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Identification of candidate miRNAs in early-onset and late-onset prostate cancer by network analysis

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The incidence of patients under 55 years old diagnosed with Prostate Cancer (EO-PCa) has increased during recent years. The molecular biology of PCa cancer in this group of patients remains unclear. Here, we applied weighted gene coexpression network analysis of the expression of miRNAs from 24 EO-PCa patients (38–45 years) and 25 late-onset PCa patients (LO-PCa, 71–74 years) to identify key miRNAs in EO-PCa patients. In total, 69 differentially expressed miRNAs were identified. Specifically, 26 and 14 miRNAs were exclusively deregulated in young and elderly patients, respectively, and 29 miRNAs were shared. We identified 20 hub miRNAs for the network built for EO-PCa. Six of these hub miRNAs exhibited prognostic significance in relapse-free or overall survival. Additionally, two of the hub miRNAs were coexpressed with mRNAs of genes previously identified as deregulated in EO-PCa and in the most aggressive forms of PCa in African-American patients compared with Caucasian patients. These genes are involved in activation of immune response pathways, increased rates of metastasis and poor prognosis in PCa patients. In conclusion, our analysis identified miRNAs that are potentially important in the molecular pathology of EO-PCa. These genes may serve as biomarkers in EO-PCa and as possible therapeutic targets.

The incidence of patients under 55 years old diagnosed with prostate cancer (PCa) (Early onset, EO-PCa) in the United States has increased during recent years. Between 1986 and 2008, the incidence of EO-PCa was from 5.6 to 32 cases per 100.00 persons years (IC 95% CI 5.0–6.7)[1,2]. In 2012, PCa was diagnosed in 241,740 men (10%) < 55 years old in the United States[3]. Thus, PCa in young patients is an emerging issue for public health[1,2]. Interest in understanding the molecular and clinical behavior of EO-PCa has been increased[4]. Several risk factors are associated with diagnosis: family's medical background, ethnicity, and genetic factors, such as single nucleotide polymorphisms and mutations in BRCA1, BRCA2, and HOXB13[5,6]. Different single nucleotide polymorphisms in germinal DNA[7] and rearranged genes in the androgen receptor axis (e.g., TMPRSS2-ERG, PTEN, and AR) have been identified EO-PCa[8]. Additionally, abnormal expression of genes involved in inflammatory and antitumoral immune-related pathways (CTL4, IDO1/TDO2) was detected[9]. A recent analysis of 1281 EO-PCa cases (≤ 60 years) identified 23 unique DNA repair genes associated with an increased predisposition or risk of aggressive PCa disease, and four genes (BRCA2, MSH2, ERCC2, and CHEK2_non1100del) were associated with more aggressive disease[10]. Other recent studies identified four molecular subgroups that included a particularly aggressive subgroup with recurrent duplications (8q22) associated with increased ESRP1 expression[11].

MicroRNAs (miRNAs) are small (~ 20–22 nucleotides), noncoding RNA molecules that are well conserved among different species of organisms and play multiple roles in several biological processes. miRNAs can interact with the RNAm of their target gene to exert its biological regulatory effect on gene expression by inhibiting the translation process[12]. This effect is achieved by binding to the cognate sequence 3′ UTR of RNAm to promote its degradation or inhibit the translation process[13]. Transcription activation is a non-canonical mechanism of miRNA action that was recently described[14]. In addition, miRNAs regulate expression of up to 30% of human

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