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miR-888: Hit it when you see it!

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Although prostate cancer is a common type of cancer in men, most cases have a good prognosis even when left untreated.[1] However, some cases are aggressive and progress to lethal disease. Prostate-specific antigen (PSA) screening, a blood test routinely used to detect prostate cancer, is insufficiently informative, benefitting only few men and harming many others as a result of unnecessary treatment.[2] Therefore, better biomarkers are needed to distinguish indolent cancers that remain asymptomatic from those that are aggressive and require therapy.

In light of these challenges, Lewis et al. offer a solution: miR-888.[3] By comparing the expression levels of 377 microRNAs (miRNAs) in high-grade and low-grade tumor cells, the researchers arrived at miR-888, which was the most upregulated miRNA in the metastatic subtype and was also more abundant in castration-resistant prostate cancer cells relative to androgen-responsive cells. An analysis of patient samples confirmed its association with the aggressive cancer type: miR-888 expression was higher in prostate tumor samples compared with normal prostate tissue and was higher in metastatic cancers that presented seminal vesicle invasion following prostatectomy, a pathological sign for poor patient outcome. The intriguing feature of miR-888 as a biomarker, however, is the observation that patients with high-grade disease showed increased levels of miR-888 in the expression prostatic secretions (EPS) of the cell-free fraction of the urine. Lack of sample quality, purity, ease of collection, and sensitivity of the diagnostic assay are common reasons why biomarker candidates stall in the transition from discovery to development. Thus, the ability to measure miR-888 expression levels in urine by quantitative PCR may prove a major advantage for miR-888 as an indicator for aggressive disease.

But there is more. The authors showed that introduction of exogenous miR-888 mimics promoted migration, proliferation rates, and colony formation of non-metastatic prostate cancer cells. Conversely, inhibiting endogenous miR-888 decreased migration and proliferation rates of metastatic cells. These results point to an oncogenic role for miR-888 in prostate cancer and suggest that blocking miR-888 could be an effective therapeutic approach. Little is known about the specific molecular functions of miR-888. In non-metastatic prostate cancer cells, exogenous miR-888 induced the repression of retinoblastoma-like protein 1 (RBL1, p107) and SMAD4.[3] These gene products contain putative miR-888 binding sites in the 3′UTRs of their respective mRNAs and encode tumor suppressors that control cell cycle and TGF-β-related pathways. Repression of these and presumably other genes not yet identified is likely to contribute to the oncogenic phenotype of miR-888.

miRNAs are known for regulating multiple molecular pathways at once and for acting as master switches that can quickly change the direction of cellular programs. Some of these small, non-coding RNAs are aberrantly expressed in cancer, and miR-888 appears to be another important candidate in high-grade prostate cancer. This discovery parallels the one of miR-34a, which is expressed at reduced levels in prostate cancer specimens and—in contrast to miR-888—is tumor-suppressive.[4] miR-34a is expressed at even lower levels in prostate cancer stem cells and specifically inhibits this dangerous species of cancer cells when brought back therapeutically. miR-34a performs several other anti-oncogenic functions in addition, such as interference with cancer cell viability, proliferation, and dissemination, which justified the development of a miR-34a-based therapy, MRX34.[5] Currently, MRX34 is the subject of a phase I cancer trial as the first and sole miRNA mimic in the clinic.[6]

The observation that miRNAs can regulate numerous cancer pathways and can be translated into novel therapies continues to raise enthusiasm, as scientists and oncologists search for new agents to fight tumor heterogeneity. In the case of miR-888, an inhibitor will need to be developed. This could be very much a feasible approach and may be similar to that of Miravirsen, a locked nucleic acid-modified DNA phosphorothioate antisense oligonucleotide directed against miR-122 that is in advanced clinical trials to treat hepatitis C virus infections.[7] A motivating value for clinical applications of miR-888 is its simultaneous use as a diagnostic: hit it when you see it—miR-888 might help identify high-grade prostate cancers, treat and monitor the disease. We should stay tuned for more information about this interesting miRNA in pre-clinical animal models of prostate cancer, patients, and perhaps also in other cancer types.

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