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MicroRNA: Neglected Biomarkers

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Abbreviations: *miR: microRNA*

COMMENT

Urological cancers, mainly prostate, bladder, and kidney tumors, comprise a major category of malignancies with significant morbidity and mortality. After early diagnosis, a curative treatment can be achieved frequently by surgical resection. However, the lack of specific symptoms in early stages of these cancers as well as a complex distinction of benign versus malignant types of tumours hinder timely diagnosis.[1] So far, urological cancers lack specific predictive biomarkers and consequently, cancer detection is restricted to pathological diagnosis. Therefore, discovery, development, and evaluation of novel biomarkers allowing early detection of urological tumours will make a significant impact to the field of oncological therapy in urology.

Reviewing the current state of biomarker research, the class of microRNAs (miR) appears as the most likely group of candidate molecules. Recently, almost 60,000 articles have been published dealing with miRs. Besides molecular biology and cell biology, the top 3 research categories by which miR publications were classified have also comprised the field of oncology.[2,3]

miRs are non-coding RNAs of about 22 nucleotides in length that regulate protein expression by targeting the corresponding mRNAs by hybridization and subsequent degradation and/or translational repression. Mature miR binds to complementary sequences mostly located in the 3' untranslated region of the targeted mRNAs. This interaction results in perfect complementary and causes full-length double-stranded miR-mRNA hybrids as well as in imperfect complementary which causes non-hybridized intramolecular loops of single-stranded miR and/or mRNA. As a result, one miR species is able to control the gene expression of hundreds of factors and thus miRs are potent modulators of essential cellular processes including initiation, proliferation, migration, and therapy resistance of cancer cells.[4]

Diagnostic and prognostic implications of miR expression profiles have been discussed in a variety of cancers including urological cancers.[5-7] The translation into clinical use, however, seems to be slow. Besides PCA3, which is not a miR but a small non-coding RNA, and which may serve as proof of principle for non-coding RNA-based diagnostics,[8] no miR biomarkers have been translated into clinical urology yet.

Given the miR's size and intracellular concentration, the first reason may be that detection and quantification of miR is still a challenging task. Detection techniques need to be exceedingly sensitive and selective for the analysis of complex biological samples such as tissue lysates and body fluids. Quantitative RT-PCR, microarray technologies and less frequently Northern blotting are basically used for miR analysis. Recently, some new hybridization techniques have become indispensable tools for miR detection and - combined with new biosensor-based methods - also for miR quantification.[9] These novel techniques combined with improved high-throughput platforms may bring miR biomarkers within reach of routine diagnostic laboratories.

As another important reason, and besides diffuse statistical parameters chosen for statistical testing and insufficient cut-off values for up- and down-regulation of miRs examined, clinical miR screening studies frequently fail to assess the tumor biological significance of potential miR biomarkers. While numerous clinical studies have been performed to uncover numerous differentially expressed miRs in urological tumours, only few of these biomarker candidates have been characterized sufficiently by experimental approaches. Subsequent biological interpretation of biomarker candidates has been typically performed, to a greater or lesser extent, by a comprehensive review of the literature. The pathological role of a miR, however, is mainly defined by miR's tumour biological properties in the given cellular context and is only to a minor degree affected by miR gene expression alterations. Either in case of slight modulated miR expression compared to non-malignant tissue, miR species may harbour an explicit regulatory impact on cancer cell progression. Therefore, experimental studies demonstrating underlying molecular and pathological mechanisms, e. g. cellular factors directly and indirectly targeted by the miR candidate including correlated cell response pathways, will provide important and valuable data and might facilitate miR biomarker's translation into clinical practice.

In conclusion, we have to recognise the need for establishing criteria for future urological biomarker evaluation not only by miR screening studies applying clinical samples, but also by following experimental approaches as an essential second step in a molecular miR biomarker concept.

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