Editorial

New insights into human testicular germ cell tumors: miR-223-3p gains oncogene function

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Testicular germ cell tumors (TGCTs) are the most common malignancy in young males and represent the major cause of cancer death in 15 to 34 years old males. The majority of TGCTs originate from germ cells and are classified into seminoma and non-seminoma germ cell tumors (NSGCTs). Tumors with different cell components, *e.g.*, seminoma and embryonic cell carcinoma, are generally indicated as mixed germ cell tumors.

In the last four decades, the incidence of TGCT doubled. The risk factors for TGCTs remain undefined and the molecular mechanisms underlying the onset, development and progression of TGCT have not yet been deeply explained. Despite the efficacy of primary therapy, a subset of patients develops resistance to the drugs used for the disease treatment resulting in reduced survival (1). Therefore it is crucial to identify the molecular events in TGCT carcinogenesis and to identify genes that are related to TGCT pathogenesis. On this basis, researchers could uncover new therapeutic targets and alternative adjuvant therapies aimed to limit relapses and prevent drug resistance. MicroRNAs (miRNAs) are small endogenous non-coding RNAs of approximately 20 nucleotides in length that regulate gene expression at post-transcriptional level through their binding to the 3'-untranslated region of target mRNA. miRNAs control several biological processes such as cell proliferation, differentiation, motility and apoptosis (2). miRNAs expression is dysregulated in cancer cells as a result of several mechanisms; miRNAs up-regulated in cancer cells commonly act as oncogene silencing tumor suppressor genes. Conversely, some miRNAs, which are often down-regulated, can inhibit tumor progression and are termed tumor suppressor miRNAs. miRNAs acting as oncogene or tumor suppressor control cancer cell behaviors. Gain-of-function approaches have shown that miRNAs acting as tumor suppressors target oncoproteins with crucial roles in various cancer pathways. For example, in chronic lymphocytic leukemia miR-15/miR-16 expression is frequently lost in cancer cells, because these miRNAs directly interact with bcl-2 mRNA inhibiting protein translation and, consequently, apoptosis of leukemic cells (2). *Vice versa*, to assess the biological effects of oncogenic miRNAs, often overexpressed in cancer cells, *in vitro* silencing was carried out using antisense oligonucleotides. For example, high expression levels of miR-21 have been observed in breast, pancreas, colon cancer and glioblastomas (2). Chan and colleagues, blocking miR-21 expression in glioblastoma cell lines, observed an increased activation of caspases and apoptosis (3). On the basis of this evidence, miRNAs became attractive candidates for cancer therapy (4,5).

In TGCT many miRNAs are dysregulated but to date only for few of them the function has been characterized. On this basis, new efforts are essential to disclose their role. Liu *et al.*, using a deep sequencing approach, discovered that miR-223-3p was over-expressed in TGCTs patients if compared to normal testicular tissue (6). Recently, altered expression of miR-223-3p has been reported in a number of cancer types. miR-223-3p acts either as an oncogene or a tumor suppressor, regulating multiple targets in different cancer types. miR-223-3p expression is frequently reduced

in prostate cancer (PCa) tissue compared to normal tissues, where miR-223-3p acts as a tumor suppressor inhibiting cancer cell migration and invasion (7,8). On the contrary, in oral squamous cell carcinoma high levels of miR-223-3p was associated with advanced tumor stage and size (9). miR-223-3p is also involved in T-cell leukemogenesis and lymphogenesis, where it might function as an oncogene (10). Again, miR-223-3p is most significantly up-regulated in gastric cancer cells compared with parental cells and controls the response to therapeutic drugs, promoting cisplatin resistance (11).

Similarly to TGCT, in gastric cancer cells, F-box/WD repeat-containing protein (FBXW7) was identified as the direct and functional target gene of miR-223-3p (11). FBXW7 is the substrate-recognition component of the SCF-(SKP1, CUL1, F-box protein)-ubiquitin-ligase complex. FBXW7 is an E3 ubiquitin ligase acting as a tumor suppressor by promoting the degradation of several oncoproteins, including c-Myc, cyclin E, MCL-1, c-JUN, NFκB2 and Notch1 (12). However, whether the expression of miR-223-3p was altered in TGCT and what was its potential function in TGCT was unknown. To disclose the role of miR-223-3p, Liu *et al.* investigated the expression of miR-223-3p and FBXW7 in TGCT clinical samples and cell lines by qRT-PCR and Western blot analysis. Their finding revealed an inverse correlation between the expression levels of miR-223-3p and FBXW7: clinical samples and cancer cell lines showed higher miR-223-3p and lower FBXW7 expression levels than control normal testicular tissue. Using different approaches Liu *et al.* clearly demonstrated that miR-223-3p regulates cell growth and apoptosis through FBXW7. miR-223-3p suppresses FBXW7 expression and promotes tumor development and progression. In addition, forced expression of FBXW7 protein impedes the anti-apoptotic and proliferative effect of miR-223-3p overexpression in cancer cells.

The miRNAs released from cancer cells and detected in many body fluids such as blood, urine and tears are novel non-invasive biomarkers (13,14). The miRNAs have a great potential as new diagnosis biomarkers because are early detectable. This characteristic is extremely important because patients' survival and prognosis is related to the stage of the tumor at the time of detection, and an early diagnosis is usually associated with the best prognosis. The circulating miRNAs are also valid tools for prognosis and in monitoring treatment response (2). Recently, several groups have reported success in using miRNAs as prognostic markers to predict cancer outcome. It could be speculated that miRNAs might also be able to predict response to specific therapies, suggesting their promising potential as therapeutic adjuvant (2). This hypothesis mostly derives from *in vitro* studies of gain- or loss-of-function, where candidate miRNAs are initially identified in tumor cell lines with different degrees of resistance to specific therapeutic drugs and then targeted in order to overcome drug resistance (2).

The study of Liu *et al.* provides additional evidence of miRNAs function in testicular germ cell tumorigenesis. These findings add new important insights into the knowledge of molecular alterations in TGCT. The deep understanding of tumor suppressor genes and oncogenes deregulation in TGCT will provide the targets of new diagnostic and therapeutic approaches.

miR-223-3p has been proved to be over-expressed in plasma or serum of patients with pancreatic cancer and esophageal squamous cell carcinoma compared with healthy patients (15,16). We speculate that, in a similar way, TGCT patients could have higher serum levels of miR-223-3p than healthy subjects. So, miR-223-3p could be a promising diagnostic biomarkers for TGCT and may be used for clinical applications in cancer management, not only for diagnosis, but also in evaluating malignant potential or therapeutic efficiency, and in monitoring tumor recurrence and progression.

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Footnote

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