Published OnlineFirst January 25, 2012; DOI: 10.1158/0008-5472.CAN-11-2201

Cancer Research

Letter to the Editor

Impact of Epithelial Organization on Myc Expression and Activity—Letter

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We reported in the work of Partanen and colleagues (1) that epithelial architecture suppresses oncogenic properties of c-Myc. In this study, we used MCF10A and HMEC human mammary epithelial 3-dimensional (3D) Matrigel cell culture models expressing conditionally active c-Myc (MycER) and found that the acute activation of c-Myc sensitizes apoptosis but fails to induce cell-cycle reentry in fully formed epithelial 3D organoids. Fully formed MCF10A and HMEC 3D organoids express features of mammary epithelial architecture as they are formed of a single layer of quiescent, polarized, and differentiated cells surrounding hollow lumen. In contrast to structurally organized epithelial structures, c-Myc did induce cell-cycle progression in quiescent but unorganized epithelial structures grown on collagen I matrix. Moreover, short hairpin RNA silencing of *Lkb1* tumor suppressor gene prevented formation of an organized architecture in Matrigel and enabled c-Myc to bypass the epithelial architecture–imposed cell-cycle block. Simpson and colleagues (2) challenge our main conclusion that architecture suppresses oncogenic c-Myc activity by claiming that the architecture transcriptionally suppresses ectopic c-Myc expression from retroviral construct. Both reports agree that epithelial architecture suppresses c-Myc function but the views on how this happens disagree. The question is important because better understanding of intrinsic mechanisms that antagonize oncogene function will offer new insights into tumor progression and for therapeutic exploitation. We showed expression of MycER construct in fully formed (day 20) acinar structures but Simpson and colleagues suggest that Partanen and colleagues missed MycER downregulation as they used E-cadherin as a loading control. We did not quantitate side-by-side the expression levels of latent MycER in 2D and 3D cultures but we showed that both MycER is and, as expected, cell adhesion protein E-cadherin are well expressed in the fully formed acinar structures. Strong MycER expression was documented in both 2D and 3D cultures by using identical antibody concentration (9E10 from G. Evan; 1:1,000), protein loading (20–40 μg), and short exposure times in Western blot analyses (see Supplementary Figs.). Simpson and colleagues harvested cells by trypsinization/scraping from 3D cultures before lysing the cells whereas we directly lysed the cells on plates/Matrigel, which is important as both c-Myc mRNA and protein have very short half-lives. It is possible that such technical differences in preparation of lysates could explain the differences in detection of MycER expression. We do not exclude the possibility that 3D culture conditions could slightly modulate the expression of retrovirally expressed constructs but we maintain that the MycER activity in mature 3D culture is high enough to induce conditional apoptosis and proliferation.

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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doi: 10.1158/0008-5472.CAN-11-2201

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received July 6, 2011; revised August 17, 2011; accepted September 6, 2011; Published OnlineFirst January 25, 2012.

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Published OnlineFirst January 25, 2012; DOI: 10.1158/0008-5472.CAN-11-2201

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The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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Cancer Res 2012;72:1035. Published OnlineFirst January 25, 2012.

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