Tensin links energy metabolism to extracellular matrix assembly

Emmanuel Dornier1 and Jim C. Norman1,2

1 Cancer Research UK Beatson Institute for Cancer Research, Glasgow G61 1BD, Scotland, UK
2 Institute of Cancer Sciences, University of Glasgow, Glasgow G61 1QH, Scotland, UK

The regulation of integrin function is key to fundamental cellular processes, including cell migration and extracellular matrix (ECM) assembly. In this issue, Georgiadou et al. (2017. J. Cell Biol. https://doi.org/10.1083/jcb.201609066) report that the metabolic sensor adenosine monophosphate–activated protein kinase influences tensin production to regulate α5β1-integrin and fibrillar adhesion assembly and thus reveal an important connection between energy metabolism and ECM assembly.

The ECM is a principal structural component of tissues that performs many important roles, including directing tissue patterning during embryogenesis and maintaining compartmentalization and homeostasis in the adult. The epithelial basement membrane is a laminin- and collagen IV–rich ECM structure, synthesized primarily by epithelial cells, which contributes to the stability, structure, and regenerative capacity of epithelia as well as the barrier function of these tissues (Rowe and Weiss, 2008). However, a very different kind of fibrillar ECM—which is fibronectin and collagen I rich—is key to neural and vascular patterning during embryogenesis. In the adult, this fibronectin-rich ECM is commonly termed the “provisional matrix” and is primarily produced and assembled by fibroblasts during wound healing (Singh et al., 2010). Furthermore, the fibronectin-rich provisional-type ECM is assembled by carcinoma-associated fibroblasts, and this is known to be a key driver of cancer invasion and metastasis (Van Obberghen-Schilling et al., 2011).

Integrins are transmembrane receptors that form well-characterized physical links between the cytoskeleton and the ECM, and these transmit mechanical signals bidirectionally across the plasma membrane to influence ECM assembly. The cell’s principal fibronectin-binding integrin, the α5β1 heterodimer, controls fibronectin assembly. Thus, α5β1 engagement with fibronectin, and the manner in which this integrin manipulates the assembly of nascent fibronectin fibrils, will dictate the organization of the resulting provisional matrix (Yamada et al., 2003).

In 2000, Pankov et al. made a series of key observations that underpin how we now view the role played by fibroblasts in fibronectin ECM assembly. They reported that when α5β1 engages with fibronectin, this integrin is initially recruited to talin-rich focal adhesions (FAs) in the cell periphery. After this, α5β1 leaves the FAs and moves inward to populate fibrillar adhesions, and it is during this centripetal journey that the physical forces that promote fibronectin assembly are brought to bear (Fig. 1). In FAs, the β1-integrin cytodomain forms a well-characterized association with the phosphotyrosine binding (PTB)–like domain of talin, an actin-binding protein, and this connects the integrin to the actin cytoskeleton (Calderwood et al., 2013). However, as α5β1 moves centripetally out of FAs into fibrillar adhesions, it detaches from talin and associates with the PTB-like domain of another actin-binding protein called tensin (Pankov et al., 2000; McCleverty et al., 2007; Rainero et al., 2015). A subsequent study deployed tensin mutants, which are incapable of binding to β1-integrin, to demonstrate that α5β1 must swap allegiance from talin to tensin in order to undertake the inward journey that coordinates fibronectin assembly (Rainero et al., 2015). Finally, α5β1’s centripetal journey is terminated by its arrival at the cell center, whereupon it is internalized by an Arf4-dependent and clathrin-independent endocytic mechanism (Rainero et al., 2015). Thus, a picture is emerging in which fibronectin assembly is coordinated by a centripetal α5β1-integrin translocator operating between the cell periphery and the cell center, and this is a process in which tensin plays a pivotal role (Fig. 1).

AMP-activated protein kinase (AMPK) is a key component of the cell’s metabolic sensing system. AMPK is activated by the increased levels of AMP that accompany various energy stresses and metabolic insults, and the phosphorylation of AMPK substrates, broadly speaking, leads to the activation of metabolic pathways that generate ATP (Hardie et al., 2012). It is now becoming clear that energy metabolism and nutrient sensing are linked to cell migration, and the likelihood that these links may be important to the acquisition of invasive and metastatic behavior in cancer has stimulated considerable interest in this area of cell biology. In this issue, Georgiadou et al. have shown that the key metabolic sensor AMPK controls β1-integrin activity and that its activity prevents integrin translocation and fibronectin remodeling in fibroblasts. The authors had previously developed functional RNAi approaches to screen for kinases that influenced integrin function, and this identified components of the AMPK complex as potential β1-integrin regulators (Rantal et al., 2011). Encouraged by this and by observations from both the Humphries (Horton et al., 2015) and Fassler (Schiller et al., 2013) laboratories showing that AMPK subunits are components of the integrin adhesome, the authors...
set out to determine how this metabolic sensing kinase might regulate β1-integrins and integrin-dependent cellular functions.

Control of centripetal α5β1 translocation and fibronectin assembly by AMPK and mTORC1. α5β1-Integrin is incorporated into FAs at the cell periphery and is associated with talin in these structures. Tensin competes with talin for binding to the β1-integrin cytodomain and displaces α5β1 from FAs. α5β1 then moves centripetally toward the cell center in association with tensin. Fibronectin is assembled as α5β1's inward journey from FAs to the cell center would be expected to be promoted by an abundance of nutrients, leading to low AMPK activity and high tensin levels. Correspondingly, α5β1's centripetral movement is terminated by an Arf4-dependent endocytic event, which is strongly inhibited by the nutrient-activated kinase mTORC1. Therefore, one might anticipate that under situations where the nutrient status of a cell is high, the combination of low AMPK, which promotes up-regulated integrin activity, fibroblast adhesion formation, fibronectin assembly, and altered cell rheology that results from the suppression of AMPK. Conversely, overexpression of the appropriate tensin isoforms drives integrin activation, and, importantly, this requires tensin interaction with the β1 cytodomain, as tensin mutants deficient in β1-integrin binding are inactive in this regard.

It is interesting to discuss how this study aligns with another recent paper linking another nutrient-regulated kinase, mTORC1, to α5β1 dynamics (Rainero et al., 2015), and to hypothesize how these studies might illuminate the role of cell metabolism and nutrient availability in controlling the ECM microenvironment of tumors. Indeed, AMPK and mTORC1 activity are commonly reciprocally regulated, as not only do these two kinases respond in opposing ways to altered nutrient status, but AMPK is also well established to phosphorylate the mTORC1 component Raptor at sites that lead to its inhibition (Hardie, 2014). As mentioned above, α5β1-integrins leave FAs in the cell periphery and move centripetally in a tensin-dependent manner toward the cell center, and the characteristics of this inward journey are likely to dictate the nature of the resulting fibronectin network (Fig. 1). The start of α5β1’s inward journey from FAs to the cell center would be expected to be promoted by an abundance of nutrients, leading to low AMPK activity and high tensin levels. Correspondingly, α5β1’s centripetral journey is terminated by an Arf4-dependent endocytic event, which is strongly inhibited by the nutrient-activated kinase mTORC1.
Tumors are composed of a variety of different cell types, and the metabolic statuses of all of these will not be equivalent. Specifically, because tumor cells are rapidly proliferating, they will be more prone to metabolic stress and will be expected to have higher levels of AMPK (and lower levels of mTORC1) activity than carcinoma-associated fibroblasts, which are less proliferative. Thus, it is probable that this could generate a microenvironment in which high levels of ECM assembly by carcinoma-associated fibroblasts are supported, whereas the tumor cells endocytose and scavenge this ECM to try to satisfy their metabolic demands. Indeed, a recent study has shown that metabolically stressed epithelial cells uptake ECM that has been deposited by fibroblasts and that this helps these epithelial cells to survive under conditions of nutrient starvation (Muranen et al., 2017).

To conclude, this study by Georgiadou et al. (2017) provides mechanistic insight that will be key to understanding how energy metabolism and ECM production are coordinated in complex microenvironments and will facilitate the development of strategies to target these processes therapeutically.

Acknowledgements

We gratefully acknowledge Cancer Research UK and Breast Cancer Now for generously funding the research conducted in the Norman lab.

The authors declare no competing financial interests.

References

Calderwood, D.A., J.D. Campbell, and D.R. Critchley. 2013. Talins and kindlins: partners in integrin-mediated adhesion. Nat. Rev. Mol. Cell Biol. 14:503–517. http://dx.doi.org/10.1038/nrm3624

Georgiadou, M., J. Lilja, G. Jacquemet, C. Guzmán, M. Rafaeva, C. Alibert, Y. Yan, P. Sahgal, M. Lerche, J.-B. Manneville, et al. 2017. AMPK negatively regulates tensin-dependent integrin activity, J. Cell Biol. https://doi.org/10.1083/jcb.201609066

Hardie, D.G. 2014. AMPK—sensing energy while talking to other signaling pathways. Cell Metab. 20:939–952. http://dx.doi.org/10.1016/j.cmet.2014.09.013

Hardie, D.G., F.A. Ross, and S.A. Hawley. 2012. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat. Rev. Mol. Cell Biol. 13:251–262. http://dx.doi.org/10.1038/nrm3311

Horton, E.R., A. Byron, J.A. Askari, D.H. Ng, A. Millon-Frémillon, J. Robertson, E.J. Koper, N.R. Paul, S. Warwood, D. Knight, et al. 2015. Definition of a consensus integrin adhesome and its dynamics during adhesion complex assembly and disassembly. Nat. Cell Biol. 17:1577–1587. http://dx.doi.org/10.1038/ncb3257

McCleverty, C.J., D.C. Lin, and R.C. Liddington. 2007. Structure of the PTB domain of tensin I and a model for its recruitment to fibrillar adhesions. Protein Sci. 16:1223–1229. https://doi.org/10.1110/ps.072798707

Muranen, T., M.P. Iwanicki, N.L. Curry, J. Hwang, C.D. DuBois, J.L. Coloff, D.S. Hitchcock, C.B. Clish, J.S. Brugge, and N.Y. Kalaany. 2017. Starved epithelial cells uptake extracellular matrix for survival. Nat. Commun. 8:13989. http://dx.doi.org/10.1038/ncomms13989

Pankov, R., E. Cukierman, B.Z. Katz, K. Matsumoto, D.C. Lin, S. Lin, C. Hahn, and K.M. Yamada. 2000. Integrin dynamics and matrix assembly: tensin-dependent translocation of αβ5 integrins promotes early fibronectin fibrillogenesis. J. Cell Biol. 148:1075–1090. http://dx.doi.org/10.1083/jcb.148.5.1075

Rainero, E., J.D. Howe, P.T. Caswell, N.B. Jamieson, K. Anderson, D.R. Critchley, L. Machesky, and J.C. Norman. 2015. Ligand-occupied integrin internalization links nutrient signaling to invasive migration. Cell Reports. 10:389–413.

Rantala, J.K., J. Prouwels, T. Pellinen, S. Veltel, E. Mattila, C.S. Potter, T. Duffy, J.P. Sundberg, O. Kallioniemi, et al. 2011. SHA RPIN is an endogenous inhibitor of β1-integrin activation. Nat. Cell Biol. 13:1315–1324. http://dx.doi.org/10.1038/nclb2340

Rowe, R.G., and S.J. Weiss. 2008. Breaching the basement membrane: who, when and how? Trends Cell Biol. 18:560–574. http://dx.doi.org/10.1016/j.tcb.2008.08.007

Schiller, H.B., M.R. Hermann, J. Polleux, T. Vignaud, S. Zanivan, C.C. Friedel, Z. Sun, A. Raducanu, K.E. Gottschalk, M. Théry, et al. 2013. β integrins cooperate to regulate myosin II during rigidity sensing of fibronectin-based microenvironments. Nat. Cell Biol. 15:625–636. http://dx.doi.org/10.1038/ncb2747

Singh, P., C. Carraher, and J.E. Schwarzbauer. 2010. Assembly of fibronectin extracellular matrix. Annu. Rev. Cell Dev. Biol. 26:397–419. http://dx.doi.org/10.1146/annurev-cellbio-101009-104020

Van Obberghen-Schilling, E., R.P. Tucker, F. Sause, I. Gasser, B. Cseh, and G. Orend. 2011. Fibronectin and tenasin-C: accomplices in vascular morphogenesis during development and tumor growth. Int. J. Dev. Biol. 55:511–525. http://dx.doi.org/10.1387/ijdb.103243eo

Yamada, K.M., R. Pankov, and E. Cukierman. 2003. Dimensions and dynamics in integrin function. Rev. Bras. Pesqui. Med. Biol. 36:959–966.