Short communication

The origins of oestrogen receptor negative breast cancer

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Human invasive breast cancers (IBCs) are categorized in many ways, including on the basis of whether the tumour cells express oestrogen receptor (ER)-α. ER status is important clinically because ER mediates the growth-stimulating effects of circulating oestrogen and because tumours expressing ER have a significant chance of responding to hormonal therapies such as tamoxifen and aromatase inhibitors [1].

Epithelia in the normal breast nearly always contain a subpopulation of ER-expressing cells [2,3]. The proportion of positive cells is regulated physiologically and varies considerably with menstrual status, averaging about 30% overall [3]. About 75% of IBCs also contain a widely variable proportion of ER-positive cells [1]. In contrast, the remaining approximately 25% of IBCs do not contain any ER-positive cells [1]. The origins of these entirely ER-negative tumours have been the topic of considerable debate. Although there is no consensus, the majority opinion on this issue appears to be that ER-negative IBCs evolve from ER-negative precursors, whereas ER-positive IBCs evolve from ER-positive precursors [4]. Many observations and assumptions support the majority opinion, especially the following. First, studies have suggested that tamoxifen prevents only ER-positive IBCs in high-risk women [5]. Second, there is speculation that the different so-called intrinsic subtypes of breast cancer, some of which are entirely ER negative (for example, the basal subtype), evolve from distinct types of stem/progenitor cells [6]. Third, related research suggests that an ER-negative stem cell is fundamentally responsible for normal breast development, that they give rise to more differentiated ER-positive progenitor cells, and that both may progress to cancers with their corresponding ER phenotypes [7-10].

However, an alternative viewpoint, argued in this discussion, is that there are multiple mechanisms for the development of ER-negative IBCs, including many from ER-positive precursors by potentially reversible mechanisms. The importance of this issue relates to the fact that ER-negative IBCs are unresponsive to conventional hormonal therapies and that finding strategies to convert them back to an ER-positive phenotype, which is potentially responsive to these therapies, would be a major contribution. Considerable evidence also supports this alternative viewpoint (Table 1). For example, epidemiological studies have demonstrated that increased oestrogen exposure is a major risk factor for developing breast cancer, presumably independent of ER status, although the latter has not specifically been addressed in these studies [11]. However, breast cancer was historically a very rare disease, and the near epidemic increase in incidence in Western cultures roughly corresponds to the dramatic increase in oestrogen exposure, consistent with the idea that oestrogen must contribute to the aetiology of all breast cancers, including those that are ER-negative. Looked at from the opposite direction, decreased oestrogen exposure associated with prophylactic oophorectomy in *BRCA1* mutation carriers dramatically decreases the risk for breast cancer, independent of ER status [12].

Histopathological studies also support the origin of ER-negative IBCs from ER-positive precursors. For example, nearly all well established premalignant lesions in the breast are strongly ER positive [13], including atypical ductal hyperplasia, and studies have shown that atypical ductal hyperplasia is a strong risk factor for development of IBCs independent of biological characteristics such as ER status [14]. Furthermore, the proportions of ER-positive and ER-negative IBCs decrease and increase with time, respectively. This is consistent with progression of the latter from the former. Perhaps the best illustration of this is the dramatic decrease in ER-negative breast cancer since the introduction of screening mammography (specifically, because of early detection) [15,16]. Similarly, the proportion of ER-negative tumours is substantially greater among large as compared with small IBCs, and all large tumours were smaller at an earlier point in time [16-19].

Although it is not widely appreciated, there is also considerable intratumour histological and biological diversity in breast cancers, arguing that ER-negative IBCs may evolve from ER-positive precursors. For example, the majority of IBCs appear to evolve from advanced precursor lesions,

Table 1

Evidence supporting the origin of ER-negative breast cancers from ER-positive precursors

Evidence	Details
Epidemiological	Increased oestrogen exposure mediated by ER is a risk factor for all breast cancers
	Prophylactic oophorectomy in *BRCA1* mutation carriers reduces all breast cancers
	ADH (>90% ER-positive cells) is a strong risk factor for all breast cancers
	The proportion of ER-negative breast cancers increases with time (tumour progression)
Histological/pathological	All early premalignant breast lesions are strongly ER positive
	ER-positive precursors associated with ER-negative cancers in same breast/patient
Molecular	MAPK activation reversibly transforms ER-positive to ER-negative breast cancers
	Methylation ER promoter reversibly transforms ER-positive to ER-negative breast cancers
	Apocrine metaplasia may reversibly transform ER-positive to ER-negative breast cancers

ADH, atypical ductal hyperplasia; ER, oestrogen receptor; MAPK, mitogen-activated protein kinase.

referred to as ductal carcinoma *in situ* (DCIS). The latter are ER-positive in about 5% of ER-negative IBCs [20], which is consistent with the idea that ER expression is suppressed during tumour progression. Interestingly, the opposite is almost never observed. Similarly, up to 20% of metastases associated with ER-positive primary IBCs are ER negative, which again is consistent with the idea that ER expression is downregulated during tumour progression [21,22]. Recent studies also show that the majority of DCISs contain cells of diverse histological grades within individual tumours, and that ER expression significantly decreases as grade increases in these cells (as they become more poorly differentiated) [23]. In fact, most DCISs contain intratumour diversity for many features, including histological grade, standard prognostic biomarkers and even intrinsic subtypes, which is also probably true for IBCs [23]. Presumably, these areas of intratumour diversity compete for dominance, and eventually the most aggressive prevail, which is a general mechanism by which poorly differentiated (ER-negative) may gradually evolve from well differentiated (ER-positive) tumours.

Several molecular mechanisms have recently been identified, which may be involved in the loss of ER expression during tumour progression. For example, recent studies have demonstrated that hypermethylation of the ER promoter can reversibly downregulate ER expression in IBCs [24]. Other recent studies have shown that activation of the mitogen-activated protein kinase pathway, especially through ligand-activated tyrosine kinase receptors at the cell surface, can downregulate ER expression in a reversible manner [25]. There is some evidence that even apparently normal physiological responses retained by tumour cells can result in ER-negative IBCs. For example, so-called apocrine metaplasia is a common phenomenon in all types of benign breast epithelia, and it is associated with a complete loss of ER expression [26]. Apocrine metaplasia is also commonly observed in breast cancers [26,27] and may be responsible for the development of a substantial proportion of ER-negative disease in a potentially reversible manner.

Overall, the evidence appears overwhelming that many ER-negative IBCs evolve from ER-positive precursors, although it also seems likely that some ER-negative IBCs may also evolve from ER-negative precursors. Finding effective therapies for these diverse types of ER-negative breast cancers will be dependent on a comprehensive understanding of the mechanisms that are responsible for their development, and there are likely to be many.

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References

1. Elledge R, Allred DC: **Clinical aspects of estrogen and progesterone receptors.** In *Diseases of the Breast.* Edited by Harris JR, Lippman ME, Morrow M, Osborne CK. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:601-617.
2. Fuqua S, Schiff R: **The biology of estrogen receptors.** In *Diseases of the Breast.* Edited by Harris JR, Lippman ME, Morrow M, Osborne CK. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:585-602.
3. Lee S, Mohsin SK, Mao S, Hilsenbeck SG, Medina D, Allred DC: **Hormones, receptors, and growth in hyperplastic enlarged lobular units: early potential precursors of breast cancer.** *Breast Cancer Res* 2005, **8:**R6.
4. Sims AH, Howell A, Howell SJ, Clarke RB: **Origins of breast cancer subtypes and therapeutic implications.** *Nat Clin Practice Oncol* 2007, **4:**516-525.
5. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, *et al.*: **Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study.** *J Natl Cancer Inst* 1998, **90:**1371-1388.
6. Anderson W, Matsuno R: **Breast cancer heterogeneity: a mixture of at least two main types?** *J Natl Cancer Inst* 2006, **98:**948-951.
7. Asselin-Labat ML, Shackleton M, Stingl J, Vaillant F, Forrest NC, Eaves CJ, Visvader JE, Lindeman GJ: **Steroid hormone receptor status of mouse mammary stem cells.** *J Natl Cancer Inst* 2006, **98:**1011-1014.

8. Dontu G, Liu S, Wicha MS: **Stem cells in mammary development and carcinogenesis: implications for prevention and treatment.** *Stem Cell Rev* 2005, **1:**207-213.
9. Mallepell S, Krust A, Chambon P, Brisken C: **Paracrine signaling through the epithelial estrogen receptor alpha is required for proliferation and morphogenesis in the mammary gland.** *Proc Natl Acad Sci USA* 2006, **103:**2196-2201.
10. Sleeman KE, Kendrick H, Robertson D, Isacke CM, Ashworth A, Smalley MJ: **Dissociation of estrogen receptor expression and in vivo stem cell activity in the mammary gland.** *J Cell Biol* 2007, **176:**19-26.
11. Henderson BE, Ross R, Bernstein L: **Estrogens as a cause of human cancer: the Richard and Hindau Rosenthal Foundation Award Lecture.** *Cancer Res* 1988, **48:**246-253.
12. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, Evans G, Isaacs C, Daly MB, Matloff E, *et al.*; Prevention and Observation of Surgical End Points Study Group: **Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations.** *N Engl J Med* 2002, **346:**1616-1622.
13. Allred DC, Hilsenbeck SG, Mohsin SK: **Biologic features of human premalignant breast disease.** In *Diseases of the Breast*. Edited by Harris JR, Lippman ME, Morrow M, Osborne CK. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:512-513.
14. Jacobs TW, Byrne C, Colditz G, Connolly JL, Schnitt SJ: **Pathologic features of breast cancers in women with previous benign breast disease.** *Am J Clin Pathol* 2001, **115:**362-369.
15. Ernster VL, Barclay J: **Increases in ductal carcinoma in situ (DCIS) of the breast in relation to mammography: a dilemma.** *Natl Cancer Inst Monogr* 1997, **22:**151-156.
16. Ries LA, Eisner MP, Kosary CL: *SEER Cancer Statistics Review 1975-2000*. Bethesda, MA: National Cancer Institute; 2003. [http://seer.cancer.gov/csr/1975_2000]
17. Clark GM, Osborne CK, McGuire WL: **Correlations between estrogen receptor, progesterone receptor and patient characteristics in human breast cancer.** *J Clin Oncol* 1984, **2:**1102-1109.
18. Harvey JM, Clark GM, Osborne CK, Allred DC: **Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer.** *J Clin Oncol* 1999, **17:**1474-1481.
19. Magne N, Toillon RA, Castadot P, Ramaioli A, Namer M: **Different clinical impact of estradiol receptor determination according to the analystic method: a study on 1940 breast cancer patients over a perio sof 16 consecutive years.** *Breast Cancer Res Treat* 2006, **95:**179-184.
20. Allred DC, Brown P, Medina D: **The origins of estrogen receptor positive and negative human breast cancer.** *Breast Cancer Res* 2004, **6:**240-245.
21. Brown P, Fuqua S, Allred DC: **Pathogenesis of estrogen receptor positive and negative breast cancer.** In *Contemporary Endocrinology: Endocrine Oncology*. Edited by Ethier SP. Totowa, NJ: Humana Press Inc; 2001:49-68.
22. Kuukasjarvi T, Kononen J, Helin H, Holli K, Isola J: **Loss of estrogen receptor in recurrent breast cancer is associated with poor response to endocrine therapy.** *J Clin Oncol* 1996, **14:** 2584-2589.
23. Allred DC, Wu Y, Mao S, Nagtegaal ID, Lee S, Perou CM, Mohsin SK, O'Connell P, Tsimelzon A, Medina D: **Ductal carcinoma in situ and the emergence of diversity during breast cancer evolution.** *Clin Cancer Res* 2007, in press.
24. Yan L, Yang X, Davidson NE: **Role of DNA methylation and histone acetylation in steroid receptor expression in breast cancer.** *J Mammary Gland Biol Neoplasia* 2001, **6:**183-192.
25. Creighton CJ, Hilger AM, Murthy S, Rae JM, Chinnaiyan AM, El-Ashry D: **Activation of mitogen-activated protein kinase in estrogen receptor alpha-positive breast cancer cells in vitro induces an in vivo molecular phenotype of estrogen receptor alpha-negative breast tumors.** *Cancer Res* 2006, **66:**3903-3911.
26. Lee S, Mohsin SK, Weiss H, Medina D, Allred DC: **Apocrine metaplasia and the development of ER-negative breast cancer [abstract 171].** *Modern Pathol* 2005, **18(suppl 1):**40A.
27. Farmer P, Bonnefoi H, Becette V, Tubiana-Hulin M, Fumoleau P, Larsimont D, Macgrogan G, Bergh J, Cameron D, Goldstein D, *et al.*: **Identification of molecular apocrine breast tumours by microarray analysis.** *Oncogene* 2005, **24:**4660-4671.