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Cadherin endocytosis

Yaron Mosesson, Gordon B. Mills and Yosef Yarden

We thank Drs Wu and Hirsch for their comments on our Review (Derailed endocytosis: an emerging feature of cancer. *Nature Rev. Cancer* **8**, 835–850 (2008))[1], in which they refer to additional studies into epithelial (E)-cadherin trafficking (Mechanism of E-cadherin lysosomal degradation. *Nature Rev. Cancer* 16 Jan 2009 (doi:10.1038/nrc2521-c1))[2].

Endocytic trafficking of junctional proteins, as a means to remodel cell–cell contacts, has recently gained considerable attention. In carcinomas, degradative sorting of E-cadherin leading to loss of epithelial cell polarity is of particular interest. In their early study, D'Souza-Schorey and colleagues indeed established a lysosome-bound endocytic trajectory for E-cadherin triggered by an oncogenic SRC. Furthermore, they detailed several of the molecular players, including small GTPases (RAB5, RAB7 and ARF6) and the ubiquitin-binding capability of the endocytic adaptor HGS (hepatocyte growth factor-regulated tyrosine kinase substrate, also known as HRS)[3]. Work from the group of Grieco underscored the early contribution of the Ras and transforming growth factor-β (TGFβ) pathways to post-translational ubiquitylation and endocytic downregulation of E-cadherin (preceding transcriptional repression)[4]. More recently, Wu, Hirsch and colleagues presented an interesting model for regulation of ubiquitylation-dependent E-cadherin trafficking, which comprises CDC42, EGFR, SRC and the E3 ligase Hakai[5]. Indeed, as highlighted in our Review, this relatively new report reinforces the multi-pronged involvement of CDC42 in disrupting cell polarity and promoting cellular transformation. All of the above works describe important advances in the realm of cadherin traffic from a cancer perspective, and would have been better explicitly raised in the body of our Review. These and other studies are starting to elucidate the machineries in ever greater detail. Notably, two recent studies performed with insect cells describe a function for polarity regulators (CDC42–aPKC–PAR6 pathway) in cadherin endocytosis, through modification of actin dynamics and dynamin activity[6,7]. Undoubtedly, this burgeoning field is only beginning to flourish.

Yaron Mosesson and Yosef Yarden are at the Department of Biological Regulation, The Weizmann Institute of Science, Rehovot 76100, Israel; and Gordon B. Mills is at the Department of Systems Biology, MD Anderson Cancer Center, Houston, Texas 77030, USA.
Correspondence to Y.Y.
e-mail: yosef.yarden@weizmann.ac.il

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