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Post-identification of Cancer Stem Cell: Ethical and Scientific Dilemmas in Therapeutic Development?

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Any discussion on cancer biology, directly or indirectly, includes stem cells, in particular, tumor initiating cells and mesenchymal stem cells (MSCs). Also, of importance are tissue-specific stem cells since these cells could be the source of the original tumor. The existence of cancer stem cells is mostly accepted by the scientific community [1,2]. The future of this field, however, could be a problem, depending on how academia, biotechnology and pharmaceutical companies use the information towards cancer eradication. Scientists in academia are focused on the basic science to identify the hierarchy of cancer cell subsets; biotechnology is also involved in the basic science, but these companies are mindful of commercial benefits. Pharmaceutical companies, on the other hand, are interested in targeting the cancer cells to achieve cell death. While, on the surface this seems to be ideal, it could also be a dilemma for targeting cancer stem cells.

In discussing cell death, it is always unclear what particular cancer cell subsets are targets? If the highly replicating cells are the intended targets, this could lead to an ethical problem since this will add a new drug to achieve similar outcome as past therapies. The ideal scientific outcome is to eradicate cancer at the level of stem cells. Answer to this could be simple since many genes linked to self-renewal and pluripotency have been identified. However, these same genes are also expressed in all stem cells. Perhaps the scientists might consider a balance of benefits with regards to eliminating cancer cells with reduced toxicity. However, this balance might be more difficult to achieve since the literature mostly indicate low frequency of cancer stem cells. This suggests that the requirement for eliminating low frequency cancer stem cells might also eliminate low frequency of healthy stem cells, resulting in overt toxicity. To achieve curative treatment requires some convergence and divergence of academia, biotechnology and pharmaceutical companies to reduce confounds facing the ultimate beneficiaries, the patients.

Scientists in academia rely on government agencies or non-profit foundations to fund the research. In most cases, academicians, without business background, do not appreciate the lack of resources as compared to pharmaceuticals with an impressive infrastructure and expertise in drug development. In these scenarios, good ideas could be curtailed due to lack of resources. The scientific dilemma, as discussed above, is for pharmaceutical companies to accept the challenge in the development of a drug for cancer stem cells, despite the obvious toxicity. The genes that maintain pluripotency in the cancer stem cells are also expressed in stem cells, which are ubiquitous. Others have identified other targets that seem almost ideal, based on the experimental outcomes. Despite this, the prediction of toxicity seems obvious. Recently miR-34a has been identified as a potential target for prostate cancer stem cells [3]. The premise is that miR-34a would suppress the expression of CD44 on the cancer stem cells to prevent metastasis. The advantage is the development of novel RNA therapy. The disadvantage could be overt toxicity since the ligand of CD44, hyaluronic acid, comprise the extracellular matrix of the bone marrow microenvironment that supports hematopoiesis [1].

Research studies have identified cytokines as a potential targets to eliminate cancer stem cells [4]. In other investigation, cytokines were implicated as regulators of other genes to establish quiescence of cancer cells in bone marrow where it is difficult to target cancer cells [5,6]. Cytokines might be attractive targets because of redundant functions. Specifically, blocking a particular cytokine is unlikely to cause deleterious effects on healthy cells, since there are other cytokines with similar effects. The same argument on functional redundancy of cytokines can be extrapolated to the cancer stem cells, but the effects could be nullified by other cytokines. Specifically, although a particular cytokine might seem an attractive target of cancer stem cells, the stem cells might produce other cytokines to counteract the targeted molecule. Therefore, this field requires further investigation to determine the effectiveness of targeting cytokines. In addition to functional redundancy, cytokines exhibit pleotropic effects, in which one cytokine can have effects on multiple downstream targets. Thus, it may difficult to achieve therapeutic specificity when targeting one cytokine in an attempt to eliminate cancer stem cells.

Added to the complex issues of cancer stem cells, is the role of MSCs in cancer biology. MSCs can protect as well as support cancer growth [7-15]. The most obvious target of cancer support by MSCs is direct target. However, targeting of MSCs could be the most toxic method, partly due to these stem cells, also referred as pericytes, which surround blood vessels [16]. The supporting role of pericytes on blood vessels appears to be an attractive target to eliminate angiogenesis. However, specificity to target tumor-associated blood vessels will be difficult and this method is likely to result in overt collapse of most, if not all blood vessels.

The ubiquitous presence of MSCs makes them relevant to tumor biology. It is ironic that the information regarding the role of MSCs is overwhelming; perhaps more than the field of cancer stem cells. Yet, targeting MSCs might be more of a challenge due to the cells endogenous functions. Among other functions, are the immune suppressive roles of MSCs, which might partly explain reduced enthusiastic outcome of immune therapy for tumor. The information on MSCs should allow scientists to re-examine the field of immune therapy for cancers and to examine methods to take advantage of the unique immune properties of MSCs to improve therapy for cancer.

In the context of the brief examples, the question is how can academia, biotechnology and pharmaceutical companies converge to overcome the scientific and ethical dilemmas in targeting cancer stem

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cells and MSCs? Ethical problems could arise from knowing that stem cells can be targeted but this would be a long period to develop a drug, due to the foreseeable toxicity to endogenous stem cells. These ethical problems are also the scientific issues that need to be addressed in long-term robust research studies. In summary, the question of targeting cancer stem cells and also the supporting MSCs in cancer cannot be achieved by one entity, but partnership among academia, biotechnology and pharmaceuticals. This could indirectly allow for combining government and private funds to eradicate a disease across all humans, regardless of geography.

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