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A Call for Perspective and Precision in Research Design and Conclusions Drawn From Preclinical Data

To the Editor:

We live in an information soundbite era in which we owe it to patients to frame our work carefully such that, to the extent possible, it is not vulnerable to premature, sensational, or simplistic headlines. Nowhere are perspective and precision more salient than in oncology, and with this assertion, we felt compelled to offer a response to a recent paper that has garnered extraordinary attention in the popular press and social media.

Two studies, reported by Pascual et al,[1] were conducted at the Institute for Research in Biomedicine (IRB) in Barcelona, Spain, have attracted global attention in suggesting that malignant tumors or malignant tumor cell lines were more likely to metastasize when exposed to elevated levels of palm oil or palmitic acid (PA), respectively. One study exposed mice that had been orthotopically inoculated with human oral squamous cell carcinoma and melanoma to a diet with added palm oil or olive oil. A second in vitro study exposed oral carcinoma cells to PA, oleic (OA), and linoleic (LA) fatty acids. The authors asserted that exposure to the PA (a component of palm oil)—increased the likelihood of metastatic spread via a putative mechanism involving expression changes in tumor-associated Schwann cells that reportedly secrete a specialized "proregenerative extracellular matrix."

While an interesting set of potential contributions to the literature on metastasis (limitations of rodent models in cancer biology notwithstanding), the speculation about potential health hazards of PA consumption by humans is not supported by the data that were reported. Moreover, the design of both studies contains significant threats to the clinical relevance, generalizability, and even validity of the investigators' conclusions. Finally, while replete with tables and figures, the scope, content, and duration of this work do not seem to justify the creation of, or the addition of the term "prometastatic memory" to the lexicon of cancer biology.

BROAD THEORETICAL THREATS TO VALIDITY

In the most general sense, emerging evidence indicates an exquisitely complex interplay between tumor metastasis and metabolic rewiring in cancer that varies significantly with tissue type. Multiple alterations in methylation patterns in relation to signaling pathways involved in regulating various cellular mechanisms such as cell cycle, transcription, apoptosis, and angiogenesis, as well as invasion and metastasis themselves, vary widely with tissue type. Breast, prostate, lung, colon, thyroid, and bone cancers are all arguably discrete diseases, essentially having immortal cell lines as a sole common feature.

To date, the understanding of the genomic and epigenetic instability has identified a myriad of candidate biomarkers that may be validated for clinical use. Indeed, it is almost conventional wisdom that metabolic rewiring may drive metastasis by one or a combination of processes including (1) generation of oncometabolites that hijack metastatic signaling cascades via regulation of gene expression, (2) generation of metabolites/cofactors that act as agonists/antagonists for functional proteins involved in metastasis, and (3) modulation of metabolic demands of cancer cells, thus allowing adaptation to the various stages of the metastatic cascade; on the other hand, metastatic-associated signaling can influence cellular metabolism by directly affecting the expression and activity of metabolic enzymes.[2]

Thus, the implication in the face of such etiologic complexity and based on brief rodent and in vitro laboratory research that implies "dietary palmitic acid" via a nondietary route of administration and at a dose level of 300 μM, along with OA and LA (50 μM) remains questionable. While the PA level, which reflects a lower end of plasma levels (300 to 4100 μM) from a small (n = 61) population of healthy adults,[3] the assertion that exogenous application over a very short duration may "trigger metastasis, or the mechanisms behind this," in humans seems utterly unsupported. The authors fail to develop any epidemiologic or clinical data demonstrating that their findings "… adequately underscore the long-term [human] health risks associated with a diet rich in PA regarding metastatic progression."

Upon a closer examination of the fatty acid concentrations used in the cell culture study, it appears that the LA level was at least one fourth to one hundredth that observed among healthy individuals (200 to 5000 μM).[3] The apparent impact on the polyunsaturated fatty acid/saturated fatty acid ratio may modulate the health effect of the seeming detrimental effects of PA, as reported by Pascual et al.[1] Adding to the inconsistent findings relative to LA and the complexities of inflammation and cancer development associated with this fatty acid, it is also noteworthy that LA may reduce the development of inflammatory pathologies, such as atherosclerosis.[4]

It is also important to note that PA is the most common fatty acid in human tissues.[5] Our current understanding of the importance of PA indicates that it represents 20% to 30% of the total fatty acids in the human body. It is also the dominant fatty acid in breast milk (~20%) and corresponds to nearly 50% of the total fat in newborn infants, thereby providing about 11% of the infant's energy requirement. In addition, PA is innate to all vegetable oils, including common canola oil (3.9%), sunflower oil (4.5%), peanut oil (8.3%), coconut oil (8.6%), soybean oil (10.3%), corn oil (11.1%), and olive oil (12.1%).[6]

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Numerous studies on the health impact of dietary PA are inconsistent with the implications of the present study. What appears to be consistent, however, is that de novo lipogenesis (DNL) is tightly regulated, is not influenced by the dietary composition or PA content, and does not have a central role in carcinogenesis.[7] In fact, some pathologies actually contribute to the disruption of DNL or the classic homeostasis of PA.[8]

Our understanding also indicates that PA and some of its metabolites, such as palmitoylethanolamide, are critical components of cell membrane phospholipids, which, in part, function as surfactants in pulmonary tissues. Importantly, it appears that palmitoylethanolamide is critical in mast-cell degranulation which ultimately may contribute to the innate anti-inflammatory processes via an array of mechanisms that involve degradation and synthetic pathways.[9,10]

With respect to the potential impact of PA on cancer, one is reminded that DNL provides a distinctive pathway among cancer cells, the Warburg effect.[11] Under these circumstances, the classic DNL is compromised so that the cancer cells can generate adequate energy for survival, thereby exceeding a cellular homeostatic PA threshold and triggering cancer cell predisposition in pathologies, such as diabetes, obesity, insulin resistance, and even nonalcoholic liver disease in addition to some types of cancer.

Certainly, a better understanding of the interplay between nutrient metabolism and metastasis could ultimately unravel novel molecular targets, whose intervention could lead to improvements in reducing the likelihood of malignant transformation or in augmenting the treatment of certain tumors. However, the present research which mixes and matches 2 fundamentally different studies is at best an intriguing and preliminary investigation of one possible, but unproven, etiologic mechanism that may or may not be clinically relevant in humans. While a mandate for precision and perspective represents a significant challenge in itself, it is tempting to speculate that a renewed multidimensional effort to improve the peer review process even at the most rarified levels may hold the key to mitigating dilemmas in scientific communication.

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The Biology and Systemic Treatments Influence Survival in Advanced Gastrointestinal Cancers While the Controlled Trial of Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) Found That Surgical Resection Could Only Have a Small If Any Effect

To the Editor:

The retrospective institutional study by Burns et al[1] of patients with pulmonary metastases from gastrointestinal cancers gives some interesting insights into the natural history of this condition. It shows that overall the prognosis of these patients is surprisingly good with prolonged survival following both systemic and localized treatment. It also reveals the very variable growth rate of such metastases and interestingly showed that solitary metastases may grow more slowly than multiple ones. All this points to the importance of underlying tumor biology in determining overall survival of these patients and, citing the meta-analysis by Ratnayake et al,[2] they suggest that this raises "further questions regarding the necessity and indications for metastasectomy in this patient population."

They state that "Lung metastasectomy has been demonstrated in multiple studies to be associated with

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