

A MicroRNA Signature of Tumor Hypoxia in Prostate Cancer

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MicroRNAs (miRNAs) are short (~22 nucleotide), non-protein coding RNAs that contribute substantially to a broad array of biological processes and are often expressed inappropriately in cancer (Iorio and Croce, 2012). miRNAs misexpressed in cancer can be detected in serum from patients and can potentially serve as biomarkers for minimally invasive cancer diagnosis, particularly for cancers that are difficult to biopsy. Work performed by postdoctoral fellow Dr. Heather Cheng and colleagues in the laboratory of Dr. Muneesh Tewari (Clinical Research, Human Biology, and Public Health Sciences Divisions) and published in *PLOS ONE* (Cheng *et al.*, 2013) suggests that overexpression of the miRNA miR-210 may reflect tumor hypoxia, or low oxygen conditions, in metastatic castration-resistance prostate cancer (mCRPC). "This study raises the possibility that non-invasive blood tests of microRNAs such as miR-210 in patients with mCRPC may give us information about cancer-associated hypoxia, a potential indicator of aggressiveness and treatment resistance of advanced metastatic prostate cancer," says Dr. Cheng.

The authors quantified the levels of 365 miRNAs in serum samples from mCRPC patients and healthy controls using microarray technology. Of the assayed miRNAs, nine were significantly elevated as measured by array, and five validated using real-time PCR. These increases were also validated in an independent set of cases and controls. Importantly, the authors showed that all five of the elevated miRNAs were expressed in laser capture micro-dissected cells from primary prostate cancers and lymph node metastases, providing evidence in support of cancer cells as the origin of these miRNAs in patient serum.

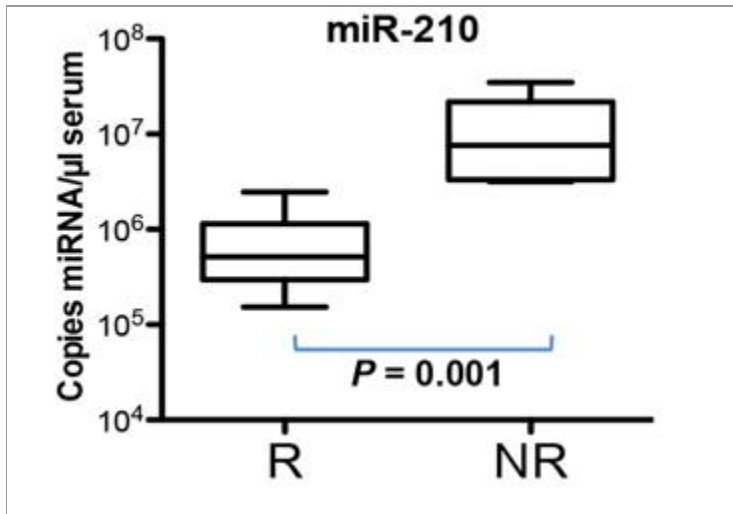
Of particular interest to the authors was the increased serum expression of miR-210 in cancer samples. miR-210 expression is strongly induced in response to hypoxia, and the authors hypothesized that the elevated levels of miR-210 in mCRPC patient serum might be due to the presence of hypoxic cells in the prostate tumor and/or its microenvironment. The authors therefore tested the ability of hypoxia to increase miR-210 expression and secretion in two prostate cancer cell lines. Hypoxic culture of both lines resulted in robust increases in both intracellular and extracellular miR-210 compared to normoxic controls, supporting the idea that increased miR-210 levels in mCRPC patient serum reflect hypoxia.

In addition to promoting cancer progression and metastasis, tumor hypoxia is often associated with resistance to various cancer therapies. To determine whether miR-210 levels were correlated with responsiveness to treatment, the authors calculated the daily change in prostate-specific antigen (PSA), a biomarker used to assess responsiveness to therapy in prostate cancer, based on clinical PSA values taken at the time of serum draw and most recently before serum draw. Patients with decreasing PSA (responsive to treatment) showed much lower levels of miR-210 than those with stable or increasing PSA (resistant to treatment), further supporting the idea that the increased levels of miR-210 in mCRPC patients are due to tumor hypoxia.

The authors suggest that levels of serum miR-210 could be used as a minimally invasive biomarker for the differentiation of mCRPC subtypes. "Serum miRNAs could provide additional information about tumor physiology and biology which could, in turn, help guide decisions about treatments and clinical trials," says Dr. Cheng. In particular, inhibitors of the mammalian target of rapamycin (mTOR) pathway are being studied for prostate cancer therapy, and mTOR inhibition can lead to activation of the HIF-1alpha transcription factor, a key regulator of the transcriptional response to hypoxia. Elevated miR-210 levels could therefore be used as a biomarker indicating which mCRPC patients could benefit most from mTOR inhibition.

[Cheng HH, Mitchell PS, Kroh EM, Dowell AE, Chéry L, Siddiqui J, Nelson PS, Vessella RL, Knudsen BS, Chinnaiyan AM, Pienta KJ, Morrissey C, Tewari M.](#) 2013. Circulating microRNA Profiling Identifies a Subset of Metastatic Prostate Cancer Patients with Evidence of Cancer-Associated Hypoxia. *PLOS ONE* 8(7):e69239.

See also: [Iorio MV, Croce CM.](#) 2013. MicroRNA dysregulation in cancer: diagnostics, monitoring, and therapeutics. A comprehensive review. *EMBO Mol Med* 4(3):143-159.



Modified from the publication

miR-210 levels in the serum of mCRPC patients responsive and non-responsive to treatment.