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Mini-review

MicroRNAs in prostate cancer: Functional role as biomarkers

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ABSTRACT

MicroRNAs (miRNAs) are small endogenous non-coding molecules that alters gene expression through post-transcriptional regulation of messenger RNA. Compelling evidence suggest the role of miRNA in cancer biology having potential as diagnostic, prognostic and predictive biomarkers. This review summarizes the current knowledge on miRNA deregulated in prostate cancer and their role as oncogene, tumor suppressor and metastasis regulators. The emerging information elucidating the biological function of miRNA is promising and may lead to their potential usefulness as diagnostic/prognostic markers and development as effective therapeutic tools for management of prostate cancer.

Introduction

Prostate cancer is the most commonly diagnosed cancer among men and the third leading cause of cancer-related deaths in the United States [1]. Prostate cancer is primarily a disease of aging males as approximately three-quarters of the cases reported worldwide in men aged 65 years and older [2]. Despite the initial success of surgery and radiation therapy for localized prostate cancer, >30% patients experience biochemical recurrence and emergence of advance-stage disease particularly, metastatic progression. The metastatic form usually responds to androgen deprivation therapy widely used as a mainstay. The disease further progresses to castration-resistant prostate cancer (CRPC) in about 12 months after androgen-deprivation therapy. New agents for hormonal therapy *viz.* abiraterone (CYP-17A inhibitor) and enzalutamide (second-generation antiandrogen) have been developed to treat CRPC, and cabazitaxel (second-generation chemotherapy) for patients who relapse to docetaxel [3,4]. However, the effects of these new therapies are limited, and patients rapidly progress to the incurable stage prostate cancer with overall survival increasing only 3–4 months [4]. Despite the significant advances in research, the establishment of new biomarkers with high accuracy and specificity that can predict tumor aggressiveness and disease prognosis in patient's remains problematic [5,6] Due to the molecular heterogeneity of prostate cancer, identification and clinical translation of routinely tested disease- and stage-specific

Abbreviations: AR, androgen receptor; ARHI, Ras homolog member I; BCR, biochemical recurrence; BPH, benign prostatic hyperplasia; BTG-2, B-cell translocation gene 2; CDK, cyclin-dependent kinase; CRPC, castration-resistant prostate cancer; DNMT1, DNA methyltransferase 1; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; GSTP1, glutathione-S-transferase-pi; IGF1R, insulin-like growth factor 1 receptor; IL6, interleukin 6; IMP-1, insulin-like growth factor mRNA binding protein 1; LASP1, LIM and SH3 Protein 1; lncRNAs, long non-coding RNAs; MDR1, multidrug resistance-1; MIEN1, Migration and invasion enhancer 1; miRNA, microRNA; MMP, matrix metalloproteinase; ncRNAs, Non-codingRNAs; NF-κB, Nuclear Factor-kappaB; PDCD4, programmed cell death; PI3K, phosphatidylinositol 3-kinase; PIK3IP1, phosphoinositide-3-kinase interacting protein 1; PIN1, Peptidyl-prolyl *cis*-trans isomerase NIMA-interacting 1; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog; RECK, Reversion Inducing Cysteine Rich Protein With Kazal Motifs; ROCK, Rho-associated protein kinase; Skp2, S-phase kinase-associated protein 2; STK4, Serine/threonine-protein kinase 4; ZEB, zinc-finger E-box binding homeobox.

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biomarkers is a rational approach to expedite prostate cancer diagnosis, prognosis, and treatment response, paving the path to precision medicine [7]. It is expected that comprehensive exploration of microRNAs (miRNAs) associated with prostate cancer development and progression will help our understanding of the molecular basis of pathogenesis which is likely to provide tools for early diagnosis and prognosis as well as additional therapeutic targets for suppressing the aggressiveness of malignant cells [8,9].

MicroRNAs in cancer

MicroRNA play important roles in either the prevention or development of cancer, as some miRNA may promote tumorigenesis and are termed as 'Oncomirs'. Similarly, miRNAs also function as a tumor suppressors which usually counteracts tumor initiation and/or its development [10,11]. Dysregulation of miRNAs in cancer may occur through epigenetic changes, commonly through promoter CpG island hypermethylation and genetic alterations [12,13]. MicroRNA biogenesis machinery may cause dysfunction, subsequently affecting the transcription of primary miRNA; it's processing to mature miRNAs and interactions with mRNA targets [7]. Each miRNA has the potential to target the expression of several genes regulating cellular pathways. Hence alteration in the expression of a few miRNAs is likely to amplify dysregulation of a broad range of cellular processes potentially promoting neoplasia [14,15]. Additionally, owing to the complexity of regulation of miRNA, each miRNA can potentially posttranscriptionally modulate the expression of multiple mRNAs affecting various target genes. Furthermore, several different miRNAs can target the expression of a single mRNA [16,17]. Numerous studies demonstrate that genomic rearrangements, hypermethylation of promoters, or transcriptional deregulation mechanisms can alter the differential expression of miRNAs potentially initiating neoplastic progression [18].

Functional consequences of miRNA dysregulation in prostate cancer

Earlier work on miRNAs in reference to prostate cancer were studied with the purpose to determine their deregulation during tumor progression [19]. Since then, several miRNA profiles have been generated in prostate cancer [20,21]. Differential expression of miRNAs in prostate cancer has potential to distinguish benign from the malignant disease. Moreover, miRNA comparative signatures have the capability to identify indolent versus aggressive disease supporting the role of miRNAs as diagnostic and prognostic biomarkers in prostate cancer [6]. A broad range of cellular processes and cell signaling pathways have been implicated in both, castration-sensitive and castration-resistant prostate cancer. The cellular pathways include but are not limited to cell cycle progression, cell proliferation, cell death, epithelial-mesenchymal transition (EMT), angiogenesis, tumor cell metabolism and metastasis [22–24]. Since miRNA fine-tune the posttranscriptional regulation of genes encompassing these pathways, differential expression of miRNAs during the process of neoplasia appears to promote and coordinate the expression of various hallmark characteristics of the cancer cell [25]. Therefore, understanding the variation in expression patterns and determining their functional role at onset and during cancer progression are likely to yield novel diagnostic and prognostic biomarkers which can aid the therapeutic regimen of prostate cancer. In particular, the regulation of miRNAs by the androgen receptor signaling pathway as well as their posttranscriptional regulation in prostate cancer is of interest in the development of CRPC and its therapeutic options [26]. Additionally, miRNA-mediated regulation of critical signaling pathways implicated in prostate cancer such as cell cycle progression, phosphatidylinositol 3-kinase (PI3K)/AKT, and EMT has also been elucidated [27–33]. However, the complexity of miRNAs function in cancer development both in general and specifically in prostate cancer remains unclear. In this review article, we have attempted to provide an overview of most miRNAs which are studied in-relation to prostate cancer. We searched all available data from National Center for Biotechnology Information PubMed database up to July 20, 2017 (last updated), limited in the title and abstract, using the following search queries and/or combining the following terms: miRNA, cancer, prostate cancer, prognosis, diagnosis, and therapeutic response. A list of records involving human subjects and studies involving animals and cell culture were assessed for eligibility and standard level of evidence.

Oncogenic miRNAs

Overexpressed miRNAs in cancer can negatively regulate tumor suppressor genes and/or genes that control apoptosis or cell differentiation are referred as 'oncogenic miRNAs' or 'Oncomirs' [11]. Oncogenic miRNAs can be used as prognostic markers as they are commonly upregulated in prostate cancer [34]. The most common overexpressed miRNAs in prostate cancer are miR-21, miR-32, miR-221, miR-222, miR-181, miR-18a, and miR-429 [6,35–50]. These miRNA are further discussed and are critical in regulating pathways such as PI3K/AKT, EMT, cell proliferation, apoptosis and AR expression [37–45]. A list of miRNA with oncogenic role in prostate cancer is shown in Table 1.

Androgen-regulated oncogenic miRNAs

There are several oncogenic miRNAs expressed in prostate cancer which are androgen regulated including miR-21 and miR-32 [42]. miR-21 is one of the most commonly implicated miRNAs in cancer [6]. Its expression is upregulated in several types of solid tumors, including prostate cancer. In prostate cancer, miR-21 is critical in tumorigenesis and invasiveness by targeting the Reversion Inducing Cysteine Rich Protein with Kazal Motifs (RECK) gene. In human prostate cancer DU145 cells, miR-21 directly inhibits RECK; a putative tumor suppressor gene which appears to control the expression of matrix metalloproteinase 9 (MMP9), and promotes cancer invasion and metastasis [35,36]. Furthermore, miR-21 directly targets and downregulates tumor suppressor genes including phosphatase and tensin homolog (PTEN) and programmed cell death (PDCD4) [37,38]. In prostate cancer, miR-21 appears to be the direct transcriptional target of the androgen receptor (AR) resulting in the upregulation of miR-21 facilitating castration-resistance phenotype [39]. Clinically, miR-21 is a useful prognostic marker for biochemical recurrence and is associated with prostate cancer relapse after radical prostatectomy [40,41]. In a cohort of radical prostatectomy samples, high levels of miR-21 were found to be significantly associated with the advanced pathological stage, the presence of lymph node metastasis and poor patient outcome. Multivariate analysis indicated miR-21 expression as an independent predictor of 5-year biochemical recurrence. Overall, the overexpression of miR-21 downregulates essential tumor suppressor genes which promote tumor progression [40].

miR-32 is another miRNA that is androgen-regulated through DHT stimulation and highly expressed in CRPC specimens compared to benign prostatic specimens. miR-32 exerts oncogenic characteristics by targeting both B-cell translocation gene 2 (BTG-2) and phosphoinositide-3-kinase interacting protein 1 (PIK3IP1). BTG-2 and PIK3IP1 regulate anti-proliferation and the inhibition of PI3K, a well-known regulator of cell proliferation, migration and survival respectively [42]. Expressions of miR-32 and BTG-2 in CRPC tumors appeared to have and inverse correlation. Data