MicroRNAs, Gene's Regulator in Prostate Cancer

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Abstract Since the discovery of microRNAs (miRNAS) in 1993, findings in gene regulation have increased in the biological scenery. miRNAs have shown an important role in the modulation of a wide collection of physiological and pathological processes, starting on embryonic evolution with carcinomas development. Nowadays, the high availability of gene expression data and the development of computational approaches that predicts miRNA targets are continuously increasing the knowledge about miRNA functions, as well as the sources and consequences of miRNA deregulation within a wide interaction network. In this chapter, knowledge of miRNA expression and its function on prostate cancer is presented.

Keywords MicroRNA · Circulating miRNA · Biomarkers · Cancer · Prostate

1 Introduction

MicroRNAs (miRNAs) are a family of small regulatory RNAs that control the expression of specific genes in a post-transcriptional level by base-pairing typically to the 3′-untranslated regions (3′UTRs) of a target messenger RNAs (mRNAs) to direct a reduction in either translation or stability [1]. They are members of the family of small non-coding RNAs that are endogenous small interfering RNAs (endo-siRNAs), such as PIWI-single-stranded non-coding RNAs ofo 20–23 interacting RNAs (pi-RNAs) [2, 3]. MiRNAs are involved in a broad range

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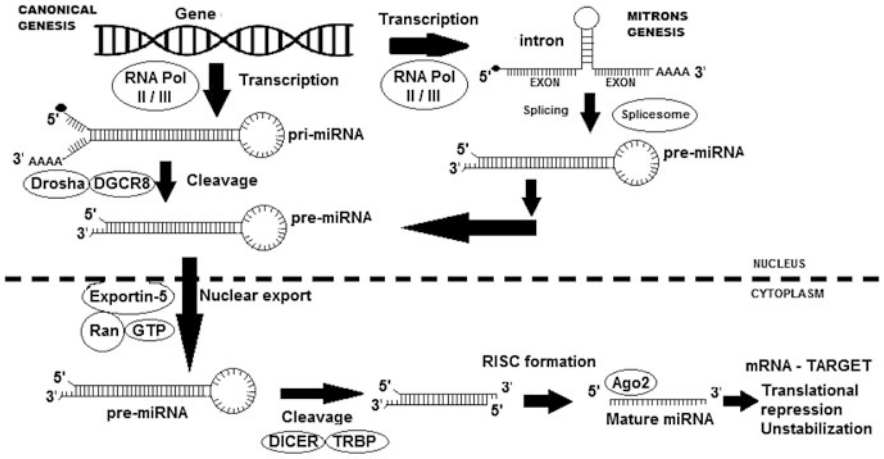

Fig. 1 Canonical and non-canonical (mitrons) microRNA genesis

of cellular functions, as developmental, cell differentiation and cell maintenance functions [4]. MiRNAs are distributed throughout the genome, they can be found as isolated transcript units or clustered and co-transcribed as polycistronic primary transcripts [5] and can either be encoded within protein coding genes in both introns and exons or transcribed from independent genes as intergenic regions. MiRNA transcription can be carried out by RNA polymerase III and II to produce the primary transcripts (primiRNAs) [6, 7], which are thousands nucleotide long capped and polyadenlylated hairpin-shaped transcripts. In the canonical miRNA genesis pathway, pri-miRNAs are recognized and cleaved in the nucleus then the mature miRNAs are generated by several processing steps of endonucleolytic cleavages in the cytoplasm. The cleave in the nucleus is carried out by an RNase III enzyme named Drosha, which acts with the microprocessor complex subunit DGCR8 (a molecular anchor necessary for the recognition of pri-miRNA at dsRNA-ssRNA junction) and cleaves 11 bp away from the junction to release hairpin-shaped pre-miRNAs that are subsequently cut by the cytoplasmic RNase III enzyme called DICER to generate mature miRNAs [8–13] (Fig. 1). An alternative miRNAs biogenesis pathway called Mitrons-pathway has been described, miRNAs is embedded in short mRNA introns, then pre-miRNAs are produced unending Drosha cleave, those are completed from splicing and debranching [14, 15]. In both miRNAs pathways, pre-miRNAs are transported into the cytoplasm by exportin 5 and Ran-GTP. In the cytoplasm Dicer joined to TRBP (Trans activated response [TAR] RNA Binding protein) cleaves the terminal loop end of the pre-miRNA producing a short double-stranded RNA duplex that measure around 20–23 bp length. The strand of the duplex with a less thermodynamically stable 5′ end is preferentially conjugated to an Argonaute protein forming the miRNA-induced silencing complex (RISC) [16], however in some cases the complementary strand can be used in the RISC complex [17, 18].

The mature miRNA joined to RISC binds to the mRNA in the 3′ UTR, or in less cases in the coding region, based on complementarity between the miRNA and the mRNA target. Seed sequence, nucleotides 2–8 (counted from the 5′ end) of the mature miRNA [1, 19] is critical for target recognition and hybridizes nearly perfectly with the target mRNA [5].

The understanding of miRNA functions into a network context and the signaling or metabolic pathways with the consequences that their deregulation can produce has been achieved by novelty advances, as the genome-wide identification of miRNA–target, the RNA sequencing.

In the last two decades, several strategies have been used to identify miRNA targets, physical association and/or the correlation of gene expression. Lists of target genes can then be examined collectively in the contexts of KEGG pathways (KEGG PATHWAY is a collection of manually drawn pathway maps representing our knowledge on the molecular interaction, reaction and relation networks for: (1) Metabolism, (2) Genetic information processing, (3) Environmental information processing, (4) Cellular processes, (5) Organismal systems, (6) Human diseases, and (7) Drug development) (http://www.genome.jp/kegg/pathway.html) [20–22], protein–protein interaction networks [23–26] and enrichment analysis for common gene ontology terms [27, 28]. Several computational tools for target enrichment analysis facilitate the identification of hierarchical functions of miRNAs in gene regulatory networks (Table 1). The involvement of miRNAs in signaling pathways and genetic networks provides a challenge to understanding their function. The level of evidence required to establish miRNA–target relationships is set too low that the genuine interactions are eclipsed by noise.

Recently it has been proposed five steps (or levels) to unravel the specific role of miRNA. In the *level 1* the objective is to find or identify a specific microRNA (from the vast list of known microRNAs) and enlist pathways expected to be involved in a disease under study, increasing the probability to associate a miRNA with the disease and create a base to identify the pathway. The condition of a miRNA under a cellular condition can be achieved by the micro-array/transcriptome technique; *level 2* The next step is to identify the status of the miRNA and the key pathway specific genes expression in the selected disease. This is achieved through a database search. Alternatively, the absence of enough published information, conducting a case-control or a pair (tumor and normal tissue) study in cancer could help to establish the status of the microRNA and the key genes, preferably representing the pathway specific markers; *level 3* the predicted miRNA targets need to be experimentally validated. Many human miRNAs are released in the latest version of miRBase (Release 20), but yet many remain to be identified. In the last ten years several algorithms have been developed to identify targets for miRNAs, those are based on the conservation of seed region and binding energy, however, recently some of the algorithms (TargetScan, miRanda, RNA22, PICTAR, PITA, RNAhybrid, DIANA-microT, mirSVR, microInspector, mirTarget2) have incorporated expression profiles in their scoring function [29], helping to increase the accuracy of prediction. It has been observed that the stability of miRNA seed sequences was evolutionarily selected according to the adaptive temperature of each organism, however non-

Table 1 Bioinformatics tools used for miRNA target prediction

Name	Web site	Observations
miTEA (miRNA target enrichment analysis)	http://cbl-gorilla.cs.technion.ac.il/miTEA	miTEA is a tool for identifying and visualizing enriched miRNA targets in ranked lists of genes It searches for enriched miRNA targets that appear densely at the top of a ranked list of genes The search is commanded by a list of genes provided by the user which also select the species and the prediction tool, obtaining a list of miRNAs predicted to target the gene list
DIANA mirPath	http://snf-515788.vm.okeanos.grnet.gr/	DIANA-mirPath is a miRNA pathway analysis web-server, providing accurate statistics, while being able to accommodate advanced pipelines. mirPath can utilize predicted miRNA targets (in CDS or 3′-UTR regions) provided by the DIANA-microT-CDS algorithm or even experimentally validated miRNA interactions derived from DIANA-TarBase. Using this analysis the user will achieve schematics pathways marking the proteins that can be affected by the selected miRNA
miRTrail	http://mirtrail.bioinf.uni-sb.de	miRTrail allows to do an analysis for potential relationships between a set of miRNAs and a set of mRNAs, the miRNA and mRNA information must be uploaded. At the moment, miRTrail supports miRBase identifiers for miRNAs and GeneSymbol identifiers for the mRNAs
CoMeTa	http://cometa.tigem.it/index.php	CoMeTa allows the Co-expression and Meta-analysis of miRNA Targets, based on the assumption that the targets of a given miRNA are likely to be co-expressed and therefore to belong to the same miRNA gene network. The CoMeTa tool aims at the inference of miRNA targets and miRNA-regulated gene networks by integrating expression data from hundreds of cellular and tissue conditions
mirTarVis	http://hcil.snu.ac.kr/~rati/miRTarVis/index	miRTarVIs is a visual analysis tool for miRNA–mRNA expression profile data, the tool is downloadable to a personal computer with all the database, making the analysis available without an internet connection

(continued)

Table 1 (continued)

Name	Web site	Observations
miRNet	http://www.mirnet.ca	miRNet is a tool with comprehensive support for statistical analysis and functional interpretation of data generated in miRNAs studies Able to support several inputs and statistics, comprehensive functional annotations, creating miRNA–Target interaction networks (miRNA-gene, miRNA-disease, miRNA-small molecule, miRNA-lncRNA, miRNA-epigenetic modifier)
Mirin	http://mirin.ym.edu.tw	Mirin is an online tool for identification of microRNA-mediated module which is formed by protein–protein interactions (PPIs). Mirin integrates microRNA regulations and PPIs with microRNA/mRNA expression data to identify the perturbed microRNA regulatory modules and reveals their functional roles in specific biological conditions
MAGIA (miRNA and genes integrated analysis)	http://gencomp.bio.unipd.it/magia	Magia tool is able to do miRNA target predictions and analysis of miRNA and gene expression profiles by a combination of expression profiles and statistical measures
miEAA (miRNA enrichment analysis and annotation)	http://www.ccb.uni-saarland.de/mieaa_tool	This tool (miEAA) facilitates the functional analysis of sets of miRNAs. It is based on GeneTrail, which is an enrichment analysis tool for gene sets
miRSystem	http://mirsystem.cgm.ntu.edu.tw	miRSystem is a database which integrates seven well-known miRNA target gene prediction programs: DIANA, miRanda, miRBridge, PicTar, PITA, rna22, and TargetScan, supporting only *Homo sapiens* and *Mus musculus* miRNAs
CORNA	http://corna.sf.net	CORNA is a tool written in R, which allows users to test for over-representation of microRNA-target associations using one of three separate statistical tests

(continued)

Table 1 (continued)

Name	Web site	Observations
MMIA (miRNA and mRNA integrated analysis)	http://epigenomics.snu.ac.kr/MMIA/mmia_main.html	MMIA integrates microRNA and mRNA expression data with predicted microRNA target information for analyzing microRNA-associated phenotypes and biological functions by Gene Set Enrichment Analysis (GSEA). To assign biological relevance to the integrated microRNA/mRNA profiles, MMIA uses exhaustive human genome coverage (5782 gene sets), including various disease-associated genes as well as conventional canonical pathways and Gene Ontology
FAME (functional assignment of miRNAs by enrichment)	http://acgt.cs.tau.ac.il/fame	FAME is a tool that uses computational target predictions in order to infer the processes affected by human miRNAs. The approach improves upon standard statistical tools by addressing specific characteristics of miRNA regulation
miSEA (miRNA set enrichment analysis)	http://www.baskent.edu.tr/~hogul/misea	miSEA, which evaluates the enrichment of predefined sets in a microRNA expression profiling experiment with two biological conditions, e.g. control vs. treatment. miSEA allows users to select amongst a large set of microRNA grouping categories, such as family classification, disease association, and genome coordinate

conserved binding sites also mediate repression in translation, so new algorithms should incorporate non-conserved binding sites to avoid false negatives predicted results. In the *level 4*, it is needed to co-relate the gene and the miRNA expression data. Those pathways should be regulated directly by the miRNA according to the results obtained in the first three levels. Bioinformatics tools as Central Pathway or Cytoscape could be used for this propose. In the *level 5* it should be proved the association of miRNA with the identified pathway experimentally and preferably in a tissue specific manner in concordance with the settled in level 1 [30].

2 MiRNAs in Cancer

As it has been discussed, miRNAs play a main role in gene expression control at post-transcriptional level, when the miRNAs are deregulated several kinds of pathological diseases can occur, one of the diseases with a main interest in the

study for miRNAs is the cancer. Key processes in cancer biology are related to the "hallmarks of Cancer" (HC). The HC comprise six biological capabilities acquired during the multi-step development of human tumors, and constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferate signaling, evading growth suppressors, resisting cell death, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks is genome instability, which generates the genetic diversity that expedites their acquisition, evasion of the immune system, deregulation of energy metabolism and inflammation, which fosters multiple hallmark functions [31].

Apoptosis plays a significant role in both animal development and disease, the deregulation of this process has been invariably linked to the progression of various neoplastic processes. miRNAs that regulate apoptosis, termed apoptomiRs, can be either pro- or antiapoptotic [32]. The first miRNA described as a regulator of apoptosis was the Drosophila bantam gene, which directly suppressed the proapoptotic factor hid, thus facilitating proliferation [33, 34]. Several miRNAs that play a role in modulating apoptosis have also been linked to the initiation and progression of various neoplastic processes. Approximately 50% of miRNAs are located at genomic sites that are disrupted or amplified in various cancers [35]. The first evidence of miRNAs playing a role in cancer development came to light in 2002 in a study [36] that attempted to find tumor suppressor genes at chromosome 13q14, which is frequently deleted in chronic lymphocytic leukemia (CLL) [37]. CLL is characterized by the presence of substantial increased numbers of predominantly non-dividing malignant B cells over-expressing the antiapoptotic B-cell lymphoma 2 (Bcl2) protein. In patients with CLL, the tumor suppressor locus on chromosome 13q14 was found to be frequently altered. However, instead of coding for a tumor suppressor protein, this region contained two miRNA genes, miR-15a and miR-16-1, which are overexpressed, regulating negatively the antiapoptotic *bcl2* gene at posttranscriptional level. Later, many miRNAs with tumor suppressor roles were identified. The miR-34 family, for example, has been shown to exert significant tumor suppressor capabilities. Up-regulation of p53 (a potent tumor suppressor/cell cycle regulator) caused increased miR-34 expression that resulted in G1 arrest in a complementary and parallel fashion to mRNAs that are directly activated by P53 [35, 38]. Also, miR-34 was shown to inhibit the silent mating information regulator 1 (SIRT1) gene resulting in the upregulation of P53, P21, and PUMA (P53-upregulated modulator of apoptosis), thus regulating cell cycle and apoptosis and functioning as a tumor suppressor by modulating the SIRT1-P53 pathway [39]. Furthermore, miR-34 has mediated growth arrest via direct regulation of cell cycle regulatory factors, such as cyclin E2 (CCNE2), cyclin-dependent kinase 4 (CDK4), the transcription factor E2F3, and the hepatocyte growth factor receptor (c-MET), ultimately leading to increased caspase-dependent cell death [34]. In a separate study, miR-34 inhibited the proliferation/growth of human pancreatic tumor–initiating cells, and its overexpression in P53-deficient human pancreatic cancer cells partially restored the tumor-suppressing function of P53 [68]. MCL-1, a member of the BCL-2 family, was also demonstrated to be posttranscriptionally

regulated by miR-29a, b, and c [40, 41]. Forced expression of miR-29b to induce tumor cell apoptosis by reducing MCL-1 expression may represent a novel intervention for cancer therapy. Along similar lines, let-7a exerts tumor suppressor functions by directly targeting the expression of *ras* and *hmga2*, 2 widely recognized oncogenes [42, 43]. Other examples of tumor suppressor miRNAs include miR-7, miR-124, miR-137, miR-146b, miR-15b, miR-128, and miR-326. Furthermore, knockdown of mature miRNAs by selectively targeting *dicer1*, *rnasen*, and its cofactor dgcr8 increased the oncogenic potential of transformed cell lines, resulting in the accelerated tumor formation in mouse models of K-RAS-driven lung cancer and Rb-driven retinoblastoma [44–47].

MiRNAs can also promote tumor development (oncomiRs) depending on the functions of the target protein(s) they regulate. These oncogenic miRNAs include miR-155 and the miR-17-92 cluster that accelerates the tumor development in B-cell lymphomas [48, 49]. Ectopic expression of miR-155 in transgenic mice resulted in pre-B-cell expansion, splenomegaly, and lymphopenia that preceded the development of lymphoblastic leukemia and lymphoma [50]. Now it is known that mir-155 plays a critical role in the development of lymphomas, the components of its regulatory pathways upstream and downstream of the targets remain unclear. It is interesting to note that even before the discovery of miRNAs in mammalian cells, Tam et al. [54] had reported that "bic" locus, the common retroviral integration site for the avian leukosis virus, generated a non-coding RNA. Later, after the discovery of miRNAs, it was found that this transcript harbored the mature miR-155 coding sequence, thus offering a potential explanation for the function of bic [55]. Members of the mir-17-92 cluster are potent activators of cell proliferation and are frequently overexpressed in several neoplasms, including lymphoma, multiple myeloma, medulloblastoma, and cancers of the lung, colon, breast, and prostate [44]. miR-21 is another commonly upregulated miRNA in cancers that include glioblastoma, lymphomas, and cancers of the breast, ovary, colon, rectum, pancreas, lung, liver, gallbladder, prostate, stomach, thyroid, and cervix [44, 51]. Increased expression of miR-21 was found in glioblastoma tumors and cell lines, and its inhibition resulted in increased cell death, suggesting that miR-21 could play the role of an oncogene that inhibited cell death in these tumors [85]. For example, in prostate cancer it has been found that miR21 controls the expression of many mRNA targets related to micro-vascular proliferation and tumor invasiveness, correlating with weak biochemical recurrence-free survival having a predictive value for biochemical recurrence risk in prostate cancer patients after radical prostatectomy [68], and also correlating with castration resistance and metastatic disease. Furthermore, in glioblastoma cells, knockdown of miR-21 induced the activation of caspase-3, transforming growth factor-β, P53, and mitochondrial apoptotic pathways mainly through upregulation of its validated targets, heterogeneous nuclear ribonucleoprotein K, P53-related TAP63, and PDCD4, acting in synergy with the aforementioned proteins [51–53].

3 miRNAs in Prostate Cancer

Prostate cancer is the second place occurring cancer in men worldwide and the first place in mortality [54]. Prostate cancer (PCa) occurrence and mortality are up to 20-fold higher in developed countries with respect to emerging ones, diet and lifestyle have been proposed as factors causing this discrepancy, both modify serum factors that slow down the growth and induce apoptosis in androgen-dependent PCa cells, while high body mass index, blood pressure, and several metabolic factors were correlated with high risk of prostate cancer death [54]. Mortality rates are clearly differentiated by ethnicity. Caribbean hold the highest rates in the world (26.3%), following sub-Saharan Africans (10%) and, at last, the Asians show the lowest (2.5%). In the United States of America it was found that the risk of developing prostate cancer is highest in African Americans, in compared to other populations [55].

As it was discussed above miRNAs are deregulated in several disorders also in cancer. Deregulation can increase or decrease their concentration into the affected cell, and according to their function in normal concentrations miRNAs can be classified as oncogenic miRNAs (oncomiR) and tumor suppressor miRNAs. It has been reported several miRNAs with their respective functions in prostate cancer (Table 2).

4 Circulating miRNAs as Possible Biomarkers in Prostate Cancer

Prostate cancer can be clinically diagnosed as local or advanced and different treatments including observation, radiotherapy, radical prostatectomy, and androgen-deprivation treatment are expected [56–59].

The main screening exams to diagnose prostate cancer include digital rectal exam (DRE), serum level of prostate-specific antigen (PSA), and transrectal ultrasound guided biopsy. A suspected DRE alone reveals prostate cancer, regardless of normal PSA level (in about 18% of all patients; moreover, a suspected digital rectal exam has a positive predictive value of 5–30% in patients who have a PSA level up to 2 ng/mL). Nowadays, PSA assessment is the most usual marker able to correlate with prostate cancer risk, aggressiveness, and outcome in order to detect prostate cancer [60]. Nevertheless, it has been found that several patients develop prostate cancer in spite of low PSA levels though a higher PSA level shows the presence of prostate cancer [61, 62]. High PSA levels could be the result of several factors as well as benign prostatic hyperplasia, gland inflammation, prostatitis, infection, and some drugs [63–66]. PSA screening is usually associated with over-diagnosis, although it has decreased the death rate of prostate cancer [67]. For this reason, efforts to find new biomarkers that enhance the accuracy of screening should be continued.

Table 2 List of miRNAs founded in prostate cancer cell lines and prostate cancer tissue

Oncogenic miRNAs	Function	Tumor suppressor miRNAs	Function
miR-221/ miR-222	Enhances cell proliferation, invasion, cell survival, increases clonogenicity and enhances tumorigenicity in vivo	miR-34a	Induces cell–cycle arrest, cell senescence, and apoptosis and inhibits cell proliferation and cell invasion
miR-375	Promotes early diagnosis	miR-145	Inhibits invasion, migration and arrests cell cycle
miR-18a	Promotes cancer progression	miR-224	Inhibits invasion and migration of PCa cells
miR-4534	Induces pro-cancerous characteristics in non-cancer cell line	miR-452	Regulates cell cycle, cellular adhesion, and motility
miR-650	Suppresses the cellular stress response1 (CSR1) expression	miR-200b	Inhibits PCa cell growth and invasion
miR-32	Inhibits apoptosis and enhances proliferation	miR-382	Inhibits PCa cell proliferation, migration, invasion, and metastasis
miR-106/ miR-25	Facilitates the tumor progression	miR-372	Inhibits proliferation, migration, and invasion of DU145 cells
miR-125b	Enhances cell proliferation and inhibits apoptosis	miR-17-92a	Decreases cell cycle regulatory, proteins and the expression of mesenchymal markers
		miR-27a	Suppresses MAP2K4 in PCa cell
		has-miR-135-a-1	Inhibits cell growth, cell cycle progression, migration, invasion, and xenograft tumor formation
		miR-204-5p	Promotes apoptosis by targeting BCL2 in PCa cell
		miR-30a	Reduces expression of cell cycle protein, cyclin E2
		let-7	Regulates cell cycle, cell
		miR-133/miR-146a	Suppresses tumor progression via targeting EGFR

Circulating miRNas in blood were described by Mitchell et al. [70, 71]. miRNAs are released to the blood stream from the tumoral tissue through several ways, as free miRNAs, into exosomes, into microvesicles, into big oncosomes, joined to apoptotic bodies, associated with high density lipoproteic complexes or joined to proteins. The presence of miRNA in the extracellular environment ignited the hypotheses that cells selectively release miRNAs which mediate cell–cell signaling via paracrine

or even endocrine routes [78–80]. Some research groups have demonstrated that extracellular miRNAs entrapped within apoptotic bodies and exosomes can be transferred to recipient cells, alter gene expression, and mediate functional effects [78, 81–85]. Patterns of mRNAs in exosomes and their donor cells correlate poorly, suggesting specific sorting of miRNA "for export" [78, 84–86]. The mechanism behind this sorting needs to be investigated in more detail.

The miRNAs released in the bloodstream are protected against degradation and readily detectable by PCR methods; mainly in cancer specific miRNAs levels have been used to correlate disease status, stage, aggressiveness, and response to therapy performing the miRNA profiling in plasma or serum. In the case of prostate cancer, cell-free miRNAs levels are able to differentiate between localized and metastatic prostate cancer or correlate with the risk score or Gleason grade, associating miRNAs with aggressiveness or indolent disease and may aid in tumor staging and treatment decisions at the time of diagnosis [72–75].

Agalogu et al. [69] assessed serum levels of three miRNAs in 51 patients with prostate cancer (subdivided into localized/locally advanced and metastatic) and 20 healthy controls. They identified increased levels of miR-21 and miR-221 in the prostate cancer group as a whole compared to the controls. miR-141 was not significantly elevated in the group as a whole, but when the metastatic group was considered in isolation, all three miRNAs were significantly elevated, with mir-141 being the most elevated of the three.

Lodes et al. [70] analyzed sera from patients with a number of malignancies using a micro-array hybridization technique, identifying 15 upregulated miRNAs in the sera of prostate cancer patients vs. healthy controls (miR-16, -92a, -103, -107, -197, -34b, -328, -485-3p, -486-5p, -92b, -574-3p, -636, -640, -766, -885-5p). This study did not confirm the finding of increased miR-141 expression; however, the group of prostate cancer patients was small ($n = 6$). Additionally, no qRT-PCR confirmation of the micro-array results was performed.

Several miRNAs have been found over-expressed in plasma/serum of patients with prostate cancer, some of them as miR-21, and miR-141 were validated about the cellular function respect prostate cancer context following the five levels assessment. Some studies [70, 76, 77] have reported an over-expression of the miRNA-107, which is encoded at 10p23.11, this miRNA has a fold change around 10; a study in a court of thirty-eight prostate cancer patients at different clinical stages (from I to IV) revealed that miR-107 is over-expressed at each clinical stage of prostate cancer relative to the control group (Fig. 2), there was not significative difference between media value at each clinical stage of cancer (*t*-test), however there is a shape showing an increasing of relative expression for miR-107 related to the clinical stage of cancer.

It should be necessary to increase the size of the assessed groups to find a clear correlation between the clinical stage of prostate cancer and the relative expression of miR-107.

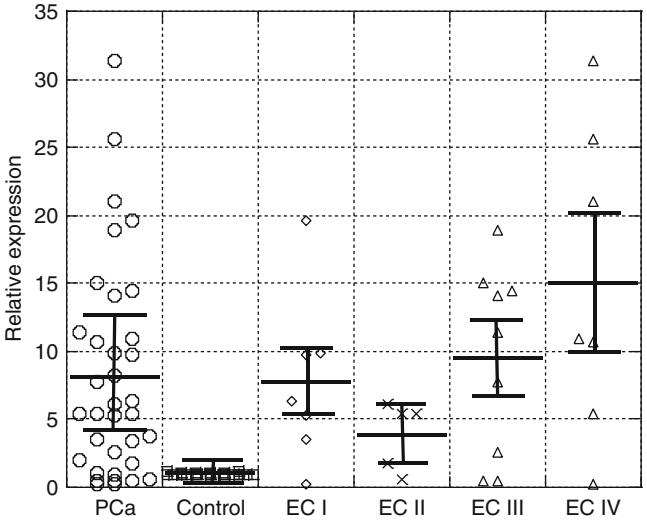

Fig. 2 Relative expression of miRNA-107 in plasma of patients with conformed PCa, diagnosis, PCa column shows the relative expression of all patients that participate in the study, EC I, II, III, and IV are the patients classified by cancer clinical stage

5 Conclusion

MicroRNAs are small biomolecules with a great number of possible targets in the cellular functions, when those are deregulated several diseases can occur, one of the most studied is cancer, miRNAs can be relevant as therapeutic targets or biomarkers, in prostate cancer there are several miRNAs that have been validated as oncogenic miRNAs and tumor suppressor miRNAs, some of the over-expressed miRNAs in plasma/serum of patients with prostate cancer have been proposed as possible biomarkers of the disease as miR-21 and miR-141, recently miR107 has been relevant by their high relative over-expression in plasma/serum, it has been tested in a cohort of patients with prostate cancer at different clinical stages showing that it is possible to find a correlation between their relative expression in plasma and the clinical stage of cancer. It makes necessary to increase the efforts to find either miRNAs functions in prostate cancer or possible new biomarkers to shelter the current prostatic specific antigen test.

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