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Clinical Cancer Research

Letter to the Editor

Plasma MicroRNAs in Ovarian Cancer—Response

Xin Huang and Anda M. Vlad

We are pleased that our research (1) has generated interest in the scientific community, and we are happy to provide our reply to the comments submitted by Dr. Haifeng Qiu.

The major concern addressed by Dr. Qiu is that the upregulation of plasma miR-21 level in endometriosis-associated ovarian cancer (EAOC) cases is due to loss of estrogen possibly present in this group of patients. Dr. Qiu's argument is based on two lines of reasoning: (i) miR-21 expression is repressed by estrogen, and (ii) our patients with EAOC are significantly older than the healthy controls and those in the endometriosis group, and therefore they are likely postmenopausal women with low estrogen levels. In addition to miR-21, Dr. Qiu also has concerns about the increased expression of miR-16 and miR-195, which have also been previously reported as estrogen targets.

Although the estrogen/progesterone imbalance is a well-documented pathogenic factor in ovarian cancer and endometriosis, the role of estrogen in regulating miR-16, 21, and 195 expressions remains inconclusive. Studies have shown miR-21 being either repressed (2, 3) or induced by estrogen (4). Furthermore, evidence from several studies on the effect of estrogen on miRNA expression (5) suggests that miR-21 was not a consistent estrogen-repressed miRNA, and miR-16 and 195 only were shown to be repressed by estrogen in one study (6) among 19 studies reviewed (5).

Second, in our study the averaged fold change of miR-21 expression between EAOC and healthy controls is dramatic (fold change = 147.4) compared with the reported repressive effect of estrogen to miR-21 expression (ranging from 50%–70% repression), making it difficult to assume that estrogen has a big effect on our experimental results.

Third, the average age of our healthy control group and endometriosis group is comparable (38.75 and 36.24 years, respectively). Although estrogen levels were not measured in our study, the patients with endometriosis are likely to have higher estrogen levels that were also suggested by Dr. Qiu. Thus, if miR-21 expression is repressed by estrogen, miR-21 levels in patients with endometriosis should be lower than that in the healthy controls. However, this was not what we found. Instead, patients with endometriosis displayed a much higher plasma miR-21 expression compared with healthy controls (fold change = 10.65).

Fourth, differences in the above miRNAs were also present in comparisons with age-matched serous versus EAOC cases (all menopausal) and with age-matched female mice (tumor bearing vs. controls), further suggesting that factors other than estrogen may have impacted these changes.

Finally, as we have shown in our study, plasma and tissue samples have distinct miRNA expression profiles. Currently, the effect of estrogen levels on plasma miRNA expression profile remains unclear.

In summary, based on our study results and the above arguments, we do not believe that estrogen plays a significant role in regulating the plasma miRNA signature we have identified, which distinguishes EAOC patients with endometriosis from healthy controls.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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