Commentary

miR-15a and miR-16 supplementation as a potential remedy for ovarian cancer

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The annual incidence of ovarian cancer is 204,000, causing 125,000 deaths per year (1). While early stages of the disease can usually be cured by surgery, non-metastatic disease tends to remain asymptomatic and suitable screening strategies are not available. Once distant metastasis has occurred, the 5-year survival rate is below 20%. The most common form, epithelial ovarian cancer (EOC) is thus the most lethal genuinely gynaecological tumour.

Clinically, debulking is usually followed by platinum-based chemotherapy, or a taxane/platinum combination. Targeted therapies for ovarian cancer are addition of bevacizumab (anti-VEGF) to the chemotherapeutic regimen (2) and PARP inhibition for maintenance therapy (3). While treatment-naïve tumours tend to respond well, resistance to platinum-based combination therapy develops in 25% of early-stage and in over 80% of late-stage carcinomas (4,5). Currently available therapies are thus only moderately effective, rather toxic and, when bevacizumab is added, also expensive. Consequently, strategies for overcoming the resistance as well as new targeted therapies are badly needed.

In their recent publication, Bhattacharya and colleagues (6) provide evidence that the frequently observed loss or downregulation of miRNA-15a and miR-16 (7) is associated with chemoresistance, tumor progression and poor prognosis in ovarian cancer. miRNAs are non-coding transcripts which preferentially bind to the 3' untranslated region of their respective mRNA targets, thereby inhibiting translation. Considering that a single miRNA can target thousands of different mRNAs, the resulting effects tend to be complex and manifold. Overexpression of miRNAs leading to downregulation of tumour suppressors is frequently observed in cancer. However, by repressing proteins involved in growth or survival miRNAs can also act as tumour suppressors. Clustered miRNAs miR-15a and miR-16, which target (among others) the anti-apoptotic gene Bcl-2, lie within a fragile genomic region that is often deleted in B cell chronic lymphocytic leukemia (CLL), prostate cancer and multiple myeloma (8,9). Consequently, modulation of miRNA expression may be of therapeutic interest, in particular since techniques for delivery of miRNAs have been improved (10).

In this context, the findings made by Bhattacharya *et al.* are of significant interest for devising new treatment options for ovarian cancer. Having already shown that miR-15a and miR-16 target the polycomb complex protein BMI1 (11), they now confirm these findings and further characterize the negative effects of these miRNAs on ovarian cancer cell growth, as well as chemosensitivity by targeting the copper efflux transporter ATP7B. BMI1 is implicated in cancer "stemness". Activation of a conserved BMI-1-driven pathway was even found to be central to a "death from cancer" signature based on activation of 11 genes (12). ATP7B, in contrast, is highly relevant for resistance to platinum-containing chemotherapy (13). Battacharya *et al.* further found that miRNAs 15a and 16 repress epithelial-to-mesenchymal transition (EMT), thereby inhibiting cancer metastasis. *In vivo*, DOPC-based, nanoliposomal delivery of miR-15a or miR-16 thus reduced A2780-CP20 ovarian cancer growth by about 80% in a therapeutic setting. In synergy with cisplatin, the combined miR-

15a/16 treatment even achieved a 94% reduction in tumour growth. In summary, these findings show quite convincingly that substitution of repressed or (in almost 25% of the tumors) even deleted miR-15a and miR-16 could reduce the growth of ovarian cancer as well as metastasis formation while improving response to platinum-based chemotherapy.

While these findings call for translation into the clinics, a number of questions and unresolved problems remain. Selection of patients who have lost normal miR-15a/miR-16 expression could easily be performed via analysis of miRNA expression. Still, the suitable reference and the relevant level of reduction need to be determined. In spite of different residual expression levels, supplementation of the repressed miRNAs 15a and miR-16 was similarly effective in A2780-CP20 and in OVSAHO cells which suggests that a relatively wide range of cancers might be treatable. It further remains to be elucidated whether specific subtypes of ovarian cancer (serous, endometrioid, mucinous or clear cell types of ovarian cancer) are particularly prone to losing these miRNAs and whether the impact of the deletion depends on the subtype of the disease. Likewise, it is not clear if loss or repression of these miRNAs is an early event present in all cancer cells or a clonal adaptation in response to treatment with platinum-based chemotherapy. While cells expressing insufficient amounts of these miRNAs will have a particular selection advantage under therapy, the manifold effects of these miRNAs and their localisation in a fragile genomic site may also argue in favour of an early event. In fact, it would be interesting to see whether a loss-of-expression can already be found in the likely precursor lesion of serous ovarian carcinoma, i.e. serous tubal intraepithelial carcinoma (STIC) (14). While this may be difficult to test in human patients, it is important to know at which stage after diagnosis the levels of the respective miRNAs should be assessed and which samples should be used for testing. Given the difficulties in repeatedly obtaining tissue from solid ovarian cancer, other sources of biomaterial like exosomes, circulating cancer cells or ascites might also be valuable—even though ascites formation often indicates an already late stage for intervention. Interestingly, miR-16 was among the miRNAs found to be over-represented in the blood of patients with ovarian cancer (15). It is, however, unclear whether this coincided with reduced levels in the tumour tissue or whether liquid biopsies could be used for representative diagnostics of miRNA levels (16).

Having chosen suitable patients, delivery of miRNAs *in vivo* then still represents a formidable challenge. In cancer patients, certain side effects like the expected stimulation of Toll-like receptors (including the "double-strand RNA sensor" TLR3) may not pose a problem but rather add to the desired anti-tumor effect (17,18). Regarding the specific effects of miR-15a and miR-16, there is the need to further characterize their respective effects on further cellular targets. Surprisingly, effects on Bcl-2 which had previously been described for miR-15a/miR-16 (8,9) were not investigated in the present study. Also mechanistic aspects should be explored in greater detail. Thus, it is not 100% clear whether the described effects are due to the interaction of the respective miRNAs with the 3´UTR of the respective targets (19) or whether indirect mechanisms are involved. Likewise, it needs to be tested whether the combined use of both miRNAs is superior (due to maximum efficiency and a broader range of targets) or whether side effects should rather be minimized by using just a single miRNA. Finally, the possibility that introduction of these miRNAs could restore sensitivity to platinum-based chemotherapy calls for a sequential application with chemotherapy being administered at a suitable time-point after miRNA supplementation. The risk that miRNA-transfected non-tumor cells might also become sensitive towards platinum compounds must, however, be considered.

Importantly, miR-15a and miR-16 were also found to be underrepresented in a number of further malignancies, including CLL, gastric cancer, prostate cancer, hepatocellular carcinoma, oral squamous cell carcinoma, non-small cell lung cancer (NSCLC), glioma, papillary thyroid carcinoma , pituitary adenoma and malignant melanoma (20). Based on these data and the new findings by Dwivedi *et al*. (6), supplementation of miR-15a and miR-16 appears highly promising and deserves to be further explored and also pharmacologically developed. While the potential of miRNA-based approaches remains to be shown, Phillip Sharp from MIT predicted in his opening comments at the recent AACR symposium that "over the next decades we will see a very large expansion of the use of microRNAs to treat cancer… It could be as large as monoclonal antibodies". If this prediction should come true, the present publication supports miR-15a and miR-16 as most attractive miRNA candidates for future cancer treatment.

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Footnote

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