Can a Selection-Centric, Strengths-Based Approach to Cancer Treatment Help Treat or Prevent Cancer and Metastatic Disease?

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Abstract:

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Abstract

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The approach of almost all current cancer therapies is essentially the same as those practiced by the Greeks and Romans, namely, to remove cancer tissues at a stage early enough to prevent cancer from overwhelming the body. While initial treatment regimens are often based on specific genomic data and are effective in many cases, they can sometimes be followed, usually after a period, by the reoccurrence of cancer as untreatable metastatic disease[1], often with poor prognoses due to treatment resistance[2]. Over the past several years generating actionable genomic data has become more complicated with the discovery of intra-tumor genetic heterogeneity (ITGH)[3]. Indeed, in the case of metastatic disease, it has been proposed that genetic and epigenetic heterogeneity has contributed to the inability to successfully eradicate the disease[4]. This has resulted in some questioning as to whether precision medicine can really be the treatment panacea that it is claimed to be[5]. Further, most genomic markers have so far provided only limited insight into the mechanisms that control both carcinogenesis and metastasis, perhaps because current cancer hypotheses fail to provide an adequate framework with which to analyze the data.

Our present understanding of carcinogenesis is based on the hypothesis that cancer cells accumulate somatic variation (mutations, amplifications, translocations, etc.), which eventually provide a growth advantage to cells undergoing carcinogenesis[6]. One indication of why this hypothesis might be inadequate is the fact that cancer-associated genes are generally not over-expressed in the tissues from which the cancer develops[7]. At present identifying *common* driver gene mutations present in tumor tissues is considered one of the keys to understanding the ontology of tumors. However, the validity of this concept is being challenged by both accumulating evidence of ITGH, and recent evidence of complex single gene variance (CSGV)[8]. Further, present cancer hypotheses have yet to really consider the role that genetic heterogeneity in normal tissues may play in carcinogenesis, or even recognize and explain the presence of genetic heterogeneity within normal tissues[9].

Therefore, to overcome these problems, a new hypothesis has been proposed based on the premise that cancer can be considered a tissue survival strategy and that post-zygotic mosaicism associated with ITGH allows tissues to survive changing environmental conditions[10]. Further, many of these somatic mutations would arise relatively early in human fetal development, presumably to prepare

organisms to survive environmental changes that they might encounter throughout their lifetime. Indeed, early genetic heterogeneity has now been observed in fetal cells[11,12]. Thus, the hypothesis could explain why genetic heterogeneity of cancer-associated genes has been observed in normal tissues[13,14], and why, post-zygotic single nucleotide mosaicism of cancer-associated genes exists in small numbers of cells in both diseased and normal individuals[15].

The hypothesis further suggests a selection-centric approach to cancer treatment that has been labeled as 'strength-based'. This approach considers *selection pressures* caused by *tissue microenvironments* to be the critical factors in carcinogenesis and metastasis, rather than the accumulation of mutation-based phenotypic changes. The key from a treatment standpoint is the evidence that normal cells with wild-type genes exist in tumors, albeit in very small numbers. Similarly, cells present in normal tissues that surround tumors can contain cancer-associated mutant variant genes. Therefore, rather than just removing cancer tissues, we should promote the selection of normal cells within cancerous tissues. Therefore, if we can create tissue micro-environmental conditions that select normal cells we can change cancerous tissues back to normal, as well as make it highly unlikely that the cancer will return. A selection-centric approach to treating metastatic disease would similarly focus on preventing the growth of metastases, by ensuring that metastatic cells are not selected for by their tissue microenvironments. Recent evidence has begun to provide some support for this radical treatment approach by examining the possible effects of tissue microenvironments on cancer tissues[16,17].

Almost all studies up until now have examined associations between environmental factors and cancer development, but not specifically of tissue microenvironments, although the importance of studying these relationships has been acknowledged[18]. Recently there has been an increased effort to identify what these factors might be in cancer tissues. Tools such as mass spectroscopy have allowed increased attention to be given to the carcinogenic role of the tumor microenvironment including in both tumorigenesis[19] and differential tissue responses to therapy[20]. However, as cells and tissues exist in complex three-dimensional environments, and contain both extra- and intracellular components, to fully analyze these environments will require new technologies including; atomic force microscopy[21], quantitative extracellular matrix proteomics[22], and single

cell analysis[23]. Finally, analysis of the effects of micro-environmental selection pressures on tissues and cells will also require the development of much more sophisticated genetic databases than presently exist[24].

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