Oral

Title: Circulating microRNAs: Novel Biomarkers in in Breast Cancer.

Breakthroughs in cancer research

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Several genetic, epigenetic and proteinaceous biomarkers have so far been found to be associated with breast cancer, but their robustness as indicators of disease remains uncertain. More significantly, most women in the developing countries present with this cancer only when it has reached an advanced stage. The treatment of advanced stage cancer presents several challenges but most important among them is the frequent development of resistance to chemotherapy and hormonal therapy, which leads to a high mortality rate. This resistance creates a need to identify sensitive biomarkers that could be useful in early detection and in following the progression of the disease; these might help to identify new therapeutic targets.

MicroRNAs (miRs) form a class of non-coding RNA that regulates post-transcriptional gene expression and thereby cellular processes. In breast cancers, dysregulation of the miRs' expression can result in the progression of cancers. In addition, miRs have been shown to play a role in the development of resistance to drug therapy by regulating signaling cascades. From a cohort of 100 disease-free individuals and 127 breast cancer patients, the levels of these circulating miRNAs are being verified by qRT-PCR. The results of this part have shown over-expression of some types of miRs in the breast tumor patients, while the level of expression among others remains lower than those in normal individuals. Another interesting pattern has emerged when the relative levels of these circulating miRNAs were compared with their expression levels in breast tissue. In addition to intergroup comparisons, plasma miRNA expression levels of all groups were analyzed against cancerous breast tissue (RNA-Seq data from The Cancer Genome Atlas-TCGA). A differential set of miRNAs were identified in the plasma of breast cancer patients and 10 miRNAs were uniquely identified on the basis of ROC analysis. The most striking findings revealed that some of the tumor suppressor miRs in the plasma of luminal breast cancer patients was elevated, irrespective of subtype, and was elevated also in the plasma of TNBC breast cancer patients. We found also that, while most miRNAs in plasma reflected cellular levels some of them had an inverse pattern, suggesting that they were being selectively secreted into plasma. The circulated miRNA patterns indicate signatures which could serve as biomarkers for detection, and might be used in screening and distinguishing the type of tumor; they could also be used as targets for therapies.

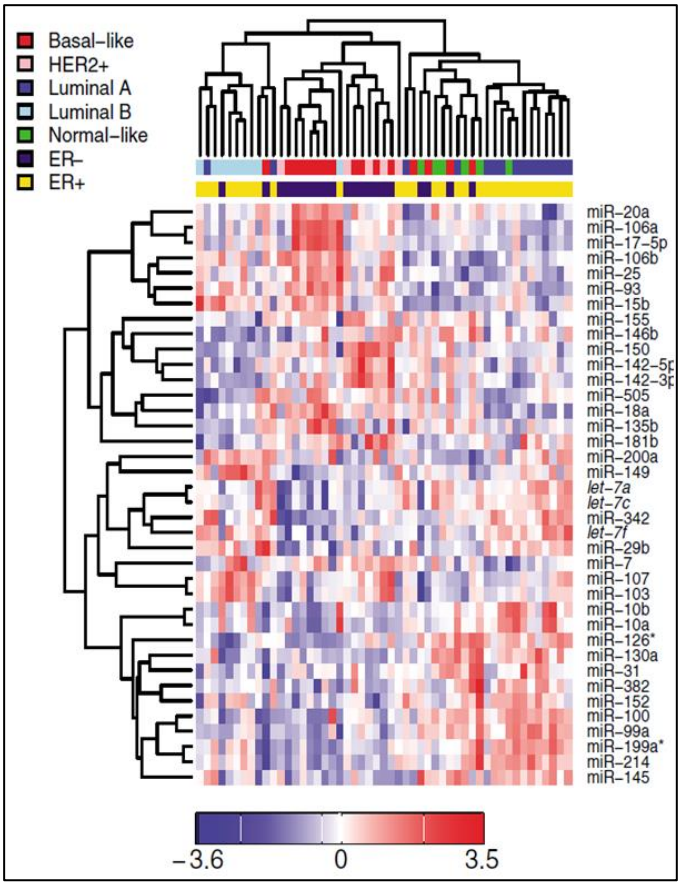


Figure: Abnormal expression of miRNAs in breast cancer has been found in both blood and tissue and correlates with the clinical characteristics of tumors, tissue sub-type, aggression and also response to therapy. The expression of miRNAs varies between normal and malignant breast tissue, and between different grades, molecular subtypes, and hormone-receptor status, whether nodal or steroid. Hierarchical clustering is supervised over selected miRNAs (Pearson correlation, average linkage). Heatmap colors represent relative miRNA expression as indicated in the color key for each panel. In the right margin are listed the members of miRNA. The clustering of 51 tumor samples can classify them as basal-like (red), HER2+ (pink), luminal A (dark blue), luminal B (light blue) or normal-like (green) over 38 miRNAs with Benjamini-Hochberg adjusted Kruskal-Wallis $p < 0.05$. (***Ref:****doi:10.1186/qb-2007-8-10-r214, PMID:17922911).*

Recent Publications:

1. **Amal Qattan**, Haya Intabli, Wafa Alkhayal, Chafica Eltabache, Taher Al-Tweigieri, Suad Bin Amer. **(2017)** "Tumor-suppressor miRNAs let-7 and mir-195 are increased in **triple negative breast cancer (TNBC) patient** plasma" ***BMC Cancer. (BCAN-D-17-00387R1).***
2. **Amal Qattan (2017). "**Metabolic Reprogramming of Triple Negative Breast Cancer: The Role of miRNAs*". MicroRNA Diagnostic and Therapeutic (**MicroRNA Dx/Rx).***
3. **Amal Qattan** and Suad Bin Amer. **(2017). "**Epi-miR and Epigenetic mechanisms cross-regulation in breast cancer*"*..
4. S. Almozyan, D. Colak, F.h Mansour, A. Alaiya, O. Al-Harazi, **Amal Qattan,** F. Al-Mohanna, M.r Al-Alwan and H. Ghebeh. **(2017).** "PD-L1 promotes OCT4 and Nanog expression in breast

cancer stem cells by sustaining PI3K/AKT pathway activation". ***International Journal of Cancer.2017 June 14. doi:10.1002/ijc.30834***

5. Pinto G, Alhaiek AA, Amadi S, **Qattan AT**, Crawford M, Radulovic M, Godovac-Zimmermann J., **(2014)** "Systematic nucleo-cytoplasmic trafficking of proteins following exposure of MCF7 breast cancer cells to estradiol". *J Proteome Res.* **2014** Feb 7;13(2):1112-27. doi: 10.1021/pr4012359.
6. **Qattan, A,**Radulovic, M., Crawford, M. & Godovac-Zimmermann, J. **(2012),** "Spatial Distribution of cellular function. The partitioning of proteins between mitochondria and the nucleus in MCF7 breast cancer cells" *J Proteome Res*, 2012 Dec 7; 11(12):6080-101. doi: 10.1021/pr300736v
7. **Qattan, A** and Godovac-Zimmermann, J. **(2011), Chapter in a Book:** "Quantitative Organelle Proteomics of Protein Distribution in Breast Cancer MCF-7 Cells", *in: Breast Cancer Recent Advances in Biology, Imaging and Therapeutics*, Susan J. Done (ed.), ISBN: 978-953-307-730-7, InTech, DOI: 10.5772/23492; pages 203-220. InTech, published: Dec14; 2011 under CC by 3.0 in *Oncology*. Croatia.

Biography

I'm working in the Department of Molecular Oncology at the King Faisal Specialist Hospital and Research Center (KFSHRC) Hospital, Riyadh-SA, and I am also a member in the scientific committee of the Zahra Breast Cancer Association and Assistant Professor in the College of Medicine at Al-Faisal University. I graduated from the Medical School at UCL-UK and have been working since 2000 in the Oncology Department at King Faisal Specialist Hospital and Research Center at KFSHRC Hospital. My primary interest is in personalized medicine using the state-of-the-art molecular, cellular, and bioinformatic technologies in support of a systems-biology based research approach to understanding the events that affect the sensitivity, or lack of it, among cancers to chemotherapy and hormonal therapies. I use gene expression, microarrays, proteomics, and metabolite profiling to combat breast cancer. The goal of my work is to better determine an individual patient's response to specific cancer therapies. I focus on understanding and controlling tumor dormancy; resistance in cancers; and microRNA as a master regulator of the expression of several genes in different phases of breast cancer. In the developing countries, breast cancer is still the most common cancer and its most daunting aspect is that 58% of all breast cancers present and are detected at an advanced stage. This makes it urgent to find and develop a panel of sensitive biomarkers for early detection before the disease becomes invasive and metastasis begins. The treatment of advanced breast cancers also presents a challenge. Therefore I'm trying, with my group, to develop different therapeutic targets, which can be used to counter drug resistance, for metastasic breast cancer in particular. The hope is to open up a way to fight and cure the disease which would be more specific than traditional cancer medicines.

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