Benedito Rodrigues da Silva Neto
(Organizador)

Conceitos Básicos da **Genética**

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APRESENTAÇÃO

Há exatos dezenove anos, mais precisamente na data de 21 de junho de 2000, um dos anúncios mais esperados nos últimos tempos pela comunidade científica era feito: simultaneamente nos Estados Unidos e em Londres o presidente Bill Clinton e o primeiro ministro Tony Blair divulgaram, o que segundo eles seria uma nova era para a humanidade, o sequenciamento do genoma humano. O “rascunho da vida” como denominaram traria novas expectativas quanto à doenças incuráveis, desafios éticos, novas propostas tecnológicas para a pesquisa, mas principalmente uma acessibilidade muito maior ao conceito de genética para a população.

Desde então uma revolução molecular pôde ser observada, novos conceitos adentraram às salas de aula, novos equipamentos evoluíram os laboratórios de pesquisa, novos e milhares de artigos passaram a publicar quase que “em tempo real” as descobertas no campo ambiental, microbiológico, industrial e da saúde. Podemos dizer também que a genética chegou como nunca às mesas das famílias, deixando de ser um assunto apenas dos cientistas.

Portanto a literatura aqui apresentada e intitulada “Conceitos básicos da genética” torna-se relevante não apenas por abordar assuntos relativos à comunidade acadêmica, mas principalmente por demonstrar a diversidade de áreas que hoje utilizam das ferramentas genéticas e moleculares em seus estudos que estão diretamente relacionados ao dia-a-dia da população.

Cada vez mais, o acelerado mundo das descobertas científicas caminha a passos largos e rápidos no sentido de transformar a pesquisa básica em aplicada, portanto é relevante destacar que investimentos e esforços nessa área contribuem grandemente com o desenvolvimento de uma nação. A genética como sabemos possui um campo vasto de aplicabilidades que podem colaborar e cooperar grandemente com os avanços científicos e tecnológicos.

Esperamos que seja apenas o primeiro de muitos outros livros na área, já que a cada dia novas tecnologias genéticas tornam-se acessíveis e novas descobertas são possíveis. Parabenizamos cada autor pela teoria bem fundamentada aliada à resultados promissores, e principalmente à Atena Editora por permitir que o conhecimento seja difundido e disponibilizado para que as novas gerações se interessem cada vez mais pelo ensino e pesquisa em genética.

SUMÁRIO

CAPÍTULO 12

EVALUATION OF PLASMA MIRNAS FOR EARLY DIAGNOSIS OF BREAST CANCER

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RESUMO: Os microRNAs (miRNAs, miRs) são pequenos fragmentos de RNA com potencial atividade no bloqueio da transcrição e podem ser oncogênicos ou supressores tumorais, dependendo a função dos genes alvejados por eles. Este capitulo de livro tem o intuito de explicar como uma análise de expressão de miRNAs poderia dar luzes sobre o processo oncológico, devido a sequências associadas a tipos de câncer específicos. Além disso, os miRNAs tornam-se bons marcadores para a detecção precoce e o monitoramento do câncer através de biopsias líquidas porque apresentam um resultado de múltiplas interações envolvidas nas neoplasias. Para isso, avaliamos a expressão de miRNAs comparando amostras de plasma de 30 pacientes com câncer de mama e 30 mulheres sanas. Os miRNAs foram extraídos com o kit miRNeasy Serum/Plasma Kit (Qiagen, Germany), convertidos a cDNA y quantificados por PCR digital (dPCR), usando a plataforma QuantStudio 3D (Thermo Fisher Scientific, Boston, MA, USA). Analisamos a expressão de miR-10b, miR-21, miR-145 e miR-202; nossos resultados indicam uma

tendência à superexpressão do miR-10b (p=0.334) e miR-21 (p=0.741) nas pacientes, aliás, achamos uma diminuição na expressão do miR-145 (p=0.0064) e no miR-202 (p=0.394). Os nossos achados concordam com informações da literatura para estudos feitos em biopsias solidas. Finalmente, nós apresentamos características nos miRNAs de plasma que abrem portas para a inclusão deles como alvos em futuros estudos com biopsias liquidas no câncer de mama.
PALAVRAS-CHAVE: miRNA, biopsia líquida, câncer de mama, PCR digital

ABSTRACT: microRNAs (miRNAs, miRs) are small RNA regions with potential anti-transcriptional activity; each miRNA has several targets and they were classify according to its function. Recently, it was propose as a useful tool for cancer analysis and sequences with altered expression could define some cancer types. Additionally, these sequences are an interesting target in liquid biopsy studies because they represent a pool of genetic interactions, associated with neoplastic development. This book chapter aims to explain how the miRNAs expression may offer an idea about the oncologic process through silencing their targets; after that, the miRNA detection in plasma as liquid biopsy could support new possibilities to early diagnosis and monitoring of cancer. We obtained plasma from 30 breast cancer patients and 30 healthy women and miRNAs were extracted with the miRNeasy Serum/Plasma Kit (Qiagen, Germany), converted to cDNA and quantified by digital PCR through QuantStudio 3D platform (Thermo Fisher Scientific, Boston, MA, USA). We analyzed regions of miR-10b, miR-21, miR-145 and miR-202. Our results show a trend on the overexpression of miR-10b (p=0.334) and miR-21 (p=0.741). In addition, we found a statistical-support for the sub-expression of miR-145 (p=0.0064) and a slight sub-expression of miR-202 (p=0.394), which is in agreement with the literature. In conclusion, we characterize the liquid biopsy as a potential early-diagnosis tool for breast cancer through miRNA analysis.
KEYWORDS: miRNA, liquid biopsy, breast cancer, digital PCR

1 I INTRODUCTION

The cancer generates a non-controlled proliferation and several modifications occurs in the cellular environment. Some of this modifications may not be heritable (epigenetic variations) and it produces effects on genetic expression (You & Jones 2012). Epigenetics mainly comprises studies of DNA methylation, histone modification and levels of microRNAs (miRNAs), considered new mechanisms of regulation of gene expression. The miRNAs are a class of non-coding RNAs, that is, those that do not code for proteins that regulate post-transcriptional gene expression (Li & Rana 2014).

In 1993, the first miRNA was discovered during a study on the Lin-4 gene of C. elegans that regulates its development and did not code for protein. However, Lin-4 produced two RNAs of short sequence, one of 22 nt and another of 61 nt in length. These RNAs showed antisense zones complementary to multiple sites of the 5′UTR

region of the Lin-14 gene. This was evidenced by a decrease in the amount of protein without affecting miRNA levels (Chuang & Jones 2007).

The apparition of these miRNAs results mainly of cell lysis; however, recently studies affirm the mobilization of microvesicles, like exosomes, carrying little sequences of RNA with anti-transcriptional activity (Turchinovich et al., 2012) and we need to know more about the miRNA resistance to degradation factors like enzymes and other factors regulating their specificity (Pritchard et al., 2012). Currently, the regulatory role of miRNAs is accepted in different biological processes carried out in multicellular organisms, such as differentiation, proliferation and apoptosis or cell death. They are expressed in serum, plasma and other body fluids in stable form allowing their use as a potential biomarker due their deregulation has been linked to some diseases (Ambros 2004; Ma et al., 2012), such as breast cancer. Also, we know almost 1000 human miRNAs (hsa-miRs) and each one might be regulated by different pathways (Ma et al., 2012) and seventy-nine of them has been described like biomarkers in fluids for breast, lung, prostate and other cancer kinds (Pritchard et al., 2012) . Many efforts builds prediction databases for sequences and targets of these miRNAs (You & Jones 2012). In several cancer types, some miRNAs were signed as subexpressed or overexpressed depending their distribution and effect in the disease.

On the other hand, the most popular cancer markers in fluids are proteins such prostate specific antigen (PSA) or carbohydrate antigen 125 (CA125); however, the main problem with them is a low sensitivity and discrimination powerful (Ma et al., 2012) generating issues to early stages identification, and subsequently, problems on treatment of these individuals. So, the discovery of miRNAs like potential fluid biomarkers for early diagnosis and monitoring is promissory, starting in the distinctive and non-invasive features of miRNAs for their utilization on liquid biopsies (Ma et al., 2012). In this book chapter, we show a pilot study with breast cancer patients, analyze their miRNA levels and discuss how some of them can drive the oncologic process.

2 I MATERIALS AND METHODS

We collected peripheral blood of 30 breast cancer patients from the Instituto Nacional de Enfermedades Neoplásicas (INEN) and 30 healthy controls from Oncosalud (AUNA) and Universidad de San Martin de Porres (USMP), all institutions from Lima, Perú. Patients and controls were asked to sign an Informed Consent approved by the USMP Ethics committee (IRB00003251-FWA0015320). The plasma was separated by double centrifugation at 4 °C, then total miRNA was extracted with the “miRNeasy Serum/Plasma Kit” (Qiagen, Germany) and converted to cDNA (TaqMan Advanced miRNA cDNA Synthesis, ThermoFisher Scientific, Boston, MA, USA). Digital PCR (dPCR/ QuantStudio 3D platform with chips (20KChips) of 20,000 independent dots for analysis, ThermoFisher Scientific, Boston, MA, USA) was performed to quantify four

human miRNAs: hsa-miR-10b (ID: 478494_mir), miR-21 (ID: 477975_mir), miR-145 (ID: 477916_mir) and miR-202 (ID: 478417_mir). The number copies was calibrated with an exogenous control (cel-miR-39) from *Caenorhabditis elegans*, included in the miRNA extraction process. The quantity of miRNA was obtained by the use of QuantStudio3D Analysis Suite v.3.1.3 Cloud Software (ThermoFisher Scientific, Boston, MA, USA) to analyze the call (dye fluorescence) and quality (0-100% qualification) for each well or dot. In this study, we used a minimal threshold above 10% due low concentration and fragility of the sample. The statistical tests was performed with the Prism 5 software (Graphpad software Inc., La Jolla, CA, USA).

3 I RESULTS

Our experimental groups showed a similar age: 56.23±11.29 in patients and 47.26±14.70 years in controls. To obtain the quantification values, we took the figures generated by QuantStudio 3D Analysis Suite and established thresholds.

Each chip was charged using just one fluorophore (VIC for this assay), so we took 300 chips to analyze the fluorescence thresholds. This analysis determines 1200 RFU (Relative Fluorescence Units) as frontier between non amplified and amplified dots, as showed in the figure 1.

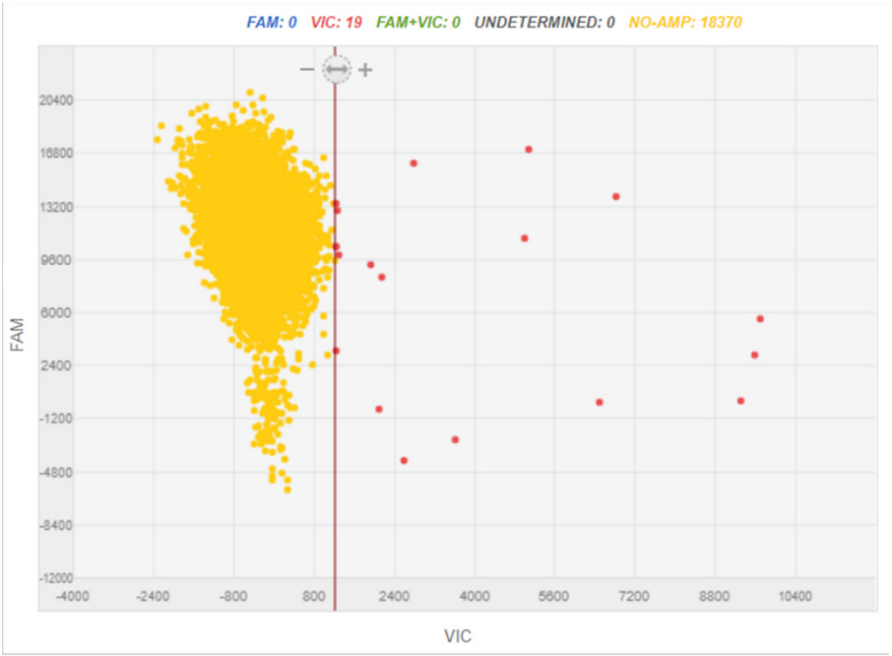

Figure 1. Establishment of threshold for digital quantification. All points located at right of threshold (red points) would be considered as positive amplification and yellow points are estimated like empty wells (without amplification).

So, for each sample, the number of red points of control marker (cel-miR-39) was used to calibrate all the quantifications with the standard quantity of exogenous copies (added at the sample in the miRNA extraction). Since it doesn´t exist differences among patient and control in exogenous marker level (p=0.8360), we can certify the

next comparisons.

In a comparison among patients and controls, just one marker showed a statistical difference (miR-145, *p*=0.03); however, all other miRNAs showed a trend to increase or decrease their expression depend the individual condition, as presented in the Figure 2.

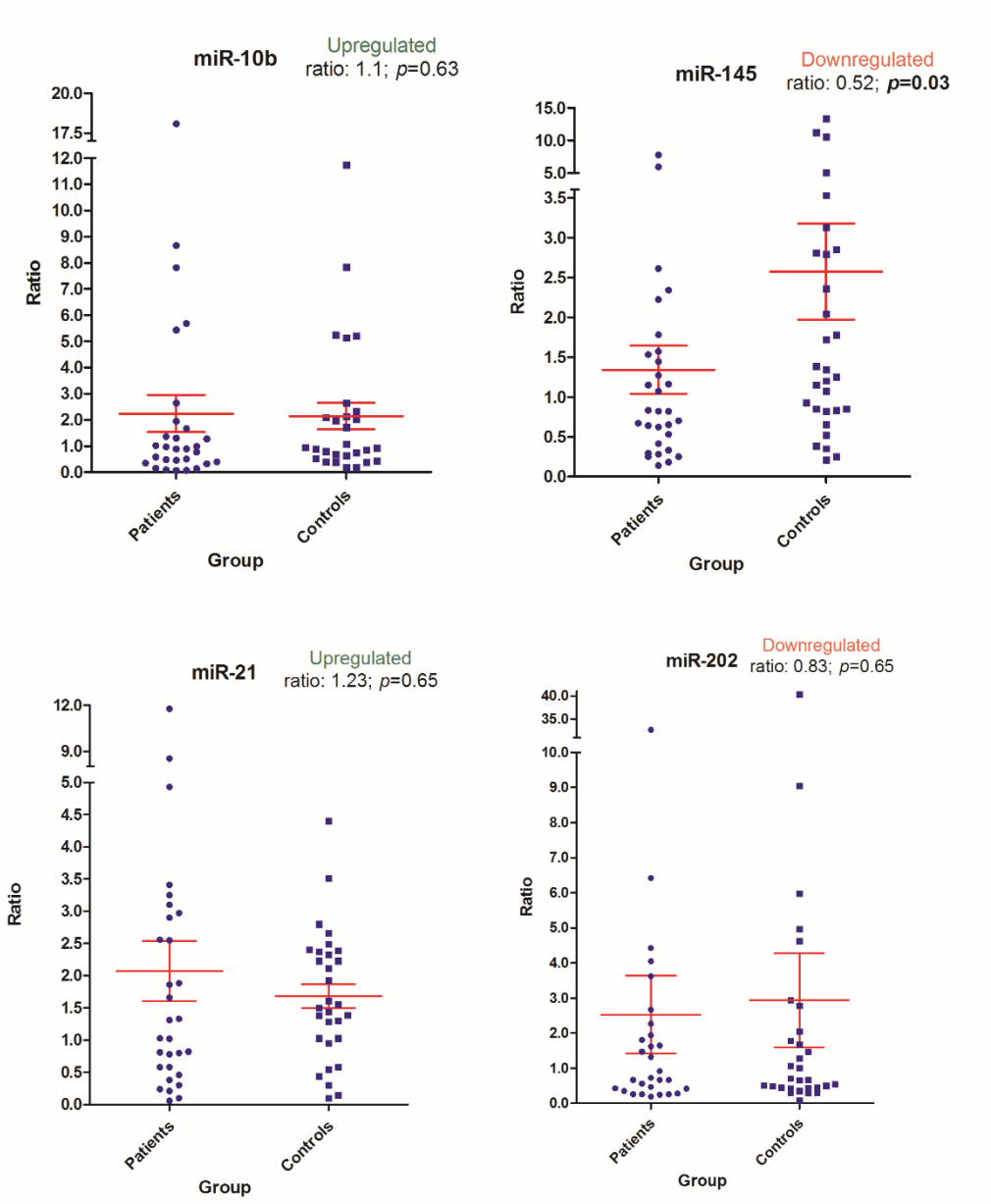

Figure 2. Comparison among breast cancer patients and controls using plasma miRNAs. Each quadrant represents a miRNA type, miR10b and miR-21 showed a trend to overexpression in patients (right half); in contrast to has seen in miR-145 and miR-202 (left half).

Then, we compare miRNA levels correlated with neoadjuvant administration, and immunopathological characteristics: Expression of HER2, progesterone (PR) or estrogen (ER) receptors. Thus we found a significant overexpression of miR-10b in patients without neoadjuvant scheme. Besides there were statistical differences in the overexpression of miR-145 and miR-202 in HER2 positive patients, also in the down regulation of miR-202 in estrogen positive patients. Our extended results are showed

in the Figure 3.

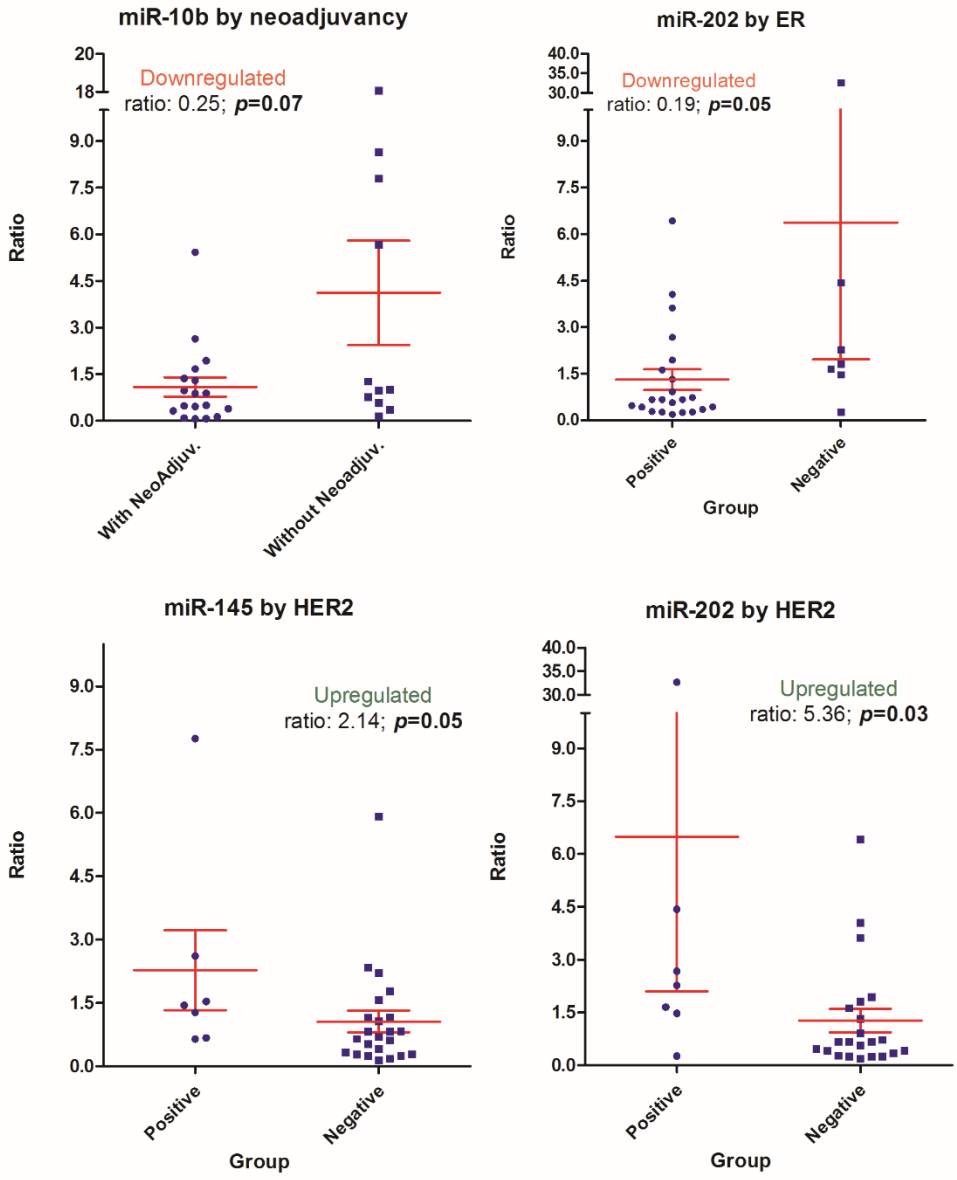

Figure 3. miRNA levels in breast cancer patients according clinical characteristics. For each miRNA and condition represented are included statistical p value (through Mann-Withney test) and the mean ratio among positive and negative conditions.

4 I DISCUSSION

In this book chapter, we show results about miRNA levels in plasma of breast cancer patients and healthy controls; and our aim is to explain why these miRNAs could be used as markers and its significance at the physiological level.

So, a critical criteria for start this study are the sample conditions; in our case, all participants are women and all of them was classified by an oncologist how cancer positive (patients) or negative (controls). The mean age among both groups showed some differences, but, it doesn´t affect our results due a population factor, where major part of old-age women don´t assist to clinical consultation if don´t show a clear suspicion

of cancer.

According with the information purposed by Pritchard et al., 2012, Turchinovich et al., 2012 and Ma et al., 2012, the circulating miRNA could have different origins and physiological responses. For example there is overexpression in hemolysis of red blood cells and on the other hand there is an overpopulation of some particular cell lines, more related with cancer types. But there are not reported variations related to age; but rather clinical characteristics can increase or decrease the miRNA levels in a sort of cause-effect cycle which deserves a specific analysis.

In the literature there are several studies involving miRNAs using different methods for data analysis (Li et al., 2014; Hoss et al., 2015; Conte et al., 2015). In our case, we used the digital PCR, this system able to analyze twenty thousand wells of amplification reaction and quantify them (Figure 1) (Conte et al., 2015). Other improvement for this analysis is represented by the normalization with a spike-in control, this offer an additional checkpoint to sample processing and reliability of the results as well has been described (Conte et al., 2015; Kobayashi et al., 2018; Tangtanatakul et al., 2018).

Clearly, different values of miRNA levels are expected depending of the selected miR (Figure 2). For instance, we select 4 miRNA markers and all have distinct behavior in different cancer kinds as shown in the figure 4.

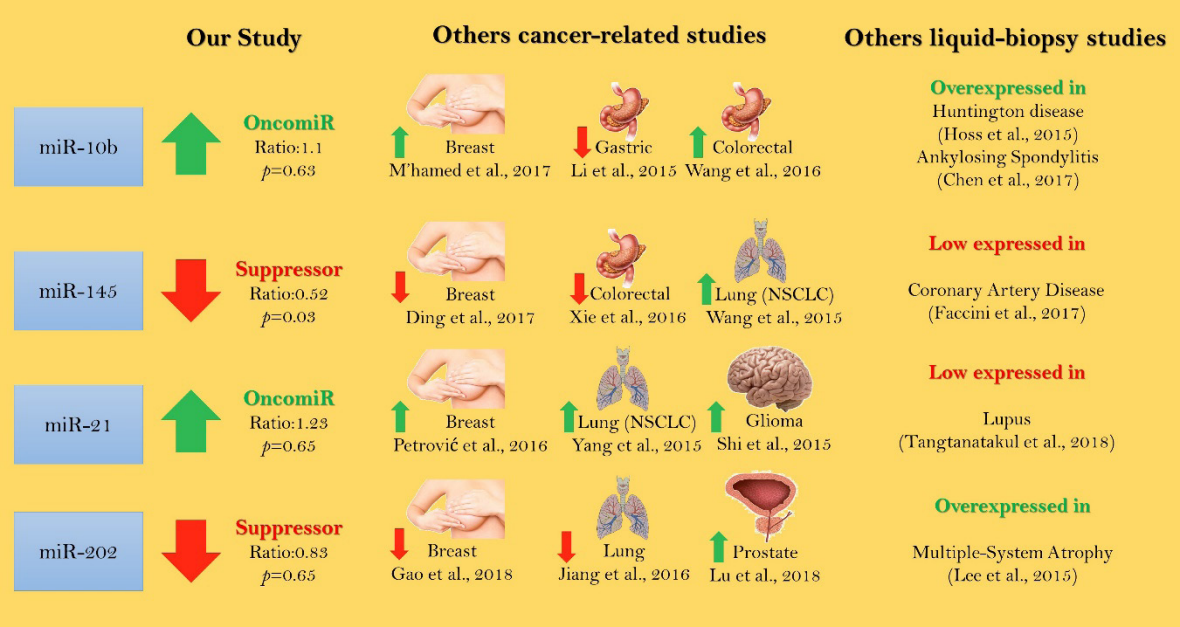

Figure 4. Results and current literature about miRNAs studied. Some miRNAs could be increased or decreased depending the cancer kind or related to other diseases, a relative variability of this results may be considerate as a barrier of this study field.

Currently, the classification of miRNAs as oncomiR or miRNA tumor suppressor is one of the more difficult challenges for cancer research. Some miRNA have been detected in high quantities in some cancer types and very low in other conditions. One example for this is the miR-21, characterized like oncomiR in breast cancer (Petrović 2016), non-small cells lung cancer (Yang et al., 2015) and glioma (Shi et al., 2015), but is decreased in diseases like lupus (Tangtanatakul et al., 2018). This is confirmed

through a fast search of gene targets of miR-21, for this, we can use the miRTarBase (Chou et al., 2017) and GOrilla (Eden et al., 2009) softwares. The miR-21 targets are grouped in 4 major categories: regulation of molecular function, response to chemical, negative regulation of biological process, and positive regulation of cellular process.

Thanks to bioinformatic tools we can support and explain an experimental result; however it could more complex because the miRNA behavior is highly susceptible. Other example, the miR-10b was characterized for a deep controversy about their function (Ahmad et al., 2015; Hagras et al., 2015; M'hamed et al., 2017). We found it like oncomir for the breast cancer, in a similar condition was reported for colorectal cancer (Wang et al., 2016) and oral cancers (Tian et al., 2015). However, miR-10b could not recognized totally as oncomiR because it was found as tumor suppressor in a gastric cancer study (Li et al., 2015). To add more confusion miR-10b is increased in non-cancer diseases as Huntington´s disease (Hoss et al., 2015) or Ankylosing spondylitis (Chen et al., 2017). A bioinformatic prediction of miR-10b shows as targets: positive regulation of biological processes, negative regulation of cell adhesion, animal organ development. Some of them are oncogenic and others act as suppressor, so the miRNA behavior could depend of the independent expression of these targets according tissue and age of the individual.

The other miRNAs analyzed in this study were decreased in breast cancer patients, concordant with the literature (Ding et al., 2017; Gao et al., 2018), but it was the opposite for other cancer types like lung (Wang et al., 2015; Jiang et al., 2016), Colorectal (Xie et al., 2016) or prostate (Lu et al., 2018). Other difference between miR-145 and miR-202 is the capacity to distinguish cancer from other diseases, miR-145 also decreased in coronary artery disorder (Faccini et al., 2017); in contrast with miR-202 who increased their levels in Multiple-system atrophy (Lee et al., 2015).

In consequence, we can view the target categories for each one of these miRNAs; for the miR-145, their categories are associated with: positive regulation of macromolecules and nitrogen compound process, developmental process and positive regulation of cellular metabolic process. Meanwhile, the miR-202 targets are related with: lung development, morphogenesis of a branching structure and epithelial tube. Notably, the miR-202 targets have a nearest relationship with formation and development of lung and airways, explaining why their decreased levels may be a marker to lung cancer (Jiang et al., 2016).

In this manner, we have different conditions to be analyzed before select a miRNA. As we show lines above, there are miRNAs with increased or decreased levels depending their functions; however, there are also some conditions that can change the level of these miRNAs.

According to our results, a neoadjuvant treatment generates an increase of all miRNAs evaluated, on the opposite side HER2 or estrogen receptors generates a decrease of the miRNAS (Figure 3).

At this point, the literature has a slight controversy, some authors indicate that

miRNA levels are down-expressed after neoadjuvant treatment (Preis et al., 2011) and others affirm that this effect depend on the particular miRNA and their basal concentration (Drebber et al., 2011; Gezer et al., 2014). Especially, the study of Drebber et al., 2011 indicate a reversal relationship among miR-21 and miR-145 after adjuvant treatment; miR-21 is the higher initially, but their levels decrease after therapy, in contrast with miR-145. This cannot verified nor rejected in our results because we just show independent samples without a monitoring before or after treatment.

These characteristics are extended for immunopathological features, where the triple negative breast cancer (TNBC) turned an interesting model to be studied. Some studies (Radojicic et al., 2011; Fang et al., 2017) report that miR-21 are overexpressed in TNBC. In comparison with our results mostly with non TNBC (28 out of 30 negative for estrogen receptors or HER2 amplification), miR-21 decreased as well as other miRNAs. However, the increase of certain miRNA could be an exclusive for TNBC and not for HER2, ER or PR separately. The last hypothesis cannot be tested in our work due low number of TNBC cases (2 of 30), but this response will open new doors to pursue this research.

Finally, we have high expectancies for future studies in liquid biopsies, studying higher number of samples, improving the technologies of extraction and the selection of targets. For example, miRNA from exosomes or platelets and other tools will increase our knowledge about the molecular biology of cancer and how it can be detected, and also to design appropriate treatments.

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