

## VIEWPOINT

# BRCA1 as a tumor suppressor linked to the regulation of epigenetic states: keeping oncomiRs under control

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### Abstract

*BRCA1* is a tumor suppressor gene known to be implicated in the development of a subset of breast and ovarian cancers. The tumor suppressor properties of *BRCA1* are generally thought to be linked to the gene's critical roles in the network of DNA damage response. In a recent report, *BRCA1*-mediated epigenetic repression at the promoter region of miRNA-155 was identified as a novel mechanism by which *BRCA1* carries out its tumor suppressor functions.

### Background

Inherited mutations in *BRCA1* greatly increase the risk of breast cancer [1]. Tumors arising in mutation carriers have generally lost the wild-type *BRCA1* allele [2]. These findings have led to the definition of *BRCA1* as a tumor suppressor. The *BRCA1* gene has well-established roles in maintenance of genomic integrity, including DNA repair by homologous recombination, DNA decatenation, and regulation of centrosomes [3]. In accordance, extensive changes in chromosome structure and number are observed in tumors derived from carriers [4,5]. The tumor suppressor functions of *BRCA1* are therefore commonly attributed to its role in genomic maintenance. The *BRCA1* gene has other roles, however, including those related to cellular differentiation and transcriptional regulation.

miRNAs are small noncoding RNAs (~22 nucleotides) that mediate post-transcriptional gene silencing by controlling the translation of mRNA into protein products [6]. In cancer, miRNAs are differentially expressed when compared with the corresponding normal tissue, and

some have tumor suppressor properties whereas others are oncogenic (so-called oncomiRs) [7,8]. In a recent report, Chang and colleagues identified a novel role for *BRCA1* as an important mediator of epigenetic repression of an oncomiR; that is, miRNA-155 [9].

### The article

Change and colleagues report substantial differences in the ability of R1669Q, a *BRCA1* mutation currently of unknown clinical significance (single amino-acid substitution), to rescue lethality of *Brca1-null* ES cells compared with wild-type *BRCA1* [9]. The functional assays carried out suggest a significant role for the R1699Q mutation in tumor suppression. Nevertheless, R1699Q-expressing embryonic stem cells (*Brca1 null*) were not sensitive to DNA-damaging agents and did not show genomic instability. This finding is interesting, given the critical role carried out by *BRCA1* gene products in the cellular response to DNA damage.

Using microarrays, high expression of miRNA-155 was found in R1699Q cells and was validated in further experiments. The *BRCA1* binding site was identified, and validated, at the promoter region of miRNA-155. The authors then show that *BRCA1* mediates chromatin remodeling at the promoter region of miRNA-155 through direct protein–protein interactions with histone deacetylase 2 [9]. This was established by experiments involving targeted mutation of promoter binding sites, chromatin immunoprecipitations and inhibition of histone deacetylases. The experiments that followed suggested oncogenic properties in association with miRNA-155, based on ectopic expression in cell lines injected into mice and data in human breast cancer samples showing high miRNA-155 in association with *BRCA1* defects.

### The viewpoint

In studying the effects of *BRCA1* R1699Q, a mutation of unknown clinical significance, Chang and colleagues discovered a novel mechanism for *BRCA1* as a tumor suppressor gene [9]. This mechanism involves the binding of *BRCA1* gene products to the promoter region of

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miRNA-155 (a known oncomiR), where they mediate epigenetic repression through protein–protein interactions with histone deacetylase 2. Interestingly, what emerges from this study is that R1699Q products retain DNA repair activities. In this regard, examining the phenotype of breast cancers arising in R1699Q carriers will be of considerable interest. Together with the analysis of sporadic cancers, with respect to miRNA-155 and basal or stem cell/progenitor markers, this could lead to a better understanding of the development of basal-like breast cancers. Clearly, this analysis will involve experimentally validating the targets of miRNA-155, and determining whether there are other genes regulated by this same mechanism – that is, BRCA1-mediated epigenetic repression.

The clinical implications that arise from this research relate to recent progress made in clinical trials showing promising anti-cancer effects from inhibitors of poly-ADP-ribose polymerase (PARP) in treatment of patients with inherited mutations in *BRCA1* or *BRCA2* [10]. The effectiveness of PARP inhibitors in this regard relates to loss of the wild-type allele in cancer cells of mutation carriers, resulting in defective DNA repair by homologous recombination [11]. PARP inhibitors will thus probably not be effective in treatment of patients with the R1699Q mutation. In sporadic cases of breast cancer, however, the *BRCA1* gene is inactivated by epigenetic mechanisms [12,13] rather than by acquired point mutations [14]. We have previously reported that a substantial fraction of sporadic breast cancers have acquired CpG island hypermethylation of the *BRCA1* gene and that their evolutionary path is similar to breast cancers arising in *BRCA1* mutation carriers [4,12,13,15]. Most importantly, BRCA1 hypermethylation predicts response to PARP inhibitors at the same level as BRCA1 germline mutations [16]. In this regard, the question arises of whether miRNA-155 can be used as a biomarker to guide treatment selection with respect to PARP inhibitors or DNA-damaging agents. Further, there have been considerable efforts in determining whether circulating miRNAs in blood can be used as biomarkers for early detection of cancer [7] – based on its potential early involvement, miRNA-155 could represent a candidate marker in this respect.

#### Abbreviations

miRNA, microRNA; oncomiR, oncogenic microRNA; PARP, poly-ADP-ribose polymerase.

#### Competing interests

The authors declare that they have no competing interests.

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