Letter to the Editor

Correspondence re: M. Tresini *et al.* A Phosphatidylinositol 3-Kinase Inhibitor Induces a Senescent-like Growth Arrest in Human Diploid Fibroblasts. Cancer Res., *58:* 1–4, 1998.

Letter

In the January 1, 1998, issue of *Cancer Research*, Tresini *et al.* (1) briefly reported a PI3K[1]-dependent signaling pathway that negatively controls certain aspects of cellular differentiation and senescence in human WI-38 fibroblasts. In the June 2, 1997, issue of *the Journal of Cell Biology*, our group (2) reported a PI3K-dependent biochemical pathway that is responsible for the negative regulation of cellular differentiation in nontransformed human primary cells. In the December 13, 1996, issue of *The Journal of Biological Chemistry*, Busca *et al.* (3) described that inhibition of the PI3K/p70^{S6} kinase pathway induces cellular differentiation of mouse transformed melanoma cells. Thus, these three papers consistently reported that the blockade of PI3K activity resulted in growth arrest and up-regulation of tissue-specific gene expression.

In their article, Tresini *et al.* (1) do not mention the two other papers. Thus, we wish to bring to the attention of the readers of *Cancer Research* that all of the above-mentioned PI3K-dependent signaling pathways that were identified in normal, transformed, and senescent cells share the same characteristic and are highly related. We believe that the discovery of a novel function for PI3K as a negative regulator of tissue-specific gene expression in normal, transformed, and senescent mammalian cells may be critical for the understanding of the common relationship among terminal differentiation, tumorigenesis, and the aging process.

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References

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2. Ptasznik, A., Beattie, G. M., Mally, M. I., Cirulli, V., Lopez, A., and Hayek, A. Phosphatidylinositol 3-kinase is a negative regulator of cellular differentiation. J. Cell Biol., *137:* 1127–1136, 1997.
3. Busca, R., Bertolotto, C., Ortonne, J. P., and Ballotti, R. Inhibition of the phosphatidyinositol 3-kinase/p70S6-kinase pathway induces B16 melanoma cell differentiation. J. Biol. Chem., *271:* 31824–31830, 1996.

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[1] The abbreviation used is: PI3K, phosphatidyl 3-kinase.

Reply

Dr. Ptasznik (1) comments on our report in the January 1, 1998, issue of *Cancer Research*. He states that our work reports the PI3K,[1] dependent signaling pathway negatively controls aspects of differentiation and senescence in WI-38 fibroblasts. This is not completely accurate. Our work deals exclusively with three phenotypic characteristics of replicative senescence and not with any aspect of differentiation. Dr. Ptasznik correctly points out that the PI3K pathway has been implicated in the negative regulation of differentiation in several settings. This pathway has also been implicated as playing a positive role in the differentiation of myocytes (2, 3). Thus, the role of this pathway in the regulation of differentiation is clearly a very complex process involving cell type-specific responses, and the decision not to discuss the role of the PI3K pathway in differentiation was purely one of space considerations. The Advances in Brief section of *Cancer Research* allows three printed pages and 20 references. An extensive review of the literature in this space is not feasible.

We agree completely with Dr. Ptasznik that a link between differentiation, senescence, and tumorigenesis involving the PI3K is potentially an important and interesting link between these processes. It would be premature, however, to draw any conclusion regarding the relationship between them until the cellular pathways involved have been more clearly defined.

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3. Coolican, S. A., Samuel, D. S., Ewton, D. Z., McWade, F. J., and Florini, J. R. The mitogenic and myogenic actions of insulin like growth factors utilize distinct signaling pathways. J. Biol. Chem., *272:* 6653–6662, 1997.

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[1] The abbreviation used is: PI3K, phosphatidyl-inositol 3-kinase.