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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

Rebuttal to: Confusion on Cell Fusion

See Point-Counterpoint articles on pages 299 and 304.

It is a truism that "the eye sees only what the mind is prepared to comprehend." Depending on the lens, cellular fusion can be viewed as either a rare phenomenon with little importance to the intestine, or a ubiquitous biological mechanism with relevance to malignant and regenerative processes within the intestine, as well as throughout the entire body.

Although fusion occurs at low levels in the homeostatic gut,[1] experimental models designed to quantify the burden of hybrid cells are fraught with challenges, and even subtle differences in assays can alter detection sensitivity; thus, variability in reported results is not unexpected and should be interpreted appropriately by examining all relevant evidence. Although horizontal gene transfer and transdifferentiation were suggested as alternative interpretations of co-expressed markers found in multiple fusion models, other studies have refuted these explanations. Only genetic transfer on the chromosomal scale could explain these observed findings, which has not been shown in organisms more complex than fungi,[2] while transdifferentiation was largely refuted by Alvarez-Dolado et al[3] and others. In addition, methodologies relying on genetic markers—such as Y-chromosomes or transgenes—are theoretically less prone to false positives, but remain susceptible to false negatives in instances in which fusion occurs but genetic material from one fusion partner is subsequently lost or inactivated. Therefore, it is more likely that the full spectrum to which fusion impacts the intestine is greater than suggested by available methodologies.[4]

Understanding that the true importance of seemingly trivial homeostatic mechanisms often are uncovered when augmented in pathologic states,[5] studies in disease models provide valuable insight on the diverse effects of fusion. Malignancy illustrates the most visible argument for the implications of cell fusion in the intestine, contributing to key steps along the entirety of the metastatic cascade.[6] Heightened levels of epithelial cell fusion in murine models of colitis[1] and human graft-versus-host disease[7] underline the importance of fusion in intestinal inflammation and repair. Furthermore, the participation of various cell lineages in intestinal epithelial regeneration depends both on the extent (superficial mucosal vs crypt) and physiologic context of the injury (chemical, physical, autoimmune, or radiation-induced).[8] Although the findings of the Shivdasani and Vermeulen labs are limited to irradiation,[9,10] the possible permutations of intestinal injury and repair are many, for which fusion may engage mechanisms involved in mesenchymal remodeling, crypt restructuring, and immune-epithelial interaction—all important features of gut health restoration, highlighting the important point that physiologic context matters.

Finally, we would argue a critical philosophical point: dispensability or rarity do not equal unimportance. The biology of complex organisms is rife with redundant processes that confer resilience. These processes are individually dispensable, yet are relevant nonetheless—intestinal fusion is no different, and may in fact have unrecognized roles beyond pure organ regeneration. We previously detailed evidence for fusion-mediated epigenetic or transcriptomic heterogeneity among a previously monoclonal population.[11] That resulting diversity may represent a resilience mechanism in an intestine exposed to myriad chemical, physical, and pathogenic threats. These possibilities are as yet unexplored, and we would echo the words of Hamlet: "there are more things in heaven and earth … than are dreamt of in your philosophy."[12] We look forward to future revelations on the importance of cell fusion in regeneration, malignancy, and in currently uncharted fields so that our philosophy may continue to broaden.

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References

1. Davies PS, et al. Inflammation and proliferation act together to mediate intestinal cell fusion. PLoS One 2009;4:e6530.
2. Akagi Y, et al. Horizontal chromosome transfer, a mechanism for the evolution and differentiation of a plant-pathogenic fungus. Eukaryot Cell 2009; 8:1732–1738.
3. Alvarez-Dolado M, et al. Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes. Nature 2003;425:968–973.
4. Weiler J, et al. Cell fusion in human cancer: the dark matter hypothesis. Cells 2019;8:132.
5. Kotas M, et al. Homeostasis, inflammation, and disease susceptibility. Cell 2015;160: 816–827.
6. Lu X, et al. Cell fusion as a hidden force in tumor progression. Cancer Res 2009;69:8536–8539.
7. Silk AD, et al. Fusion between hematopoietic and epithelial cells in adult human intestine. PLoS One 2013;8:e55572.
8. Wang Y, et al. Long-term culture captures injury-repair cycles of colonic stem cells. Cell 2019; 179:1144–1159.e15.
9. Murata K, et al. Ascl2-dependent cell dedifferentiation drives regeneration of ablated intestinal stem cells. Cell Stem Cell 2020; 26:377–390.e6.
10. de Jong JH, et al. Fusion of intestinal epithelial cells with bone

marrow derived cells is dispensable for tissue homeostasis. Sci Rep 2012;2:271.

11. Powell AE, et al. Fusion between intestinal epithelial cells and macrophages in a cancer context results in nuclear reprogramming. Cancer Res 2011;71:1497–1505.

12. Shakespeare W. The tragedy of Hamlet, Prince of Denmark. New Folger's ed. New York: Washington Square Press/Pocket Books, 1992.

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