A local basis for progesterone action during mammary tumorigenesis - no longer RANK and file

Whitney K Petrie and Russell C Hovey*
of epithelial proliferation in the mammary glands. A first, cyclin D1-dependent wave occurred in PR-positive cells and was RANKL-independent. The second round of cyclin D1-independent proliferation that occurred beyond 48 hours in PR-negative cells was then RANKL-dependent [12]. This chronology of progesterone-induced proliferation and RANKL secretion supports the model that PR-positive cells stimulate proliferation in adjacent PR-negative cells by a paracrine mechanism [10], within which there is likely a key role for RANKL. These data also suggest that progesterone induces cyclin D1 independent of RANKL. By contrast, these most recent reports [8,9] and others [10] find that the progesterone-dependent induction of cyclin D1 is also RANK/RANKL-dependent. Indeed, RANKL also modulates expression of other proliferative cues, including cyclin E, Id2, and Id4 [6,7,13], suggesting that multiple targets lie downstream of progesterone-induced RANK activation. The hierarchy of proliferative pathways within mammary epithelial cells that lie downstream of RANKL/RANK may well prove to be context-specific in terms of other regulatory events, including the effects of other hormones or growth factors, the extracellular matrix, or pregnancy-associated differentiation. Indeed, both prolactin and parathyroid hormone-related peptide are capable of inducing RANKL in the mammary glands [3] while others reported that estrogen was required to facilitate progesterone-induced RANKL expression [4].

As pointed out by both groups, the present findings may firmly implicate RANK as a key player during progesterone-dependent breast cancer, given that women receiving combined estrogen plus progesterone replacement therapy, but not estrogen alone, have an increased risk of developing breast cancer [14]. However, any effect of progesterins such as MPA on breast cancer risk, and therefore RANK signaling, presents an opportunity for detailed resolution given that MPA at comparable doses also serves as the primary progestin in hormonal contraception that has no consistent effect on breast cancer risk [15]. Therefore, the role of progesterone and RANK/RANKL during breast cancer onset may well prove to be context-specific. Along these lines, different strains of mice respond differently to progesterone in terms of both mammary development and RANKL expression [13]. Likewise, in both of the present studies the ability of MPA-dependent tumorigenesis was enhanced by DMBA that induces a unique mammary cancer pathotype distinct from that typical for human breast cancer [16].

In conclusion, these important recent findings lend support to a growing body of data pointing to a key role for RANK and its ligand during progestin-dependent epithelial proliferation and cancer in the mammary glands. These findings may prove to be even more important for delineating the role of RANK and RANKL in managing hormone-dependent and/or -independent breast cancer.

Abbreviations
DMA, dimethybenz[a]anthracene; MMTV, mouse mammary tumor virus; MPA, medroxyprogesterone acetate; PR, progesterone receptor; RANK, receptor of activated NF-κB; RANKL, RANK ligand.

Competing interests
The authors declare that they have no competing interests.

Published: 28 January 2011

References

1. Höffbauer LC, Rachner T, Singh SK: Fatal attraction: why breast cancer cells home to bone. Breast Cancer Res 2008, 10:101.
2. Jones DH, Nakashima T, Sanchez OH, Koziara D, I. Komarno SV, Sarosi I, Morony S, Rubin E, Sarao R, Hojilla CV, Komenovic V, Kong YY, Schreiber M, Dixon SJ, Sims SM, Khokha R, Wada T, Penninger JM: Regulation of cancer cell migration and bone metastasis by RANKL. Nature 2004, 440:692-696.
3. Fata JE, Kong YY, Li J, Sasaki T, Irie-Sasaki J, Moorehead RA, Elliott R, Scully S, Vouea EB, Lacey DL, Boyle WJ, Khokha R, Penninger JM: The osteoclast differentiation factor osteoprotegerin-ligand is essential for mammary gland development. Cell 2000, 103:41-50.
4. Srivastava S, Matsuda M, Hau Z, Bailey J, Kitazawa R, Herbst MP, Horsemann ND: Receptor activator of NF-kappaB ligand induction via Jak2 and Stat5a in mammary epithelial cells. J Biol Chem 2003, 278:4617-1-46178.
5. Gonzalez-Suarez E, Brainstett D, Armstrong A, Dinh H, Blumberg H, Dougall WC: RANK overexpression in transgenic mice with mouse mammary tumor virus promoter-controlled RANK increases proliferation and impairs alveolar differentiation in the mammary epithelia and disrupts lumen formation in cultured epithelial acini. Mol Cell Biol 2007, 27:1442-1454.
6. Kim NS, Kim HJ, Koo BK, Kwon MC, Kim YW, Cho Y, Yokota T, Penninger JM, Kong YY: Receptor activator of NF-kappaB ligand regulates the proliferation of mammary epithelial cells via Id2. Mol Cell Biol 2006, 26:1002-1013.
7. Fernandez-Valdivia R, Mukherjee A, Creighton CJ, Buser AC, DeMayo FJ, Edwards DP, Lydon JP: Transcriptional response of the murine mammary gland to acute progesterone exposure. Endocrinology 2008, 149:6236-6250.
8. Gonzalez-Suarez E, Jacobs AP, Jones J, Miller R, Roudier-Meyer MP, Erwert R, Pinkas J, Branstett D, Dougall WC: RANK ligand mediates progestin-induced mammary epithelial proliferation and carcinogenesis. Nature 2010, 468:109-110.
9. Schramek D, Leibbrandt A, Sigl V, Kenner L, Pospisilik JA, Lee HJ, Hanada R, Joshi PA, Aliprantis A, Gilmcher L, Pasparakis M, Khokha R, Ormandy CJ, Widschwendter M, Schett G, Penninger JM: Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. Nature 2010, 468:98-102.
10. Mukherjee A, Soyal SM, Li J, Ying Y, He B, DeMayo FJ, Lydon JP, Targeting RANKL to a specific subset of murine mammary epithelial cells induces ordered branching morphogenesis and alveologenesis in the absence of progesterone receptor expression. FASEB J 2010, 24:4408-4419.
11. Muzlcic-Radonic B, Lydon JP, DeMayo FJ, Conneely OM: Defective mammal gland morphogenesis in mice lacking the progesterone receptor B isoform. Proc Natl Acad Sci U S A 2003, 100:9744-9749.
12. Belovut M, Rajaram RD, Caikovski M, Ayavan A, Germano D, Choy Y, Schneider P, Brisken C: Two distinct mechanisms underlie progesterone-induced proliferation in the mammary gland. Proc Natl Acad Sci U S A 2010, 107:2989-2994.
13. Aupepil G, Grogg PA, Durairaj S, Wang W, Schwartz HC, Haslam SW: Strain-specific differences in the mechanisms of progesterone regulation of mammary gland development. Endocrinology 2009, 150:1485-1494.
14. Chlebovscky RT, Anderson GL, Gass M, Lane DS, Agaraki AK, Kuller LH, Manson JE, Stefanick ML, Ockene J, Sarto GE, Johnson KC, Waclawski-Wende J, Radvan PM, Schenken R, Hertweek R, Cohlin T, Prentice RL, WHI Investigators: Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA 2004, 301:1684-1692.
15. Breast cancer and hormonal contraceptives: further results. Collaborative Group on Hormonal Factors In Breast Cancer. Contraception 1996,
16. Currier N, Solomon SE, Demicco EG, Chang DL, Farago M, Ying H, Dominguez I, Sonenshein GE, Cardiff RD, Xiao ZX, Sherr DH, Seldin DC. Oncogenic signaling pathways activated in DMBA-induced mouse mammary tumors. Toxicol Pathol 2005, 33:726-737.

doi:10.1186/bcr2802
Cite this article as Petrie WK, Hovey RC. A local basis for progesterone action during mammary tumorigenesis - no longer RANK and file. Breast Cancer Research 2011, 13:301.