JCB Journal of Cell Biology

SPOTLIGHT

Food for thought: How cell adhesion coordinates nutrient sensing

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Cell adhesion controls cell survival and proliferation via multiple mechanisms. Rabanal-Ruiz et al. (2021. *J. Cell Biol.* https://doi.org/10.1083/jcb.202004010) demonstrate that focal adhesions are key signaling hubs for cellular nutrient sensing and signaling.

Cells must coordinate their responses to intracellular and extracellular cues under different physiological conditions and challenges. In the case of cell growth, cells require both amino acid building blocks and growth factor signals and an efficient system to monitor both cues simultaneously and mount an appropriate response. Mammalian target of rapamycin complex 1 (mTORC1) is a key sensor of growth-promoting signals. The activation of mTORC1 entails its recruitment to the lysosomal membrane and lysosome relocalization to the cell periphery (1), where mTORC1 is in optimum position to monitor both amino acid release from lysosome-degraded proteins and the influx of extracellular nutrients. While the functional importance of peripheral lysosome-bound mTORC1 has been underscored in a number of studies, the mechanistic links between lysosome positioning and mTORC1 activation in cells has remained poorly understood. In this issue, Rabanal-Ruiz et al. undertook an unbiased proximity labeling (BioID) and proteomics approach to uncover spatially regulated mTORC1 associations at the cell periphery in response to cell feeding. Their dataset, particularly rich in molecules linked to cell–substrate interaction and components of integrin adhesion complexes (IACs), indicates a fundamental link between cell adhesion and mTORC1 signaling (2).

In adherent cells, contacts with the extracellular matrix (ECM) are mediated by integrins, a family of transmembrane cell adhesion receptors. Once activated, integrins nucleate dynamic recruitment of kinases, small GTPases, scaffolding proteins, and associated actin filaments to give rise to a spectra of distinct adhesion structures falling under the general term IAC (3). The largest and most stable IACs include focal adhesions (FAs) and fibrillar adhesions. FAs are dynamic contractile actin stress fiber-linked structures, predominantly localized to the cell periphery in 2D cultured epithelial and mesenchymal cells, which mediate cell spreading, migration, and integrin signaling. Fibrillar adhesions are elongated and relatively stable structures with a more central localization and are involved in ECM assembly (3). Interestingly, the BioID dataset generated by Rabanal-Ruiz et al. revealed associations between mTORC1 and components from both adhesion types, but the researchers focused their attention on FAs. They found, using different methods, that nutrient-induced translocation of active mTORC1 to FAs correlated with lysosome redistribution to the cell periphery. Moreover, these peripheral lysosomes colocalized with activated growth factor receptors (GFRs) and SLC3A2 (an amino acid transporter) within FAs, suggesting the formation of a spatially regulated nutrient-sensing hub composed of integrins, mTORC1, and GFRs at cell adhesion sites. These data further cement the well-established crosstalk between integrins and GFRs in IACs (4) and suggested a spatial confinement of activated GFRs to FAs upon refeeding. The authors demonstrate that disruption of FA abrogated not only mTORC1 activation but also upstream growth factor signaling and nutrient uptake. Conversely, under senescence-inducing conditions (constitutive mTORC1 signaling) cells exhibited a higher number of FAs than proliferating cells. The pharmacological disruption of FAs in senescent cells triggered reduced mTORC1 activity and IGFR signaling. Whether reduced FAs, and the effect on mTORC1, would lead to loss of senescence in these cells was not investigated. The authors also established that mTORC1 localization proximal to FAs was necessary and sufficient for its activation upon feeding and was an essential mechanism for cellular nutrient sensing. Indeed, tethering mTORC1 to FAs by tagging the mTORC1 component RPTOR with an FA-targeting sequence enabled mTORC1 activation in cells even when peripheral lysosome positioning was disrupted by depletion of the lysosome transport regulator small GTPase ARL8B.

In several cell types, FAs mature into fibrillar adhesions through centripetal translocation of α5β1 integrins and a gradual switch from talin- to tensin-bound integrins (3, 5; Fig. 1). Rabanal-Ruiz et al. detected both talin (FA-enriched scaffold protein)

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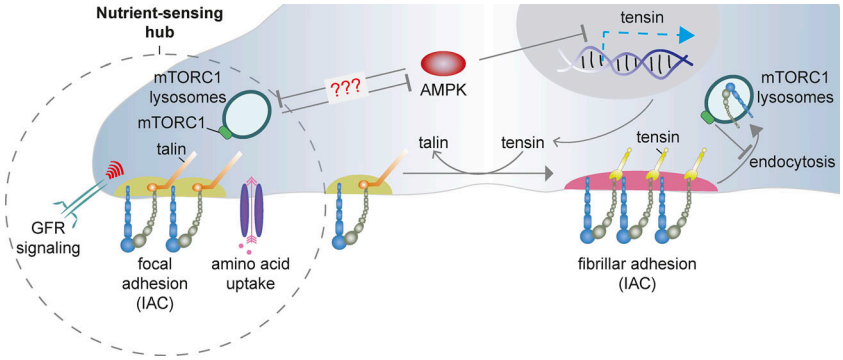

Figure 1. **Cell adhesion crosstalk with metabolism.** FAs associate with mTORC1-positive lysosomes and form a nutrient-sensing hub, which controls spatially restricted GFR signaling, nutrient uptake, and mTORC1 activity. FAs mature into fibrillar adhesions through centripetal movement of α5β1-integrin and a talin-tensin switch. Active mTORC1-positive lysosomes are recruited to fibrillar adhesions, suppress integrin endocytosis, and stabilize fibrillar adhesions. In addition, inhibition of AMPK under nutrient-rich conditions induces tensin transcription, further supporting fibrillar adhesions and integrin activity. Reciprocal control of mTOR and AMPK pathways may play a key role in orchestrating crosstalk between IACs and metabolism.

and tensin1 and tensin3 (fibrillar adhesion–enriched scaffold proteins) in their BioID search for mTORC1-associated proteins (2). A previous study demonstrated mTORC1-positive lysosomes are recruited to fibrillar adhesions, where active mTORC1 spatially inhibits α5β1 integrin endocytosis and cellular uptake of ECM fragments for lysosomal degradation (6). These studies suggest that mTORC1 activation may be regulated by different IACs and depend on ECM composition and cell type. For example, prominent FAs are rarely observed in 3D ECM conditions; therefore, mTORC1 activation and nutrient sensing might be coordinated through other IACs in 3D microenvironments.

In addition to the mTOR pathway, the AMP-activated protein kinase (AMPK) pathway is central to cellular metabolism and cell proliferation. Interestingly, both signaling networks are implicated in regulating integrin function and ECM assembly within fibrillar adhesions (Fig. 1). Inhibition of AMPK results in transcriptional up-regulation of tensin1 and tensin3, prolonged activation of β1-integrins, and accumulation of tensin-rich fibrillar adhesions (5). Conversely, activation of mTORC1 stabilizes fibrillar adhesions via increased retention of integrins in these structures (6). Therefore, under nutrient-replete conditions, low AMPK and high mTORC1 would support fibrillar adhesion stability through distinct mechanisms impinging on transcriptional regulation of adhesion components and integrin endocytosis (Fig. 1). Given the strong connection between FAs and fibrillar adhesion formation, one might also anticipate that the positive link between FAs and mTORC1 activity described by Rabanal-Ruiz et al. would contribute to the crosstalk between nutrient sensing and fibrillar adhesions. A recent study adds another level of possible synergy that might influence the links between energy metabolism and cell adhesion. AMPK signaling is a well-established inhibitor of mTORC1 activity; new evidence suggests that mTORC1 directly down-regulates AMPK activity, indicating reciprocal regulation of the two pathways (7). Whether this is relevant for adhesion-regulated metabolism remains to be investigated.

There is a growing appreciation of mechanical forces regulating cell behavior through different mechanisms, including stiffness-induced cell spreading and adhesion maturation (8). Cell metabolism is also subject to mechanical control, though this remains an understudied area (9). Cell adhesion and ECM mechanics regulate cell metabolism directly and indirectly. The first entails cell spreading and ECM stiffness-mediated control of glycolytic enzymes and of intracellular pH. The latter involves stiffness-induced transcription through yes-associated protein/transcriptional co-activator with PDZ-binding motif and serum response factor/myocardin-related transcription factor complexes (9). In most cell types, FA size increases with increased stiffness (8) and fibrillar adhesions are also mechanosensitive (10). In light of the observations made by Rabanal-Ruiz et al., we might expect mTORC1 activity to be supported by increasing ECM stiffness; this would provide another mechanistic link between matrix rigidity and the regulation of cell proliferation and survival. Altogether, the connection between metabolism, adhesions, and stiffness would be an exciting avenue for future investigation, particularly in the context of developing therapies related to accelerated stiffness-induced cancer cell proliferation.

Acknowledgments

The authors declare no competing financial interests.

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