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Commentary

Is *BECN1* a Target Gene of Chromosome 17q21 Alteration in Breast Cancer?

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In this issue of EBioMedicine, Tang et al. describes their results obtained from analysing the expression of *BRCA1* and *BECN1* in breast cancer patients from two large datasets (TCGA and METABRIC datasets) (Tang et al., 2015). They found reproducible associations in both datasets of *BECN1* expression with oestrogen receptor negative cancers (HER2-OE and basal like breast cancers) as well as molecular features related to the subtypes. Intriguingly, no such correlations were found with *BRCA1* expression. A similar relationship was also observed in the analysis of *BRCA1* deletion cases. In addition, *BECN1*, but not *BRCA1*, was shown to be an independent prognostic factor in multivariate analysis.

Both *BECN1* and *BRCA1* are closely located on 17q21, a region frequently deleted in sporadic breast cancers. For many years, BRCA1 has attracted much more attention in breast cancer than BECN1. *BRCA1* encodes a multifunctional protein that plays key roles in DNA repair, cell cycle control and transcriptional regulation (Turner et al., 2007). Mutations in *BRCA1* are well known to be responsible for the development of familial breast cancer. Although *BRCA1* dysfunction has been linked also to basal-like breast cancer, it is important to note that it is mainly based on studies from familial cases with *BRCA1* mutation. These cancers shared many phenotypes and gene expression signature associated with basal like breast cancers, suggesting similarities in pathogenic mechanisms (Turner et al., 2007). Although these have been corroborated by some studies in sporadic cancers, controversy still exists among different studies (Rakha et al., 2008).

BECN1 is an essential regulator of autophagy. *BECN1*, with its close proximity with *BRCA1*, is frequently co-deleted with *BRCA1* (Turner et al., 2004). Given that it is a haplo-insufficient tumour-suppressor, its co-deletion with *BRCA1* may also contribute to mammary tumorigenesis and cancer characteristics attributable to BRCA1 dysfunction. However, its role in breast cancer remains debatable and may depend on cellular context. Mono-allelic deletion of *BECN1* in C67/B6 mice has led to the formation of spontaneous lung and liver cancers as well as lymphoma but only mammary hyperplasia (Qu et al., 2003). However, different results were obtained from other breast cancer models. In *ERBB2*- or *PyMT*-driven mammary tumorigenesis, there are no effects of monoallelic deletion of *BECN1* (Lozy et al., 2014); whereas it delays tumour formation due to mammary gland-specific biallelic *Palb2* deletion in a wild-type *Tp53* background (Huo et al., 2013). In contrast, monoallelic *BECN1* loss can promote mammary tumour formation following parity and in *Wnt1*-driven oncogenesis (Cicchini et al., 2014). The findings may indicate that the interactions of BECN1 with various cellular pathways can result in different consequences. Regarding the relationship of *BECN1* with specific breast cancer subtypes, so far, there is very limited information available. Of note, in *Wnt1* mouse model, the tumour developed has been shown to exhibit basal cytokeratin upregulation as well as augmentation of mammary progenitor cell activities, i.e. characteristic of basal-like breast cancer (Cicchini et al., 2014). It is also interesting to note that there could be some synergies in functional roles of BECN1 and BRCA1. As for BRCA1, recent findings have suggested the involvement BECN1 in the maintenance of genomic integrity (Mathew et al., 2007) and regulation of oestrogen receptor signalling (John et al., 2008).

In all, BECN1 could have potential significance in breast cancers that have not been fully appreciated previously. However, its precise roles in breast cancer biology remain elusive. Breast cancer is a heterogeneous disease comprised of different subtypes with different underlying biology. As shown by the different findings from various model systems, functional impacts of *BECN1* alteration could be context dependent. Examination and evaluation of large datasets in light with signalling pathway alterations within different breast cancers will be necessary to have a clear understanding of clinical impacts as well as biology of *BECN1* alterations. In fact, when Tang et al. stratified *BECN1* expression into three expression levels, the intermediate groups did not show a consistent outcome in different subgroups of breast cancers, possibly reflecting the different biology underlying this group in contrast to the low and high *BECN1* expressing cases. The clinico-pathological characteristic and nature of this group in comparison with the others remains to be explored, in particular in different subgroups of breast cancers. Findings from Tang et al. suggested the prognostic implication of *BECN1* mRNA contributed to the pathogenesis of breast cancer. However, the application of mRNA prognostic marker in routine clinical practice still has some limitations. It would be interesting to explore whether similar findings could be also observed with BECN1 protein expression. While transcriptional deregulation of *BECN1* appears to play a significant role in breast cancer pathogenesis, other post-transcriptional regulatory mechanisms could be involved in BRCA1 deregulation, for example, aberrant subcellular localisation and deregulation in protein expression of BRCA1 (Rakha et al., 2008). The contribution of BRCA1 deregulation in the pathogenesis of breast cancer cannot be ruled out. Evaluation on

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their protein expressions and other regulatory mechanisms will be essential to draw a more definitive conclusion on their respective significance in breast cancer.

Disclosure

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