Author's response to reviews

Title: MiR-190b, the highest up-regulated miRNA in ERalpha-positive compared to ERalpha-negative breast tumors, a new biomarker in breast cancers?

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To the Editors,

Please find attached a manuscript entitled “MiR-190b, the highest up-regulated miRNA in ERα-positive compared to ERα-negative breast tumors, a new biomarker in breast cancers?” by Cizeron-Clairac, Lallemand et al., that we are submitting for consideration as a research article by the BMC Cancer Journal. To date, it is well documented that endogenous estrogens known as an important regulator of development, growth and differentiation of the normal mammary gland play also a major role in the development and progression of breast cancer. Although the majority of primary breast cancers are ER-positive (ER+) and respond well to antiestrogen therapy, up to one-third of patients with breast cancer lack ER (ER-) at the time of diagnosis, and a fraction of breast cancers that are initially ER+ lose ER expression during tumor progression. Numerous datas are available regarding the miRNA expression in ER+ and ER- breast cancer tissues and come mainly from studies using miRNA microarray techniques but results and conclusions from these old studies are generally not consistent and sometimes even conflicting. In this work, we used the robust quantitative RT-PCR technology to identify miRNAs that are differentially expressed in ER+ and ER- breast primary tumors with the aim to better understand the molecular basis for the phenotypic differences between these two sub-types of carcinomas and to find potential clinically relevant miRNAs.

We used the robust and reproductive tool of quantitative RT-PCR in a large cohort of well-annotated 153 breast cancers with long-term follow-up to identify miRNAs specifically differentially expressed between ER+ and ER- breast cancers. We identified a robust collection of 20 miRNAs significantly deregulated in ER+ compared to ER- breast cancers: 12 up-regulated and 8 down-regulated miRNAs. MiR-190b retained our attention as it was the miRNA the most strongly over-expressed in ER+ compared to ER-. It was also significantly up-regulated in ER+/Normal breast tissue and down-regulated in ER-/Normal breast tissue. Functional experiments showed that miR-190b expression is not directly regulated by estradiol and that miR-190b does not affect breast cancer cell lines proliferation. Expression level of miR-190b impacts metastasis-free survival independently of ER status.

This study reveals for the first time miR-190b as the highest up-regulated miRNA in hormone-dependent breast cancers. With the advantage to be highly expressed and easy to detect by RQ-PCR, miR-190b could be used as a circulating biomarker for minimal residual disease follow-up in hormone-dependent breast cancers to detect therapeutic resistance and early relapses. Due to its specificity, miR-190b could therefore represent a new biomarker in hormone-dependent breast cancers even if its exact role in carcinogenesis remains to elucidate.

Thank you in advance for your consideration.

Yours sincerely,

Celine Callens, PharmD PhD