Breast Cancer RESEARCH

VIEWPOINT

A functional link between FOXA1 and breast cancer SNPs

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Abstract

Genome-wide association studies have revealed a multitude of breast cancer-associated SNPs. The majority of these SNPs are located in noncoding regions of the genome. Yet how they contribute to breast cancer development is unknown. Recently, a groundbreaking study by the Lupien group has shown that risk-associated SNPs of breast cancer are enriched for FOXA1 binding sites, which influences the function of this transcription factor.

Background

Breast cancer is a heterogeneous disease and the most frequent tumors are positive for the expression of estrogen receptor (ER) [1] or the epidermal growth factor receptor 2 (HER2) [2]. The transcription factor FOXA1 is a common feature for the majority of these tumors [3,4]. Genomic analyses have revealed that the binding of FOXA1 shows a tissue-specific occupancy and that it is associated with the binding of ER or androgen receptor [5-8]. FOXA1 recruitment to chromatin is mediated by the epigenetic signature consisting of monomethylated and dimethylated histone H3 on lysine 4 (H3K4me1,2) [6].

In the last years, genomic studies have uncovered a multitude of SNPs associated with the risk of breast cancer. However, given that these SNPs are often found in non-coding regions [9], it was unclear how they could be contributing to the development of the disease [10].

Article

In a seminal study published in *Nature Genetics*, Cowper-Sal Lari and colleagues have integrated genomic methodologies to identify the functional relationship between risk-associated SNPs with high linkage disequilibrium and the transcription factor binding or histone modifications in ER-positive breast cancer subtype [11]. To check the enrichment of risk-associated SNPs in chromatin regions, the authors employed variant-set enrichment analysis. Using this statistical analysis tool, they identified that the breast cancer-associated variant set is strongly enriched for FOXA1, ER binding regions and histone modification H3K4me1 marks. Importantly, the associated variant set from other diseases (for example, prostate cancer, colorectal cancer and bone cancer) did not show the same correlation. Based on these findings, the authors state that the enrichment of the breast cancer-associated SNPs for these transcription factors and histone mark are both cancer type specific and tissue specific.

Having shown that breast cancer risk-associated SNPs are enriched with FOXA1 binding sites, the authors tested how these SNPs modulate the binding of the transcription factor to chromatin. They used the intragenomic replicates method, which establishes the effect of individual SNPs on the affinity of a transcription factor binding to chromatin. The authors focused on one of the most studied risk-associated SNPs: rs4784227, which maps within the forkhead motif for FOXA1 genomic interaction. Interestingly, FOXA1 binding affinity was increased for the [T] variant allele compared with the [C] reference allele. Extensive intragenomic replicates analysis and variant-set enrichment analysis on all SNP clusters indicated that more than one-half of them are associated with altered affinity of FOXA1 to chromatin.

To verify the effect of the SNP on breast cancer progression the authors focused on the *TOX3* gene, which is localized in the rs4784227 risk-associated region. They used chromatin conformation capture assays and they confirmed a physical interaction between the rs4784227 region and the promoter of the *TOX3* gene. This result confirms that *TOX3* is a gene target of the regulatory region harboring the SNP. Furthermore, the authors analyzed the impact of the different alleles on *TOX3* gene expression performing allele-specific expression assay. With this method they showed that the [T] variant allele has a repressive effect on *TOX3* expression. Finally, the

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depletion of *TOX3* gene increased significantly the proliferation of breast cancer cells.

Viewpoint

The published study opens a new way to understand the impact of risk-associated SNPs on breast cancer disease. Importantly, the authors have identified a subset of FOXA1 binding regions enriched for risk-associated SNPs, which immediately raises the question of whether the remaining FOXA1 regions also play a critical role in the progression of the disease. On the contrary, not all breast cancer-associated SNPs were associated with FOXA1 binding regions. In future studies it will therefore be of interest to investigate the effect of these SNPs on other transcription factors.

Furthermore, the study concludes that more than one-half of the risk-associated SNPs influence FOXA1 binding [11]. FOXA1 has been described to function as a pioneer factor that allows the binding of ER and Androgen Receptor [5]. Recently, the expression of FOXA1 both in ER and HER2 breast cancer cell lines has been also reported to repress transcription [12]. Whether the SNPs are influencing both or any of these functions needs to be determined.

Finally, the study also reports that the depletion of *TOX3* increased significantly the proliferation of breast cancer cells, suggesting that the rs4784227 risk-associated region might be used as a clinical marker for cancer prognosis. Investigating how other SNPs could impact current breast cancer treatments will be important. The use of SNPs as biomarkers to predict anticancer drug efficacy and risk levels in breast cancer patients is a promising path to explore.

Abbreviations

ER, estrogen receptor; HER2, epidermal growth factor receptor 2; SNP, single nucleotide polymorphism.

Competing interests

The authors declare that they have no competing interests.

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