miRNA Dysregulation in Breast Cancer

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Abstract
miRNAs have emerged, in the last decade, as key players in the carcinogenic process, with many candidates identified as playing important roles in many aspects of tumor development, growth, metastasis, and drug resistance. More recently, polymorphisms in miRNAs themselves or in their binding sites in target genes have been identified to incur increased risk of breast cancer in certain populations. In addition, epigenetic regulation and differential expression of processing enzymes has been shown to contribute to the aberrant expression of miRNAs in breast cancer. This review focuses on the area of miRNA dysregulation in breast cancer through both genetic and epigenetic mechanisms, and the impact of this dysregulation on breast cancer risk and resistance to therapies. Cancer Res; 73(22); 6554–62. ©2013 AACR.

Introduction
miRNAs are small noncoding RNA molecules, ranging in length from 20 to 25 nucleotides, which primarily bind to the 3′ untranslated region (UTR) of messenger RNAs, resulting in a downregulation of target proteins through the degradation of this mRNA or through translational inhibition. Pri-miRNA sequences are transcribed within the nucleus and cleaved to form the pre-miRNA transcript by the Microprocessor, which consists of RNase III enzyme Drosha and its partner protein DiGeorge Syndrome Critical Region Gene (DGCR8). The pre-miRNA is then exported to the cytoplasm by the nuclear export protein Exportin 5, where it is processed by Dicer, interacting with an RNA-binding protein [trans-activator RNA (tar)-binding protein] to produce short RNA duplexes. These are loaded onto an Argonaute protein, which generates the effector complex RISC by dissociating the RNA duplex, leaving the single-stranded mature miRNA to guide gene silencing (for a comprehensive review on miRNA biogenesis, see ref. 1).

miRNAs are known to be aberrantly expressed in cancer, with some functioning as tumor suppressors and others acting as oncogenes (oncomiRs), depending on which genes or pathways they regulate. They are documented to be involved in just about every complex cellular process, from the cell cycle to apoptosis to migration and invasion, which is indicative of their importance in cellular function and, thus, disease. This review will focus on miRNA dysregulation in breast cancer, its mechanisms, and consequences with regard to disease risk and drug resistance.

Mechanisms of Dysregulation of miRNAs in Breast Cancer
miRNA dysregulation in cancer can occur both at the genetic and epigenetic levels via the introduction of single-nucleotide polymorphisms (SNP) into the miRNA sequence itself, that of its target mRNA binding site, or, indeed, via aberrant DNA methylation and histone modification (2). The importance of this and other genetic mechanisms of miRNA dysregulation in cancer is highlighted by the discovery that 50% of all annotated human miRNA genes are located at fragile sites within the genome associated with deletions, amplifications, or translocations implicated in tumorigenesis. Indeed, an array comparative genomic hybridization (CGH) study of epithelial tumors showed that 73% of miRNA genes in breast cancer reside in genomic regions affected by copy number variations (3).

In the context of cancer, where miRNA expression is frequently downregulated, miRNA silencing via hypermethylation of miRNA-associated CpG islands is most frequently seen. Indeed, recent examples of this in breast cancer include the discovery that the miR-125b promoter is hypermethylated in invasive breast cancers, where it predicts poor survival by derepression of its target gene ETS1, a member of the ETS (v-ets erythroblastosis virus E26 oncogene) family of transcription factors (4). Similarly, the miR-335 locus has been found to undergo promoter hypermethylation in breast cancer cell lines and tumor samples, interfering with its role as a suppressor of invasion and metastatic colonization, in addition to tumor reinitiation (5). Notably, the discovery of the epigenetic regulation of miRNA expression highlights the potential use of epigenetic-based cancer therapies [e.g., decitabine (5-aza-2′-deoxycytidine) or histone deacetylase inhibitors] to restore normal miRNA expression in cells.

Another area that can significantly influence miRNA expression patterns, and is of growing area interest at present, is miRNA biogenesis (See Fig. 1). Transcription is the first stage and represents a major point of regulation with an important role for the RNA polymerase II or III transcription factors that promote the transcription of normal protein-coding genes. For example, recent studies have shown that activation of the
oncogenic protein MYC, which is upregulated in several cancers, results in widespread repression of miRNA expression, with implications for cell-cycle control and apoptosis (6). Another key point emerging in the regulation of miRNA biogenesis is that of miRNA cleavage by the RNase III enzymes Drosha and Dicer, which process immature pri-miRNAs into approximately 60-nucleotide pre-miRNA and an approximately 22-nucleotide RNA duplex, respectively. Downregulation of these enzymes has been shown in numerous cancers, including breast cancer (7), where it has been associated with specific breast cancer subgroups as well as more progressive disease (8). Indeed, reduced levels of Dicer in breast cancer have been identified as an independent prognostic factor in primary breast cancer (9) as well as in metastatic disease (10), whereas Dicer-mediated upregulation of breast cancer resistance protein (BRCP) was shown to confer tamoxifen resistance (11). In addition, loss of the protein was predictive of better response to chemotherapy and antiendocrine therapy (9).

Central to the function of Dicer is TARBP, which is a double-stranded RNA-binding protein that functions as a biosensor identifying the double-stranded RNA to be loaded into RISC. Recently, a frameshift mutation in TARBP2 was discovered, which significantly reduced the efficiency of miRNA processing and mediated reduced expression of Dicer in microsatellite-instable colorectal cancer (12). It has yet to be determined, however, whether such lesions exist in breast cancer. Notably, the importance of TARBP2 in the efficient processing of miRNA was recently exploited in a study where the small molecule
enoxacin, a fluoroquinolone antibiotic, was used to enhance miRNA production by binding TARBP2 (13).

Furthermore, additional frameshift mutations were discovered in the nuclear export protein, XPO5, which is responsible for transporting pre-miRNA to the cytoplasm for processing by Dicer (14). The mutations, which were again identified in microsatellite instable colorectal cancer, inhibit XPO5 from associating with pre-miRNA, resulting in impaired miRNA processing due to the accumulation of pre-miRNA in the nucleus (14). However, a role for both genetic and epigenetic alterations in XPO5 has been shown in breast cancer, where mutant forms were associated with increased breast cancer susceptibility, whereas hypermethylation (and, thus, transcriptional inactivation) conferred a reduced risk of breast cancer (15). Moreover, a recent study has noted that some polymorphisms within genes involved in the biogenesis of miRNAs associate significantly with breast cancer risk (16). Moreover, it has been shown that numerous miRNAs can be regulated by nuclear receptors (reviewed in ref. 17). As aberrant signaling is often seen through the estrogen/progesterone receptors (ER/PR) in breast cancer, this may potentially lead to further miRNA dysregulation.

miRNA Polymorphisms Associated with Breast Cancer

In addition to epigenetic modifications, SNPs have been identified as a key mechanism for the dysregulation of miRNAs in multiple disease states (reviewed in ref. 18). These polymorphisms can exist not only in the mature miRNA sequence but also in the pre- and pri- forms of the miRNA, potentially altering the processing of the mature sequence, as well as within their binding sites in target genes. In many cases, these SNPs have been shown to associate with breast cancer risk in certain populations.

Polymorphisms within miRNAs

The most comprehensively studied miRNA polymorphism in breast cancer is undoubtedly that in miR-196a2, which was first reported as being associated with increased risk of developing the disease in 2008 (19). Hoffman and colleagues reported similar findings with the T allele of the miR-196a2 rs11614913 polymorphism being associated with decreased risk of breast cancer (20), although they note that it was the C allele that was common in their population, whereas with the aforementioned study, this was the rare allele. Further functional work was carried out showing that the T allele miR-196a altered the expression of less than half of the number of transcripts altered by the C allele miRNA in vitro, suggesting that the change in sequence in the T allele may result in diminished capacity to regulate its targets. A meta-analysis of this SNP concluded that there was an increased risk of breast cancer in individuals homozygous for the C allele (21). This was mimicked by another group who found statistically significant association between the T allele and decreased cancer risk (22). However, these results have been disputed by additional studies which found no significant association between the polymorphism and breast cancer risk (23–25).

Furthermore, a SNP in miR-146a (rs2292832) has been linked to earlier onset of breast cancer (26, 27), although the data, once again, is not clear cut. Further functional analysis of this miRNA showed that it targets BRCA1 and BRCA2, with a stronger binding capacity between the variant with the C allele with the target site in BRCA1. However, another study found no association between the SNP and breast cancer risk in BRCA1/2 mutation carriers (28), and further meta-analyses found no increased risk of breast cancer (21) or other cancers (22). Interestingly, a SNP in the pre-miRNA form of miR-27a (rs958519) was shown to have a protective effect against breast cancer, mainly in those younger than age 50 (29). In addition, this polymorphism was seen to associate decreased risk of both breast and ovarian cancer (30).

Polymorphisms within miRNA target binding sites

Mature miRNAs incorporated into an active RISC complex generally bind to the 3’ UTR of their target gene transcript, resulting in either the cleavage of the target miRNA and its degradation or the prevention of translation. As such, SNPs in the miRNA binding site of a target miRNA have the ability to reduce or to completely abrogate binding and, thus, regulation of the gene is in question. Undoubtedly, SNPs in some target genes may be of as much importance in breast cancer as those located within the miRNAs themselves.

For example, a polymorphism in the putative binding site for miR-453 within the estrogen receptor α gene (ESR1) (rs2747648) was associated with a decreased breast cancer risk in 2009 (31). However, a further study failed to find an association between this and breast cancer risk in postmenopausal women (32). Another interesting example of a SNP within a miRNA binding site is that in the 3’UTR of KRAS (rs61764370), which is a putative binding site for let-7, a miRNA known to be aberrantly expressed in breast cancer. Although this SNP has mostly been studied in the context of ovarian carcinoma, a recent study associated it with triple-negative breast cancer in premenopausal women (33). However, this result is disputed by Pharoah and colleagues, citing small sample size and the use of incorrect methods for estimation of significant association (34). Furthermore, two additional studies found no association between this SNP and breast cancer risk either in BRCA1/2 carriers or noncarriers (35, 36). Clearly, much additional work is needed to confirm these associations.

Another SNP in a miRNA binding site is that in the DNA repair protein, X-ray repair cross-complementing group 1 (XRCC1; rs1799782), which has been shown to have a protective effect in multiple cancers (37), in breast cancer (38–41), and in benign breast disease (42), with miR-138 seen to bind more strongly to the T allele, thus increasing inhibition of XRCC1. However, this was not supported by another study in 2008 (43).

SNPs have not only been associated with breast cancer risk but also prognosis, with a polymorphism in integrin-β4 (ITGB4; rs743554) correlating with decreased breast cancer-specific survival (44) independent of other clinicopathologic factors. The authors note that this SNP may affect the binding of miR-34a, which has been shown to have differential expression in breast cancer (45). Furthermore, recent studies into
polymorphisms within miRNA biogenesis pathway genes revealed that SNPs in AGO1, AGO2, and p68 associated significantly with breast cancer risk (16), potentially through further dysregulation of miRNA expression.

Despite the work on the polymorphic status of miRNAs and their binding sites being in its infancy, already significant associations of numerous SNPs with breast cancer risk and onset are coming to light. If true associations are validated in large-scale studies, these SNPs may be of use for the identification of a high-risk subgroup of patients, with subsequent monitoring potentially yielding earlier tumor detection.

miRNAs: Treatment Resistance in Breast Cancer

Dysregulation of miRNAs affects not only cellular processes involved in carcinogenesis but can have a direct consequence on the success of therapeutic interventions, as recent studies have highlighted. Drug resistance can be caused by many mechanisms including the removal or detoxification of the drug, upregulation of antiapoptotic and cell survival processes, or alteration of drug transporters such that the molecule cannot gain entry to the target cell or is immediately removed.

In breast cancer, numerous well-studied oncogenic miRNAs (oncomiRs; e.g., miR-155, -21) have been shown to induce chemoresistance in vitro through their regulation of key resistance-associated proteins. To date, miRNAs have been associated with resistance to almost all forms of treatments employed in the management of breast cancer, including chemotherapy, antiendocrine therapy, radiotherapy, and drugs targeted at particular signaling molecules (Fig. 2).

Chemotherapy

The importance of ATP-binding cassette (ABC) transporter proteins [multidrug resistance protein 1 (MDR1/P-glycoprotein), multidrug resistance-associated proteins 1 and 2 (MRP1/MRP2), and breast cancer resistance protein (BCRP/ABCG2)] has long been established in the development of a chemoresistant phenotype (46). However, it is only recently that miRNAs have been documented as being key regulators of these drug transporter proteins. For example, miR-328 was shown to negatively regulate BCRP, causing greater response to the chemotherapeutic agent, mitoxantrone (47), whereas miR-21 upregulates MDR1 through interaction with its target.
PDCD4 (48). Numerous other miRNAs have since been found to target MDR1, including miR-451 (49), miR-7, miR-345 (50), and miR-326 (51), leading to increased sensitivity to numerous chemotherapeutic agents. In addition, miR-128 has been implicated in the response to docetaxel treatment, both in vitro and in patients through the targeting of BMI1 and ABCC5 (also known as MRP5; ref. 52).

Furthermore, miRNA may elicit their effects on chemotherapy response through the targeting of proteins involved in apoptosis or cell survival processes. For example, miR-34a was associated with docetaxel response through the targeting of BCL2 (53), whereas miR-125b targets BCL-2 antagonist killer 1 (BAK1), inducing resistance to paclitaxel (54). A summary of miRNAs involved in sensitivity to chemotherapeutic agents in breast cancer can be seen in Table 1.

Radiotherapy

miR-34a has been linked to response to radiotherapy in breast cancer, with increased expression leading to an increase in resistance to treatment (68). Furthermore, modulation of miR-182 in vitro was shown to affect DNA damage repair following treatment with ionizing radiation (69), whereas inhibition of miR-155 was shown to sensitize breast cancer cells to ionizing radiation (70). Notably, many miRNAs that have been seen to be involved in drug resistance in breast cancer show similar involvement in radioresistance in other cancer types, including the let-7 family of miRNAs, miR-451, miR-21, miR-101, and miR-221/222, indicating that these miRNAs may play a more extensive role in resistance to multiple types of therapy.

### Table 1. miRNAs involved in modulation of response to chemotherapeutic agents in breast cancer

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Drug</th>
<th>Protein target(s)</th>
<th>In vitro/in vivo</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Let-7i</td>
<td>Cisplatin</td>
<td>No proven targets in this study</td>
<td>In vitro</td>
<td>(55)</td>
</tr>
<tr>
<td>miR-19</td>
<td>Taxol/VP-16, Mitoxantrone</td>
<td>PTEN</td>
<td>In vitro/in vivo (xenograft mouse study)</td>
<td>(56)</td>
</tr>
<tr>
<td>miR-21</td>
<td>Doxorubicin/paclitaxel</td>
<td>PDCD4</td>
<td>In vitro</td>
<td>(48)</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>PTEN</td>
<td>In vitro</td>
<td>(57)</td>
</tr>
<tr>
<td>miR-34a</td>
<td>Docetaxel</td>
<td>BCL2</td>
<td>In vitro</td>
<td>(53)</td>
</tr>
<tr>
<td>miR-125b</td>
<td>Paclitaxel</td>
<td>BAK1</td>
<td>In vitro</td>
<td>(54)</td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil/epirubicin/cyclophosphamide</td>
<td>E2F3</td>
<td>In vivo (56 BC patients)</td>
<td>(58)</td>
</tr>
<tr>
<td>miR-128</td>
<td>Doxorubicin/docetaxel</td>
<td>BMI1, ABCC5</td>
<td>In vitro, in vivo (77 BC patients)</td>
<td>(52)</td>
</tr>
<tr>
<td>miR-155</td>
<td>Doxorubicin/paclitaxel/VP-16</td>
<td>FOXO3a</td>
<td>In vitro</td>
<td>(59)</td>
</tr>
<tr>
<td>miR-200 family (miR-200b/c)</td>
<td>Doxorubicin</td>
<td>ZEB1</td>
<td>In vitro</td>
<td>(60)</td>
</tr>
<tr>
<td>miR-200 family (miR-200c)</td>
<td>Epirubicin</td>
<td>MDR1</td>
<td>In vitro/in vivo (39 BC patients)</td>
<td>(61)</td>
</tr>
<tr>
<td>miR-200 family (miR-200b/c &amp; -429)</td>
<td>Vincristine/VP-16/cisplatin/doxorubicin</td>
<td>BCL2, XIAP</td>
<td>In vitro</td>
<td>(62)</td>
</tr>
<tr>
<td>miR-203</td>
<td>Cisplatin</td>
<td>SOCS3</td>
<td>In vitro</td>
<td>(63)</td>
</tr>
<tr>
<td>miR-221</td>
<td>Neoadjuvant chemotherapy</td>
<td>No proven targets in this study</td>
<td>In vivo (93 BC patients, 32 controls)</td>
<td>(64)</td>
</tr>
<tr>
<td>miR-298</td>
<td>Doxorubicin</td>
<td>MDR1</td>
<td>In vitro</td>
<td>(65)</td>
</tr>
<tr>
<td>miR-326</td>
<td>VP-16/Doxorubicin</td>
<td>MRP1</td>
<td>In vitro/in vivo (10 normal breast tissues/5 early BCs/10 advanced BCs)</td>
<td>(51)</td>
</tr>
<tr>
<td>miR-328</td>
<td>Mitoxantrone</td>
<td>BRCP</td>
<td>In vitro</td>
<td>(47)</td>
</tr>
<tr>
<td>miR-345</td>
<td>Cisplatin</td>
<td>MDR1</td>
<td>In vitro</td>
<td>(50)</td>
</tr>
<tr>
<td>miR-451</td>
<td>Doxorubicin</td>
<td>MDR1</td>
<td>In vitro</td>
<td>(66)</td>
</tr>
<tr>
<td>miR-505</td>
<td>Docetaxel</td>
<td>No proven targets in this study</td>
<td>In vitro</td>
<td>(67)</td>
</tr>
</tbody>
</table>

Abbreviation: BC, breast cancer.
attributed in part to the activation of β-catenin and the repression of TGF-β-mediated growth inhibition (74). In the first in vivo study of miR-222, it was found that it was possible to suppress the growth of tamoxifen-resistant xenografts through the administration of an anti-miR directly to the tumor (75). The same was true of miR-181b. The authors subsequently found that miR-221, -222, and -181b target TIMP3 directly, with knockdown of TIMP3 in MCF7 cells enabling tumors to grow in the presence of tamoxifen. It has since been postulated that plasma miR-221 may be of use as a predictive marker for chemoresistance in patients with breast cancer who have been treated previously with neoadjuvant chemotherapy, with differing levels of the miRNA correlating with overall response rates (64). Notably, miR-221/222 have yet to be probed in antiendocrine-treated clinical cohorts in breast cancer, but one can only assume these studies are ongoing, given the building evidence of the involvement of these miRNAs in endocrine resistance. The one study that has investigated expression of miR-221 in breast cancer patients found that it was, in fact, a good prognostic marker, and expression of the miRNA was associated with ER-positivity (76), which is at odds with the fact that it has been shown to target the protein in vitro (73). Furthermore, miR-30c has been shown to be an independent predictor of tamoxifen response and was associated with increased progression-free survival (77). More recently, miR-301 was found to be upregulated in tumor versus normal tissue, with levels increased again in patients that relapsed following tamoxifen treatment versus those that remained relapse-free (78). Downregulation of the miRNA in vitro restored sensitivity to the drug. A summary of miRNAs involved in sensitivity to chemotherapeutic agents in breast cancer can be seen in Table 2.

Table 2. miRNAs involved in modulation of response to antiendocrine agents in breast cancer

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Drug</th>
<th>Protein target(s)</th>
<th>In vitro/in vivo</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>let-7b/i</td>
<td>Tamoxifen</td>
<td>ERα36</td>
<td>In vitro</td>
<td>(79)</td>
</tr>
<tr>
<td>miR-15a/16</td>
<td>Tamoxifen</td>
<td>BCL2</td>
<td>In vitro</td>
<td>(80)</td>
</tr>
<tr>
<td>miR-26a</td>
<td>Tamoxifen</td>
<td>Predicted to target EZH2</td>
<td>In vivo (235 BC patients treated with tamoxifen)</td>
<td>(81)</td>
</tr>
<tr>
<td>miR-30c</td>
<td>Tamoxifen</td>
<td>No proven targets in this study</td>
<td>In vivo (246 BC patients treated with tamoxifen)</td>
<td>(77)</td>
</tr>
<tr>
<td>miR-101</td>
<td>Tamoxifen resistance</td>
<td>MAGI2</td>
<td>In vitro</td>
<td>(82), not supported in vivo by (81)</td>
</tr>
<tr>
<td>miR-101</td>
<td>Tamoxifen sensitivity</td>
<td>STMN1</td>
<td>In vitro</td>
<td>(83), not supported in vivo by (81)</td>
</tr>
<tr>
<td>miR-128a</td>
<td>Letrozole</td>
<td>TGFβ, IR1</td>
<td>In vitro</td>
<td>(84)</td>
</tr>
<tr>
<td>miR-181b</td>
<td>Tamoxifen</td>
<td>TIMP3</td>
<td>In vitro/in vivo (xenograft mouse study)</td>
<td>(75)</td>
</tr>
<tr>
<td>miR-221/222</td>
<td>Tamoxifen</td>
<td>p27Kip1, ERα, TIMP3</td>
<td>In vitro/in vivo (xenograft mouse study)</td>
<td>(72, 73, 75)</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td></td>
<td>β-catenin upregulated following expression of miR-221/222</td>
<td>In vitro</td>
<td>(74)</td>
</tr>
<tr>
<td>miR-301</td>
<td>Tamoxifen</td>
<td>FoxF2, PTEN, BBC3, Col2A1</td>
<td>In vitro/in vivo (71 BC patients treated with tamoxifen)</td>
<td>(78)</td>
</tr>
<tr>
<td>miR-342</td>
<td>Tamoxifen</td>
<td>GEMIN4, BMP7</td>
<td>In vitro/in vivo (16 BC patients treated with tamoxifen)</td>
<td>(85)</td>
</tr>
<tr>
<td>miR-375</td>
<td>Tamoxifen</td>
<td>MTDH</td>
<td>In vitro</td>
<td>(86)</td>
</tr>
<tr>
<td>miR-451</td>
<td>Tamoxifen</td>
<td>14-3-3ζ</td>
<td>In vitro</td>
<td>(87)</td>
</tr>
</tbody>
</table>

Abbreviation: BC, breast cancer.

**Targeted therapies**

As targeted therapies themselves are a relatively new phenomenon, very few studies have yet been done to elucidate the mechanisms of resistance to these drugs. However, miR-21 has already been implicated in resistance to trastuzumab (targeting the ERBB2 oncogene) through the downregulation of its protein target PTEN (88). In addition, miR-205 targets HER3 in human breast cancer cell lines, thus increasing sensitivity to tyrosine kinase inhibitors gefitinib and lapatinib (89), whereas miR-182 has been shown to be involved in the response to both radiotherapy and to PARP inhibitors, 4-amino-1,8-naphthalamide and olaparib, both in vitro and in vivo (69). Moreover, miR-210 appears to be increased in trastuzumab-resistant cell lines and patients (90).

**Conclusions**

Dysregulation of miRNAs in breast cancer, whether through polymorphisms in the sequence of the miRNA, its binding sites in target genes, or through epigenetic mechanisms, has been shown to play a key role in not only the carcinogenic process as a whole, but also in the stratification of patients at risk of developing the disease as well as predicting those that may
respond to therapy. Although this is still a relatively under-studied field of research, the volume and caliber of publications in the last 2 years is indicative of the excitement in this area as it represents a whole new level of complexity in epidemiology and patient stratification. Furthermore, continued research may soon yield important candidate miRNAs for progression to clinical application. Indeed, a miR-122 inhibitor, the first of its kind to be approved for clinical testing, has recently shown positive results in its phase IIa trial for the treatment of hepatitis C (91). Furthermore, the first miRNA mimic to be used to treat cancer patients has recently moved into phase I trials (Trial Identifier NCT01829971). This drug is formulated to reintroduce expression of miR-34 in malignant cells, leading to growth arrest and apoptosis. With many other candidates in preclinical development, it is envisioned that miRNA-altering drugs may, one day, form an important class of targeted therapies for cancer.

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