CORRESPONDENCE

RE: A Cancer Theory Kerfuffle Can Lead to New Lines of Research

Frederic J. Kaye

Affiliation of author: Department of Medicine, University of Florida College of Medicine, Gainesville, FL.

Correspondence to: Frederic J. Kaye, MD, University of Florida College of Medicine, 2033 Mowry Rd, CGRC Rm 364, Gainesville, FL 32610 (e-mail: fkaye@ufl.edu).

Because there is widespread agreement about the importance of tissue microenvironment and cell differentiation signals in tumor biology (combined >100 000 citations in PubMed), the commentary by Dr. Baker (1) could be regarded as a “straw man” kerfuffle, except that it also argues against a role for acquired cancer gene mutations as a critical event in tumorigenesis. Dr. Baker quotes Peyton Rous, who was unable in 1959 (2) to reconcile the ability of animal viruses to rapidly induce tumor formation within the emerging somatic cancer gene mutation framework. If alive, Rous would have been delighted to learn the role Rous sarcoma virus ultimately played in helping to define cellular cancer genes that not only validated the somatic cancer gene model leading to two additional Noble prizes (3–5), but also allowed numerous predictions based on this evolutionary cancer gene model that have continued to provide a solid framework for targeted cancer therapy.

For example, investigators modeled a specific ABL1 mutation seen in chronic myelogenous leukemia patients with acquired drug resistance to imatinib to predict the biology of a hypothetical epidermal growth factor receptor (EGFR) resistance allele (6) prior to the identification of activating EGFR mutations and the subsequent selection of recurrent T790M mutations in lung cancer clinical samples with gefitinib/erlotinib drug resistance (7). Dr. Baker’s concern about tumor cell proliferation rates also ignores the key role of aberrant tumor cell survival as the primary oncogene target, and I could address other misinterpretations in the commentary. However, as noted by Dr. Baker, I have also sensed among clinical colleagues a waning of excitement regarding the direction of molecular oncology because of the large number of candidate cancer genes combined with detection of genetic heterogeneity within tumor subclones. I feel these concerns are misplaced, as efforts are underway to define core mutational events and to organize cancer genes into a manageable number of parallel and interconnecting signaling pathways by studying concurrent and mutually exclusive patterns of mutations within individual tumor subclones. In addition, the requirement for somatic alterations within multiple cancer pathways for most common adult cancers paradoxically increases our therapeutic opportunities. However, current pharmaceutical strategies are largely limited to small molecule blockade of gain-of-function mutations in accessible subcellular localizations and we will need more creativity to target these opportunities more broadly, as well as a deeper understanding to overcome compensatory feedback loops and selection for drug resistant alleles. I am pleased the Journal is a venue where commentaries proposing alternate and revolutionary ideas can find an outlet through a peer review system. However, I am also aware of controversial commentaries questioning the value of childhood vaccinations and whether HIV causes AIDS. These actions led to consequences, and I fail to see the need for the unnecessary exercise of pitting the role of host and tissue microenvironment and cell differentiation influences against the role of acquired somatic mutations in tumorigenesis. We must work together to advance science and improve patient outcomes.

Funding

This study was supported by the University of Florida College of Medicine Gatorade Fund.

References