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ZO-oming on growth control by junctional proteins

Comment on: Qiao X, et al. Different effects of ZO-1, ZO-2 and ZO-3 silencing on kidney collecting duct principal cell proliferation and adhesion. Cell Cycle 2014; 13(19):3059-75; http://dx.doi.org/10.4161/15384101.2014.949091

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Tight junctions (TJ) are specialized macromolecular structures that connect two adjacent epithelial cells at the border between the apical and the basolateral membranes.[1] While these structures are best known for their role as barriers against the diffusion of solutes and fences constraining the intermixing of membrane components, they are also involved in tissue homeostasis. Indeed, destruction of TJ structure by physiological or pathological causes has been connected to the re-acquisition of a proliferative state in otherwise quiescent epithelial cells.[2,3]

Several mechanisms have ben proposed to explain the anti-proliferative role of TJ, most of which involve the members of the Zonula Occludens (ZO) protein family, ZO-1, ZO-2 and ZO-3.[4] These proteins are located on the cytoplasmic side of TJ in epithelial monolayers, and display the ability to interact with some transcription factors involved in the control of cell growth. A point in case is the interaction between ZO-1 and ZONAB, a transcription factor required for cell growth.[4] Consistently with its role, ZONAB is mainly nuclear in sparse cells, and becomes junctional in contact-inhibited epithelial cells. ZO-1 overexpression impairs the entry of ZONAB in the nucleus and inhibits the proliferation of MDCK cells in a way that is rescued by concomitant expression of ZONAB. Starting from these data it has been postulated that endogenous ZO-1 titrate ZONAB in the junctions, thereby inhibiting cell proliferation.[4] However, this simple model is inconsistent with the early embryonic lethality of ZO-1 knockout mice, caused by their inability to grow.[3] Potential explanations for this discrepancy include the possibility that the absence of ZO-1 may unleash ZO-2 or ZO-3 to restrain cell growth, or that ZO-1 becomes an inhibitor of cell proliferation only in adult tissues. Therefore, a detailed study on the role of ZO proteins in adult epithelial cells was required to clarify their role in cell proliferation.

In this issue of Cell Cycle, Xiaomu Qiao and colleagues examine the influence of each of the 3 ZO proteins on proliferation of primary cells from the collecting duct (CD) of the kidney.[5] They found that depletion of ZO-1 or ZO-2 decreased cell cycle progression, causing CD cells to accumulate in the G1 phase, whereas ZO-3 knockdown caused only cell detachment, without interfering with proliferation. Interestingly, ZO-1 and ZO-2 impact on cell growth through different molecular pathways: ZO-2 is required for Cyclin-D1 expression, whereas ZO-1 promotes cell proliferation by restraining the expression of the CDK inhibitor p21. Unexpectedly, the authors also found that ZO-1 depletion reduces the stability and nuclear accumulation of a ZONAB isoform. Similar to ZO-1 depletion, ZONAB knockdown induces p21 expression and promotes growth arrest.

These results have some important implications. First, this study reveals that the ZO proteins do not always act as inhibitors of cell growth; instead, ZO-1 and ZO-2 are required to support the proliferation of CD cells. Second, the connection between ZO-1 and ZONAB in CD cells appears to work in an opposite direction to what predicted by the current models: the evidence suggests that ZO-1 is actually fostering, instead of restraining ZONAB nuclear activities.

This study is expected to pave the way to new lines of future research. Indeed, more experiments will be required to clarify whether the observations made by the authors on CD cells can be expanded to other systems and may provide insights on the general mechanisms by which ZO proteins affect cell proliferation. In this regard, it should be noted that the requirements of ZO-1 and ZO-2 for cell proliferation presented in this study are in good accordance with the phenotypes of ZO-1 and ZO-2 knockout mice.[3] Several other aspects remain obscure and need more research to be clarified: Does the recruitment of ZO proteins to TJ impact on their ability to promote cell proliferation? How does ZO-2 impact on Cyclin D1 expression and cell growth in general? Do ZO-1 and ZO-2 play any redundant role for cell growth, as hinted by another recent work[6]? Do these pathways intersect with other regulators of contact inhibition of growth, such as YAP/TAZ transcription cofactors?[7] Answering these questions will be important not only for clarifying the role of ZO proteins in growth control, but may also provide crucial information to understand tissue homeostasis and tumor initiation.

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