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Editorial

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Call of duty: advanced anti-CSC Ops

"We have two options, medically and emotionally: give up or fight like hell." – Lance Armstrong on Cancer

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Editorial

Cancer is one of the leading causes of death in the United States claiming at least half-a-million lives annually (http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm). Unlike other diseases caused by pathogens, the fight against cancer has been difficult and complicated as these are maladies of the self and are resistant to- or develop resistance to- most therapies. Typically, a cancer is characterized by several hallmark features- namely

a) The presence of multiple kinds of cells termed heterogeneity.

b) The presence of dormant cells with increased longevity.

c) Cells with elevated or de-regulated potential to proliferate.

d) Acquired resistance to radiotherapy and/or chemotherapy.

If one draws a parallel, above hallmarks are remarkably similar to those of tissue Stem Cells (SCs) that are dormant, long-lived, self-renewing cells and upon receiving the right environmental cues, proliferate and differentiate into heterogeneous populations of cells that make up the tissue or organ.

Over the last decade our understanding of cancer has fundamentally accepted the paradigm that cancer is a disease of stem cells. Rather than accumulate a multitude of mutations that would confer a normal cell all these variant properties, deregulatory mutation(s) arise in a cancer stem cell (CSC) or *progenitor* cell that already has several hallmarks of cancer as part of normal biological function such as tissue homeostasis, wound healing and repair. CSCs divide under influence of driver mutations and give rise to cells that differentiate into heterogeneous populations of tissue cells and set aside stem cells with self-renewal properties and cell-division potential. The heterogeneous populations then acquire secondary and tertiary mutations that aid the tumor evolve cells into gaining invasive and metastatic properties. Since most DNA-damaging agents and chemotherapy target DNA or cell division in replicating cells, these agents tend to target the heterogenic populations that results in de-bulking of the tumor and creates the illusion of therapy. However CSCs are metabolically inactive and contain mechanism(s) to repair their DNA, rendering them refractory and acquiring resistance to therapy. Inability to target CSCs has been the Achilles heel to developing therapeutics against cancer.

It isn't sufficient that we combat potential *Toxicities* of *targeting* cells that are our own. We have to deal with a moving target with a constantly changing and evolving genetic landscape. If a tumor is previously sensitive to a treatment and we do manage to kill some populations of cells, others quickly replenish them that are refractory to the erstwhile drug. So while there will be some areas such as *Brain cancer* whereas de-bulking/ reducing tumor mass relieves pressure and provides relief to patients, in other areas therapies have mainly worked to improving the quality of life for a certain number of years and delaying the inevitable. The only long term curative option is in targeting the CSCs and eliminating the self-renewal or tumorigenic properties of the cancer.

To target CSCs therapeutically, we must have ways to identify and propagate them and have reliable biological assays to test therapeutic agents against. That's easier said than done. We exploit characteristics of SCs to identify them for e.g. plating at low density or limiting dilution assays (LDA) *in vitro* with the hypothesis that only cells with self-renewal abilities will divide and produce enough cell mass (and growth factors) to support its own growth. Alternatively, only SCs will divide and differentiate into various heterogenic populations that constitute the original tissue or tumor. The above approaches have been plagued by the inability to model the endothelial stem cell niche for keeping CSCs viable and making matters worse these assays have identified the more robust *progenitor* cells as CSCs in vitro. While the progenitors have some replication and differentiation potential, they may be a step removed from elusive stem cell. Theoretically they may be better de-bulking agents but one would still expect tumors to acquire resistance if the CSCs are untargeted.

To aid reliable and reproducible identification it is perhaps best to identify live cells based on cell surface markers and sort them using flow cytometry. Instead of getting involved with the complications or artifacts of studying cancer in a Petri dish, inject these cells directly in mouse tumor-forming assays. Cells enriched in tumorigenic populations such as CSCs will form tumors with greater frequency at lower seeding densities. A typical LDA experiment is set up where each mouse is injected with 10, 100, 1000, 10000, or 100000 cells and there are (8-10) replicates per arm/ cell number. A tumor in which CSCs have been targeted by therapy will exhibit a reduced frequency in tumor formation and where it previously required (1000) cells to form a tumor 50% of the time, after therapy it would now require (10000 or 100000) cells to form a tumor 50% of the time. This assay allows us to identify CSC therapeutics even in tumors where the CSC marker profile is not completely known. As long as there is sufficient enrichment of CSCs, it gives us an indication whether the therapeutic targets CSC frequency.

The biggest challenge in targeting CSCs therapeutically may be the nature of the beast itself. As these are stem cells, their primary role is in maintaining tissue homeostasis in the adult. Prior to that, these cells may have had a role in development and differentiation of the organs themselves so it is possible that the biochemical pathways we are likely to target are developmental pathways that impact and influence many kinds of cell types. For example in targeting

ancient pathways such as the Wnt pathway there is an element of *gastrointestinal toxicity* or *bone toxicity* that must be controlled by dose as the pathway is common to both tissue SCs and CSCs.

These are the hurdles faced by scientists trying to develop therapeutics against cancer. Like a wise person one said- "*When solving problems, dig at the roots instead of just hacking away at the leaves*". What choice do we have?

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Conflict of interest

The author declares no conflict of interest.