation) later if not sooner, depending upon how long it can take the abuse of modern day all-round living habits, styles and environmental pollution. Unless unrelated which seems to be unlikely, brushing it off will land us, or our near and dear / kith and kin, at some point in lifespan, into a life threatening medical condition irrespective of the age of the individual.

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