Journal of
Steroids & Hormonal Science
ISSN: 2157-7536

Han and Wu, J Steroids Horm Sci 2012, 3:2
DOI: 10.4172/2157-7536.1000e110

Editorial Open Access

Accelerating the Application of ER α Cofactor in the Therapy of Breast Cancer

Weidong Han* and Zhiqiang Wu

Institute of Basic Medicine, College of Life Science, Chinese PLA General Hospital, Beijing, 100853, China

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of all cancers [1]. The relationship between estrogens and breast cancer has long been investigated, and the carcinogenic effects of estrogens seem to be mainly mediated by the stimulation of cellular proliferation through their receptor-mediated hormonal activity [2]. The Estrogen Receptor (ER) has two subtypes, ERα and ERβ, and it has been proven that ERα is the single most important target in breast cancer over the last 30 years. So blocking estrogen-ERα signal is desirable in endocrine therapy for breast cancer. And selective estrogen receptor modulators such as tamoxifen are well-established treatment modalities for ER-positive breast cancer. However, their effectiveness and ability in blocking ER activity in breast cancer can decrease with time, a phenomenon termed "hormone resistance" [3], which has become a major obstacle in the treatment of breast cancer [4]. Furthermore, the estrogenic effects of tamoxifen in other tissues and organs can increase the risk of endometrial cancer [5], thromboembolic events and stroke [6]. Hence, new therapeutic modalities are required to overcome endocrine resistance of breast cancers and its deleterious consequences.

The transcriptional activity of ERα is largely depended on the regulation of co-activators and co-repressors. In addition to the ability of regulating ER physiology, these cofactors also play an important role in estrogen-associated pathologies. And data implicating coactivator overexpression in human breast cancer pathogenesis have been steadily accumulating. Therefore, interfering with the interaction of the coactivators and ERα may lead to an appreciable antitumor activity, even in cases of endocrine resistance. Over the past 17 years, more than 20 coactivator molecules have been identified using biochemical approaches as well as yeast two-hybrid screens (Table 1), and most of the interactions are mediated by LXXLL motifs (L = leucine, X = any amino acid) of cofactors. It indicated that the synthesis of peptides containing LXXLL motifs may specifically disrupt the interactions of ERα and its cofactors. So many investigations were conducted in several laboratories to assess the validity of this view. Unfortunately, no peptides are used in clinical application for breast cancer therapy until now. The considerable challenge may include: 1) the peptides must inhibit the protein-protein interactions in the breast, yet retain the beneficial effects of ERα activity in the bone, brain and immune systems; 2) characteristics of such protein-peptide interactions are much more complex than the endogenous interactions they are planned to mimic [7]; 3) when folding during interaction process, most peptides exhibit a low specificity and selectively [8,9]. Although there are some obstacles, we believe that, if successful, this approach will provide a second class of pharmaceutical agents for the treatment of breast cancer. And we also believe that antagonizing the recruitment of cofactor is one way to antitumor, but not unique.

MicroRNAs, which are a class of non-coding RNA gene, have recently come to the fore of molecular research into underlying mechanisms of many diseases and cellular processes, in particular cancer [38,39]. Although there is a paucity of information about interactions between specific MicroRNAs and ERα cofactors in normal and malignant breast tissues, many MicroRNAs are predicted to target cofactors of ERα [40]. In spite of the fact that a lot of experimental work must be done, MicroRNAs targeting ERα cofactor may be another class of pharmaceutical agents for the treatment of breast neoplasms.

References

1. Jemal, A., F. Bray, M. M. Center, J. Ferlay, E. Ward, and D. Forman Global cancer statistics. CA Cancer J Clin. 61: 69-90.
2. Kulendran, M., M. Salhab, and K. Mokbel (2009) Oestrogen-synthesising enzymes and breast cancer. Anticancer Res. 29: 1095-1109.
3. Schiff, R., S. A. Massarweh, J. Shou, L. Bharwani, G. Arpino, M. Rimawi, and C. K. Osborne (2005) Advanced concepts in estrogen receptor biology and breast cancer endocrine resistance: implicated role of growth factor signaling and estrogen receptor coregulators. Cancer Chemother Pharmacol. 56 Suppl 1: 10-20.
4. Ring, A., and M. Dowsett (2004) Mechanisms of tamoxifen resistance. Endocr Relat Cancer. 11: 643-658.
5. Cohen, I. (2004) Endometrial pathologies associated with postmenopausal tamoxifen treatment. Gynecol Oncol. 94: 256-266.
6. Venturini, M., and L. Del Mastro (2006) Safety of adjuvant aromatase inhibitor therapy. Cancer Treat Rev. 32: 548-556.
7. Lafont, V., M. Schaefer, R. H. Stote, D. Altschuh, and A. Dejaegere (2007) Protein-protein recognition and interaction hot spots in an antigen-antibody complex: free energy decomposition identifies "efficient amino acids". Proteins. 67: 418-434.
8. Peczuh, M. W., and A. D. Hamilton (2000) Peptide and protein recognition by designed molecules. Chem Rev. 100: 2479-2494.
9. Stanfield, R. L., and I. A. Wilson (1995) Protein-peptide interactions. Curr Opin Struct Biol. 5: 103-113.
10. Lee, S. K., S. L. Anzick, J. E. Choi, L. Bubendorf, X. Y. Guan, Y. K. Jung, O. P. Kallioniemi, J. Kononen, J. M. Trent, D. Azorsa, B. H. Jhun, J. H. Cheong, Y. C. Lee, P. S. Meltzer, and J. W. Lee (1999) A nuclear factor, ASC-2, as a cancer-amplified transcriptional coactivator essential for ligand-dependent transactivation by nuclear receptors in vivo. J Biol Chem. 274: 34283-34293.
11. Brunnberg, S., K. Pettersson, E. Rydin, J. Matthews, A. Hanberg, and I. Pongratz (2003) The basic helix-loop-helix-PAS protein ARNT functions as a potent coactivator of estrogen receptor-dependent transcription. Proc Natl Acad Sci U S A. 100: 6517-6522.
12. DiRenzo, J., Y. Shang, M. Phelan, S. Sif, M. Myers, R. Kingston, and M. Brown (2000) BRG-1 is recruited to estrogen-responsive promoters and cooperates with factors involved in histone acetylation. Mol Cell Biol. 20: 7541-7549.
13. Qi, C., Y. T. Zhu, J. Chang, A. V. Yeldandi, M. S. Rao, and Y. J. Zhu (2005) Potentiation of estrogen receptor transcriptional activity by breast cancer amplified sequence 2. Biochem Biophys Res Commun. 328: 393-398.

***Corresponding author:** Weidong Han, Institute of Basic Medicine, College of Life Science, Chinese PLA General Hospital, Beijing, 100853, China, Tel: 86-10-66937463; Fax: 86-10-66937516; E-mail: hanwdrsw69@yahoo.com

Received May 01, 2012; **Accepted** May 02, 2012; **Published** May 03, 2012

Citation: Han W, Wu Z (2012) Accelerating the Application of ERα Cofactor in the Therapy of Breast Cancer. J Steroids Horm Sci 3:e110. doi:10.4172/2157-7536.1000e110

14. Fritah, A., C. Saucier, J. Mester, G. Redeuilh, and M. Sabbah (2005) p21WAF1/CIP1 selectively controls the transcriptional activity of estrogen receptor alpha. Mol Cell Biol. 25: 2419-2430.

15. den Hollander, P., S. K. Rayala, D. Coverley, and R. Kumar (2006) Ciz1, a Novel DNA-binding coactivator of the estrogen receptor alpha, confers hypersensitivity to estrogen action. Cancer Res. 66: 11021-11029.

16. Nawaz, Z., D. M. Lonard, C. L. Smith, E. Lev-Lehman, S. Y. Tsai, M. J. Tsai, and B. W. O'Malley (1999) The Angelman syndrome-associated protein, E6-AP, is a coactivator for the nuclear hormone receptor superfamily. Mol Cell Biol. 19: 1182-1189.

17. Meng, Q., L. Zhou, J. Cao, B. Gao, R. Shao, J. Li, and S. Fan (2003) Identification and function of coactivator of estrogen receptor: ERIAP. Sci China C Life Sci. 46: 546-558.

18. Zhu, Y., L. L. Sullivan, S. S. Nair, C. C. Williams, A. K. Pandey, L. Marrero, R. K. Vadlamudi, and F. E. Jones (2006) Coregulation of estrogen receptor by ERBB4/HER4 establishes a growth-promoting autocrine signal in breast tumor cells. Cancer Res. 66: 7991-7998.

19. Wu, X., H. Li, and J. D. Chen (2001) The human homologue of the yeast DNA repair and TFIIH regulator MMS19 is an AF-1-specific coactivator of estrogen receptor. J Biol Chem. 276: 23962-23968.

20. Toyama, T., H. Iwase, H. Yamashita, Y. Hara, H. Sugiura, Z. Zhang, I. Fukai, Y. Miura, K. Riabowol, and Y. Fujii (2003) p33(ING1b) stimulates the transcriptional activity of the estrogen receptor alpha via its activation function (AF) 2 domain. J Steroid Biochem Mol Biol. 87: 57-63.

21. Sisci, D., C. Morelli, S. Cascio, M. Lanzino, C. Garofalo, K. Reiss, M. Garcia, A. Russo, S. Ando, and E. Surmacz (2007) The estrogen receptor alpha:insulin receptor substrate 1 complex in breast cancer: structure-function relationships. Ann Oncol. 18 Suppl 6: vi81-85.

22. Han, W. D., Y. L. Zhao, Y. G. Meng, L. Zang, Z. Q. Wu, Q. Li, Y. L. Si, K. Huang, J. M. Ba, H. Morinaga, M. Nomura, and Y. M. Mu (2007) Estrogenically regulated LRP16 interacts with estrogen receptor alpha and enhances the receptor's transcriptional activity. Endocr Relat Cancer. 14: 741-753.

23. Imachi, H., K. Murao, H. Dobashi, M. M. Bhuyan, X. Cao, K. Kontani, S. Niki, C. Murazawa, H. Nakajima, N. Kohno, H. Yamashita, H. Iwase, S. Hayashi, T. Ishida, and A. Yamauchi Menin, a product of the MENI gene, binds to estrogen receptor to enhance its activity in breast cancer cells: possibility of a novel predictive factor for tamoxifen resistance. Breast Cancer Res Treat. 122: 395-407.

24. Mishra, S. K., A. Mazumdar, R. K. Vadlamudi, F. Li, R. A. Wang, W. Yu, V. C. Jordan, R. J. Santen, and R. Kumar (2003) MICoA, a novel metastasis-associated protein 1 (MTA1) interacting protein coactivator, regulates estrogen receptor-alpha transactivation functions. J Biol Chem. 278: 19209-19219.

25. Wei, X., H. Xu, and D. Kufe (2006) MUC1 oncoprotein stabilizes and activates estrogen receptor alpha. Mol Cell. 21: 295-305.

26. Wang, R. A., A. Mazumdar, R. K. Vadlamudi, and R. Kumar (2002) P21-activated kinase-1 phosphorylates and transactivates estrogen receptor-alpha and promotes hyperplasia in mammary epithelium. EMBO J. 21: 5437-5447.

27. Vadlamudi, R. K., R. A. Wang, A. Mazumdar, Y. Kim, J. Shin, A. Sahin, and R. Kumar (2001) Molecular cloning and characterization of PELP1, a novel human coregulator of estrogen receptor alpha. J Biol Chem. 276: 38272-38279.

28. Endoh, H., K. Maruyama, Y. Masuhiro, Y. Kobayashi, M. Goto, H. Tai, J. Yanagisawa, D. Metzger, S. Hashimoto, and S. Kato (1999) Purification and identification of p68 RNA helicase acting as a transcriptional coactivator specific for the activation function 1 of human estrogen receptor alpha. Mol Cell Biol. 19: 5363-5372.

29. Hanstein, B., R. Eckner, J. DiRenzo, S. Halachmi, H. Liu, B. Searcy, R. Kurokawa, and M. Brown (1996) p300 is a component of an estrogen receptor coactivator complex. Proc Natl Acad Sci U S A. 93: 11540-11545.

30. Elangovan, S., S. Ramachandran, N. Venkatesan, S. Ananth, J. P. Gnana-Prakasam, P. M. Martin, D. D. Browning, P. V. Schoenlein, P. D. Prasad, V. Ganapathy, and M. Thangaraju SIRT1 is essential for oncogenic signaling by estrogen/estrogen receptor alpha in breast cancer. Cancer Res. 71: 6654-6664.

31. Onate, S. A., S. Y. Tsai, M. J. Tsai, and B. W. O'Malley (1995) Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. Science. 270: 1354-1357.

32. Azorsa, D. O., H. E. Cunliffe, and P. S. Meltzer (2001) Association of steroid receptor coactivator AIB1 with estrogen receptor-alpha in breast cancer cells. Breast Cancer Res Treat. 70: 89-101.

33. Deblois, G., and V. Giguere (2003) Ligand-independent coactivation of ERalpha AF-1 by steroid receptor RNA activator (SRA) via MAPK activation. J Steroid Biochem Mol Biol. 85: 123-131.

34. Le Douarin, B., C. Zechel, J. M. Garnier, Y. Lutz, L. Tora, P. Pierrat, D. Heery, H. Gronemeyer, P. Chambon, and R. Losson (1995) The N-terminal part of TIF1, a putative mediator of the ligand-dependent activation function (AF-2) of nuclear receptors, is fused to B-raf in the oncogenic protein T18. EMBO J. 14: 2020-2033.

35. Voegel, J. J., M. J. Heine, C. Zechel, P. Chambon, and H. Gronemeyer (1996) TIF2, a 160 kDa transcriptional mediator for the ligand-dependent activation function AF-2 of nuclear receptors. EMBO J. 15: 3667-3675.

36. Warnmark, A., T. Almlof, J. Leers, J. A. Gustafsson, and E. Treuter (2001) Differential recruitment of the mammalian mediator subunit TRAP220 by estrogen receptors ERalpha and ERbeta. J Biol Chem. 276: 23397-23404.

37. Ding, L., J. Yan, J. Zhu, H. Zhong, Q. Lu, Z. Wang, C. Huang, and Q. Ye (2003) Ligand-independent activation of estrogen receptor alpha by XBP-1. Nucleic Acids Res. 31: 5266-5274.

38. Bartel, D. P. (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 116: 281-297.

39. Lu, J., G. Getz, E. A. Miska, E. Alvarez-Saavedra, J. Lamb, D. Peck, A. Sweet-Cordero, B. L. Ebert, R. H. Mak, A. A. Ferrando, J. R. Downing, T. Jacks, H. R. Horvitz, and T. R. Golub (2005) MicroRNA expression profiles classify human cancers. Nature. 435: 834-838.

40. Griffiths-Jones, S., R. J. Grocock, S. van Dongen, A. Bateman, and A. J. Enright (2006) miRBase: microRNA sequences, targets and gene nomenclature. Nucleic Acids Res. 34: D140-144.

Cofactor	Full Name	Interaction with ER	References
AIB3	Amplified in breast cancer 3	Binds ER AF-2 through LXXLL motifs	[10]
ARNT	Aryl hydrocarbon receptor nuclear translocator	Binds ERα LBD	[11]
BRG-1	Brahma-related gene 1	Binds ERα AF-2 domain	[12]
BCAS2	Breast cancer amplified sequence 2	ND	[13]
CIP1	Clin-dependent kinase inhibitor 1A	ND	[14]
Ciz1	Cip-interacting zinc finger protein 1	Binds ERα DBD	[15]
E6-AP	E6-associated protein	Binds ERα AF-2	[16]
ERIAP	Estrogen Receptor Interacting and Activating Protein	Binds ERα LBD/AF-2	[17].
HER4	Proto-oncogene-like protein c-ErbB-4	Binds ERα AF-1 or AF-2	[18]
hMMS19		ND	[19]
ING1b	Inhibitor of growth family, member 1	ND	[20]
IRS-1	Insulin receptor substrate 1	Binds ERα AF-1 or DBD	[21]
LRP16	Leukemia related protein 16	Binds ERα AF-1	[22]
Menin	Multiple endocrine neoplasia type 1	Binds ERα AF-2	[23]
MICoA	MTA1-interacting coactivator	Binds ERα AF-2 through LXXLL motifs	[24]
MUC1	mucin 1, cell surface associated	Binds ERα DBD	[25]
Pak1	p21-activated kinase 1	Binds ERα AF-1 or AF-2	[26]
PELP1	proline-,glutamic acid-,and leucine-rich protein-1	Binds ERα AF-2 through LXXLL motifs	[27]
p68	p68 RNA helicase	Binds ERα AF-1	[28]
p300	Histone acetyltransferase p300	Binds ERα AF-2 through LXXLL motifs	[29]
SIRT1	sirtuin 1	ND	[30]
SRC1	Steroid receptor coactivator 1	Binds ERα AF-2 through LXXLL motifs	[31]
SRC-3	Steroid receptor coactivator-3	Binds ERα AF-2 through LXXLL motifs	[32]
SRA	Steroid receptor RNA activator	Binds ERα AF-1	[33]
TIF1	Transcriptional intermediary factor 1	Binds ERα AF2 domain	[34]
TIF2	Transcriptional intermediary factor 2	Binds ERα AF-2 through LXXLL motifs	[35]
TRAP220	Thyroid hormone receptor activating protein of 220 kDa	Binds ER AF-2 through LXXLL motifs	[36]
XBP-1	X-box binding Protein I	Binds ERα DBD	[37]

Table 1: Estrogen receptor cofactors.