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The courage (necessary) to go further

Mariano Bizzarri [*]

[*] *Dept. Of Experimental Medicine, Sapienza University, Systems Biology Group Lab, Rome, Italy*

Corresponding author: Mariano Bizzarri mariano.bizzarri@uniroma1.it

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Commentary on
Gatenby, RA, 2017 Is the Genetic Paradigm of Cancer Complete?, *Radiology*, vol. 284, n. 1, pp. 1-3.

1. Something wrong in the current cancer paradigm

In a recent paper, Robert A. Gatenby (Gatenby, 2017) quotes a study in which it is claimed that no significant difference in the mutational burden of cancer-associated genes are found when prostate cancer specimens were compared with normal adjacent tissue regions. "As a result, cancer cells can display a seemingly paradoxical state in which their mutational burden is similar to and perhaps even lower than that of adjacent normal cells". This finding is at odds in "the context of the conventional, almost universally accepted, genetic model of cancer. Interestingly, the results are consistent with a growing number of observations that collectively challenge the long dominant gene-centric model of cancer initiation and progression". Gatenby goes further when he outlines the inconsistency of cancer as a disease of old age, as long as recent observations indicate that replications and mutations occur mostly in early life, while the supposed correlation between cancer incidence and longevity is devoid of any reliable evidence (Caulin, 2011).

Gatenby rightly suggests that "tissue perturbations such as injury, infection, or inflammation can cause loss of normal signaling functions, which effectively allows the local cells to become autonomous [and cancerous] even when they retain the capacity to receive and respond to tissue signals". This is a pivotal point, as it outlines that scientific investigation should focus on the tissue level – namely the cell-microenvironment interplay.

2. The right level of observation

The tissue level is properly 'the level' where the cancerous process 'happens'. We commend Gatenby for that observation - however late it may have come. Indeed, disruption of cell-microenvironment relationships as 'causative' factor in carcinogenesis was vindicated by the Tissue Organization Field Theory (Sonnenschein & Soto, 1999) a long time ago, receiving compelling support over the last few years (Bizzarri & Cucina, 2016).

As aptly asserted by Gatenby, "a number of experimental studies have found that placement of cancer cells within a normal stroma can reverse the malignant phenotype. In this instance, no specific set of genetic changes occurred to promote carcinogenesis". Thereby, the question is, how really important are genes (and mutations) in triggering cancer development and progression?

Moreover, a recent article provides further support in favor of the hypothesis that metastatic dissemination is not a matter of 'metastatic genes', instead it depends principally on the dynamic interplay between cells and microenvironment, as previously stated (Sonnenschein & Soto, 2015). Indeed, in pre-malignant lesions, both cancer cells and myeloid cells attract CD206+/Tie2+ macrophages and induce Wnt-1 upregulation that in turn downregulates E-cadherin junctions in the HER2+ early breast cancer cells. Then, macrophages from tumor microenvironments operate as portals for intra-vasation and promote early dissemination that affects long-term metastasis development (Linde et al, 2018). These findings are further reinforced by results of a study which highlights that adjuvant chemotherapy promotes distant metastasis by favoring disruptive processes in the microenvironment (Karagiannis et al, 2017).

Overall, this data suggests that the Somatic Mutation Theory – on which carcinogenesis studies have been based in the last 50 years – should be dismissed and replaced by a different theoretical approach – like that proposed by TOFT – able to deal with such controversial results.

The time has come to find the courage to say it openly.

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