

# Lawrence Berkeley National Laboratory

## Biological Systems & Engineering

### Title

Who is in the driver's seat in 8p12 amplifications? ZNF703 in luminal B breast tumors

### Permalink

<https://escholarship.org/uc/item/7j88t4kw>

### Journal

Breast Cancer Research, 13(3)

### ISSN

1465-5411

### Authors

Bazarov, Alexey V

Yaswen, Paul

### Publication Date

2011-06-01

### DOI

10.1186/bcr2873

Peer reviewed

VIEWPOINT

# Who is in the driver's seat in 8p12 amplifications? ZNF703 in luminal B breast tumors

Alexey V Bazarov<sup>1,2</sup> and Paul Yaswen<sup>2\*</sup>

## Abstract

Two recent reports identify *ZNF703* as an oncogene driving selection of frequent chromosome 8p12 amplifications in luminal B breast tumors. The estrogen-responsive *ZNF703* gene encodes a transcriptional cofactor that, when overexpressed, induces cell proliferation and interferes with transforming growth factor beta signaling. In MCF7 cells, increased ZNF703 expression results in activation of genes involved in stem cell self-renewal – while in primary human mammary epithelial cells, ZNF703 increases the ratio of luminal to basal progenitors. Expression of the murine homolog of ZNF703 reduces cell adhesion and promotes metastasis. ZNF703 overexpression thus alters regulation of proliferation and differentiation in luminal B tumors.

## Introduction

Five major breast cancer subtypes – basal, luminal A, luminal B, ERBB2-positive, and normal breast-like – are distinguishable on the basis of molecular profiling [1]. Both luminal A and luminal B subtypes are estrogen receptor (ER)-positive, but luminal B tumors are more metastatic [2] and have poorer prognoses [3]. Each of the breast cancer subtypes is characterized by a specific pattern of genomic abnormalities [4]. Luminal B tumors often contain high-level amplifications of chromosome region 8p12, and patients bearing tumors with amplifications in this region exhibit significantly poorer outcomes than patients whose tumors do not contain such amplifications [4]. The most commonly amplified 1 Mb segment in the 8p12 region contains only five genes for which amplification correlates with the gene expression: *ZNF703*, *ERLIN2*, *PROSC*, *BRF2*, and *RAB11FIP1* [5,6].

Until now, however, the identity of the driver oncogene within this group remained elusive.

## Articles

Two recent reports describe high-density array comparative genomic hybridization analyses of the 8p12 region using independent panels of breast tumors and cell lines [6,7]. In one case, 1,001 primary breast cancers were used to define the boundaries of the minimal amplicon [6]. Both sets of these comparative genomic hybridization results implicate *ZNF703* as the main gene whose amplification is selected for in luminal B cancers. The evidence includes two tumors in which *ZNF703* was the only gene amplified within the 8p12 region. High levels of *ZNF703* amplification and mRNA expression were associated with poor outcomes in ER-positive and luminal tumors.

The association studies are supplemented by experimental data obtained using cell culture models. Transfection of *ZNF703* resulted in transformation of NIH 3T3 cells, and induced proliferation of both nonmalignant human mammary epithelial cells and malignant MCF7 cells. Holland and coworkers [6] further demonstrated that increased levels of ZNF703 resulted in decreased expression of transforming growth factor beta (TGF $\beta$ ) receptor II and prevented TGF $\beta$  from inhibiting proliferation of MCF7 cells. Binding of ZNF703 to the TGF $\beta$  receptor II promoter was demonstrated by chromatin immunoprecipitation, and was associated with repressive chromatin modifications. ZNF703 contains a single zinc finger domain and is unlikely to bind to DNA directly, however [8]. Sircoulomb and colleagues [7] found that ZNF703 forms complexes with DCAF7, PBH2, and NCOR2 factors involved in transcriptional repression, in agreement with the proposed function of the ZNF703 homolog Nlz1 in zebrafish development [9].

While the *ZNF703* promoter contains estrogen-responsive elements and its expression is responsive to estrogen, *ZNF703* transfection led to reduced ER expression and activity in MCF7 cells, indicating the existence of negative feedback regulation [7]. *ZNF703* transfection, however, also resulted in reduced expression of cell cycle inhibitors p27 and p15, increased pRb phosphorylation,

\*Correspondence: P\_Yaswen@lbl.gov

<sup>2</sup>Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA

Full list of author information is available at the end of the article

and increased E2F1 transcriptional activity. Based on these data, the authors of this work propose that ZNF703 expression leads to a shift from an ER-regulated to an E2F1-regulated transcriptional program, characteristic of luminal B tumors. Additional data indicate that ZNF703 expression leads to activation of pathways involved in stem cell self-renewal, and that it increases the ratio of luminal to basal progenitors, suggesting that, in addition to promoting proliferation, its oncogenic function includes altering differentiation kinetics.

The new findings in human tissues and cells complement another recent study showing that Zeppo1 (*Zpo1*), the murine homolog of ZNF703, reduces cell–cell adhesion and increases invasiveness as well as proliferation in three-dimensional cultures [10]. At the molecular level, Zeppo1 represses E-cadherin expression and causes increased expression of the promigratory p120-catenin isoform. Consequently, Zeppo1 overexpression promotes metastasis in a murine tumor model. These results may explain invasiveness and poor prognosis in human luminal B tumors.

### Viewpoint

While ZNF703 has been largely unknown in the breast cancer field, the new reports firmly establish it as a functional contributor to luminal B tumors. The preponderance of clinical correlations and experimental data are commensurate with the classical definition of an oncogene. As elegantly pointed out [7], however, the oncogene concept is evolving and expanding to accommodate context-dependent genetic and epigenetic features, as well as novel functions. For example, while ZNF703 transfection by itself can cause anchorage-independent growth of NIH 3T3 cells – a classical demonstration of oncogenicity – it does not cause transformation of MCF10A cells unless p53 is also compromised [11]. Under normal circumstances, aberrant proliferation is insufficient for malignancy. Regulation of proliferation, however, is intimately connected to differentiation. The major oncogenic role of amplified/overexpressed ZNF703 may be dysregulation of differentiation rather than abrogation of cell cycle checkpoints.

Now that ZNF703 has been firmly implicated in the pathogenesis of luminal B breast cancers, the next challenges will be to determine how expression/function of the encoded protein can be regulated and to determine the major downstream effectors of its oncogenic functions. For example, cyclin D<sub>1</sub>, located at chromosome 11q13, induces ZNF703 expression in an E2F1-dependent fashion [11]. As ZNF703 is in turn involved in E2F signaling, these results may explain frequent coamplifications of 8p12 and 11q13 regions. By mapping ZNF703 connections to other biochemical pathways, it may be

possible to find pharmacologically tractable points at which the effects of ZNF703 amplification might be mitigated.

### Abbreviations

ER, estrogen receptor; TGFβ, transforming growth factor beta.

### Competing interests

The authors declare that they have no competing interests.

### Author details

<sup>1</sup>Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, CA 94143, USA. <sup>2</sup>Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA.

Published: 25 May 2011

### References

1. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, Deng S, Johnsen H, Pesich R, Geisler S, Demeter J, Perou CM, Lonning PE, Brown PO, Borresen-Dale AL, Botstein D: **Repeated observation of breast tumor subtypes in independent gene expression data sets.** *Proc Natl Acad Sci U S A* 2003, **100**:8418-8423.
2. Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, Nielsen TO, Gelmon K: **Metastatic behavior of breast cancer subtypes.** *J Clin Oncol* 2010, **28**:3271-3277.
3. Dawood S, Hu R, Homes MD, Collins LC, Schnitt SJ, Connolly J, Colditz GA, Tamimi RM: **Defining breast cancer prognosis based on molecular phenotypes: results from a large cohort study.** *Breast Cancer Res Treat* 2011, **126**:185-192.
4. Chin K, DeVries S, Fridlyand J, Spellman PT, Roydasgupta R, Kuo WL, Lapuk A, Neve RM, Qian Z, Ryder T, Chen F, Feiler H, Tokuyasu T, Kingsley C, Dairkee S, Meng Z, Chew K, Pinkel D, Jain A, Ljung BM, Esserman L, Albertson DG, Waldman FM, Gray JW: **Genomic and transcriptional aberrations linked to breast cancer pathophysiologies.** *Cancer Cell* 2006, **10**:529-541.
5. Garcia MJ, Pole JC, Chin SF, Teschendorff A, Naderi A, Ozdag H, Vias M, Kranjac T, Subkhankulova T, Paish C, Ellis I, Brenton JD, Edwards PA, Caldas C: **A 1 Mb minimal amplicon at 8p11-12 in breast cancer identifies new candidate oncogenes.** *Oncogene* 2005, **24**:5235-5245.
6. Holland DG, Burleigh A, Git A, Goldgraben MA, Perez-Mancera PA, Chin SF, Hurtado A, Bruna A, Ali HR, Greenwood W, Dunning MJ, Samarajiva S, Menon S, Rueda OM, Lynch AG, McKinney S, Ellis IO, Eaves CJ, Carroll JS, Curtis C, Aparicio S, Caldas C: **ZNF703 is a common luminal B breast cancer oncogene that differentially regulates luminal and basal progenitors in human mammary epithelium.** *EMBO Mol Med* 2011, **3**:167-180.
7. Sircoulomb F, Nicolas N, Ferrari A, Finetti P, Bekhouche I, Rousselet E, Lonigro A, Adelaide J, Baudalet E, Esteyries S, Wicinski J, Audebert S, Charafe-Jauffret E, Jacquemier J, Lopez M, Borg JP, Sotiriou C, Popovici C, Bertucci F, Birnbaum D, Chaffanet M, Ginestier C: **ZNF703 gene amplification at 8p12 specifies luminal B breast cancer.** *EMBO Mol Med* 2011, **3**:153-166.
8. Nakamura M, Runko AP, Sagerstrom CG: **A novel subfamily of zinc finger genes involved in embryonic development.** *J Cell Biochem* 2004, **93**:887-895.
9. Nakamura M, Choe SK, Runko AP, Gardner PD, Sagerstrom CG: **Nlz1/Znf703 acts as a repressor of transcription.** *BMC Dev Biol* 2008, **8**:108.
10. Slorach EM, Chou J, Werb Z: **Zeppo1 is a novel metastasis promoter that represses E-cadherin expression and regulates p120-catenin isoform expression and localization.** *Genes Dev* 2011, **25**:471-484.
11. Kwek SS, Roy R, Zhou H, Climent J, Martinez-Climent JA, Fridlyand J, Albertson DG: **Co-amplified genes at 8p12 and 11q13 in breast tumors cooperate with two major pathways in oncogenesis.** *Oncogene* 2009, **28**:1892-1903.

doi:10.1186/bcr2873

Cite this article as: Bazarov AV, Yaswen P: Who is in the driver's seat in 8p12 amplifications? ZNF703 in luminal B breast tumors. *Breast Cancer Research* 2011, **13**:308.