Developmental Cell
Previews

A Role for β3-Integrins in Linking Breast Development and Cancer

Ahmet Ucar[1] and Charles H. Streuli[1,*]
[1]Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, University of Manchester, Oxford Road, Manchester M13 9PT, UK
*Correspondence: cstreuli@manchester.ac.uk
http://dx.doi.org/10.1016/j.devcel.2014.07.009

Pregnancy induces a rapid and controlled expansion of mammary stem cells. In this issue of *Developmental Cell*, Desgrosellier et al. (2014) show that β3-integrin is required downstream of hormonal signaling and TGFβ2 to regulate mammary stem cell number and alveolar development specifically during early pregnancy.

Numerous extraordinary changes in mammalian physiology mark the early stages of pregnancy. One of these is the rapid and exquisitely coordinated proliferation of epithelial cells in the breast, which equips the mother for nursing. However, the question of how mammary epithelial cells divide so fast and yet become carefully crafted into alveoli has not been solved. Perhaps the answer lies in a unique period of stem cell expansion within a specific window of breast development, which provides a large number of cells that can subsequently differentiate into milk factories (Figure 1A). Rapid proliferation is also a hallmark of cancer but is fundamentally distinguished from normal growth by its disorganization. A new study from Cheresh and colleagues in this issue of *Developmental Cell* reveals that a cell-matrix adhesion receptor, β3-integrin, may link these events of normal development and pathology (Desgrosellier et al., 2014).

Integrins are α/β-heterodimeric extracellular matrix adhesion receptors that regulate cellular responses to their microenvironment by activating intracellular signaling (Glukhova and Streuli, 2013). The most prominent integrins in the breast are β1-integrin heterodimers; without them, epithelial cells have severe defects in proliferation, polarity, milk production, and stem cell function. However, cells express different integrin heterodimers depending on their developmental stage and microenvironmental context, and separate epithelial lineages arising from the same precursors in the breast can be distinguished on the basis of their integrin profiles. Luminal cells, which are adjacent to the luminal space of ducts and alveoli, express low levels of β1-integrin and α6-integrin (sometimes known as CD29 and CD49f, respectively), while the basal myoepithelial cells and mammary epithelial stem cells (MaSCs) express high levels of these integrins (Figure 1B). A separate integrin subunit, β3 (CD61), is also expressed in breast epithelia, and its levels distinguish luminal progenitors (β3+) from mature, differentiated luminal cells (β3−).

The function of β3-integrin in the breast has not been fully understood. Desgrosellier and colleagues find that this integrin subunit is crucial for MaSCs at a very particular time of mammary development, during the period of alveologenesis in early pregnancy (Desgrosellier et al., 2014). Deleting the β3-integrin gene largely prevents the appearance of alveoli, but its absence has no effect on duct formation or on the differentiation of luminal precursors into milk-producing alveolar cells. The increased expression of β3-integrin in early pregnancy suggests that this subunit may be under the control of ovarian hormones, and indeed it was previously shown that progesterone might indirectly regulate β3-integrin expression in MaSCs (Joshi et al., 2010). The authors of the current study find that TGFβ2, which is also increased during midpregnancy, is able to induce β3-integrin transcription in MaSCs. The mechanisms controlling integrin expression are not particularly well understood, so the observation that the β3-integrin gene can be transcribed in response to endocrine-induced paracrine signals is particularly intriguing.

The requirement of a specific integrin subunit for stem cell expansion during early pregnancy suggests that there may be previously unidentified changes in the extracellular matrix (ECM) around newly forming alveoli that contribute to their development. This would make sense, given the dramatically different architecture of mammary alveoli in comparison with ducts and given the specific requirement for just alveolar, but not ductal, cells to proliferate at this time. While it is not clear whether β3-integrins require ligand binding for their stem cell activity, fibronectin is present in mammary basement membranes, so it could be a ligand for β3-integrins in early alveoli (Woodward et al., 2001). It would also be valuable to know whether other β3-integrin ligands are expressed specifically during early pregnancy.

In addition to being classically associated with linking the ECM to the intracellular cytoskeleton, integrins are also signaling engines. The authors find that this latter aspect of β3-integrin's function is crucial in MaSCs, because cells containing a β3ΔC knockin allele—which encodes a signaling-defective β3 lacking its C′-terminal three amino acids—display the same phenotype as those with a full deletion of the β3-integrin. The integrin-signaling pathway involves Src family kinases and stabilization of Slug, a transcription factor previously associated with MaSCs (Guo et al., 2012).

Thus, Desgrosellier et al. (2014) paint a new picture of integrins in breast development, whereby the pregnancy hormone progesterone indirectly activates a TGFβ2>β3-integrin>SFK>Slug pathway to increase the number of stem cells in preparation for lactation. We know that β1-integrins ensure the self-renewal of MaSCs by regulating their asymmetric cell division (Taddei et al., 2008). They are also required in late pregnancy and lactation for luminal cell proliferation and for differentiation into polarized alveoli that can synthesize and secrete milk

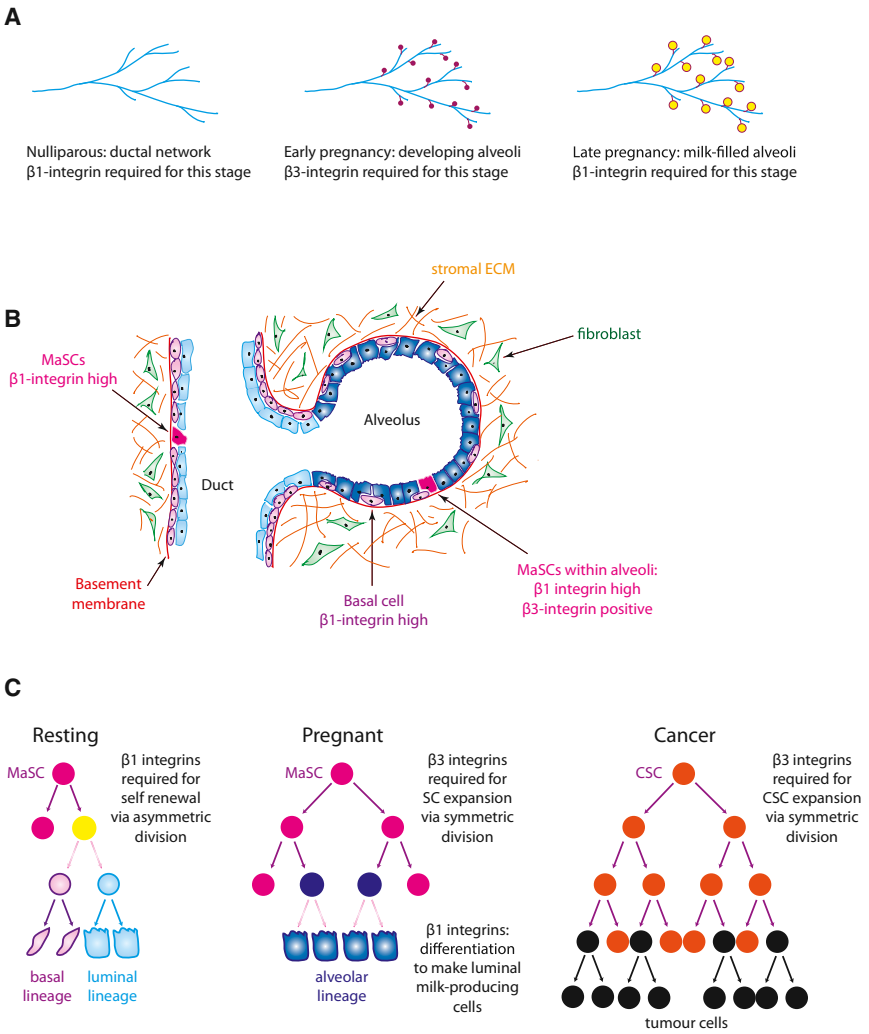

Figure 1. Roles for β-Integrins in Breast Development

(A) The requirement of β3-integrins in breast development is restricted to early pregnancy, where there is an expansion in the numbers of alveoli that subsequently differentiate into polarized milk-producing epithelial cells in preparation for lactation. (B) Simplified architecture of the breast, showing integrin expression profile in the stem cells of ducts and alveoli. (C) Left: In resting breast, the stem cell pool is self-renewed through asymmetric division, most likely requiring β1-integrins. Middle: In early pregnancy, rapid expansion of stem cells occurs through symmetric divisions coordinated by β3-integrins. Right: Cancer stem cells rapidly divide to form tumors through symmetric cell division.

(Akhtar and Streuli, 2013; Li et al., 2005). β3-integrins may have a unique function in driving the symmetric division of MaSCs to rapidly increase their numbers in the early stages of pregnancy (Figure 1C).

Unfortunately, this developmental control mechanism may have disastrous consequences on the rare occasions in which it becomes dysregulated, particularly in aggressive tumors in which the cancer stem cell pool expands through symmetric divisions. Moreover, some aggressive breast cancers are associated with higher numbers of tumor-initiating stem cells, which probably undergo symmetric division more frequently than normal stem cells (Pece et al., 2010). Thus, it may not be surprising that β3-integrins are associated with aggressive cancer subtypes (Desgrosellier et al., 2009).

Given that integrin switching to a β3-dependent process has a central role during a stage of breast development that is nonessential to the mother, targeting this subunit, and its associated signaling members, may provide a specific way to treat cancers without affecting the host tissue. β3-integrins may also represent a target for cancer stem cells, thereby reducing disease progression and recurrence.

REFERENCES

Akhtar, N., and Streuli, C.H. (2013). Nat. Cell Biol. *15*, 17–27.

Desgrosellier, J.S., Barnes, L.A., Shields, D.J., Huang, M., Lau, S.K., Prévost, N., Tarin, D., Shattil, S.J., and Cheresh, D.A. (2009). Nat. Med. *15*, 1163–1169.

Desgrosellier, J.S., Lesperance, J., Seguin, L., Gozo, M., Kato, S., Franovic, A., Yebra, M., Shattil, S.J., and Cheresh, D.A. (2014). Dev. Cell *30*, this issue, 295–308.

Glukhova, M.A., and Streuli, C.H. (2013). Curr. Opin. Cell Biol. *25*, 633–641.

Guo, W., Keckesova, Z., Donaher, J.L., Shibue, T., Tischler, V., Reinhardt, F., Itzkovitz, S., Noske, A., Zürrer-Härdi, U., Bell, G., et al. (2012). Cell *148*, 1015–1028.

Joshi, P.A., Jackson, H.W., Beristain, A.G., Di Grappa, M.A., Mote, P.A., Clarke, C.L., Stingl, J., Waterhouse, P.D., and Khokha, R. (2010). Nature *465*, 803–807.

Li, N., Zhang, Y., Naylor, M.J., Schatzmann, F., Maurer, F., Wintermantel, T., Schuetz, G., Mueller, U., Streuli, C.H., and Hynes, N.E. (2005). EMBO J. *24*, 1942–1953.

Pece, S., Tosoni, D., Confalonieri, S., Mazzarol, G., Vecchi, M., Ronzoni, S., Bernard, L., Viale, G., Pelicci, P.G., and Di Fiore, P.P. (2010). Cell *140*, 62–73.

Taddei, I., Deugnier, M.-A., Faraldo, M.M., Petit, V., Bouvard, D., Medina, D., Fässler, R., Thiery, J.P., and Glukhova, M.A. (2008). Nat. Cell Biol. *10*, 716–722.

Woodward, T.L., Mienaltowski, A.S., Modi, R.R., Bennett, J.M., and Haslam, S.Z. (2001). Endocrinology *142*, 3214–3222.