

WG 5

## Biological effect marker: Circulating nucleic acids in human blood

DiMoPEx



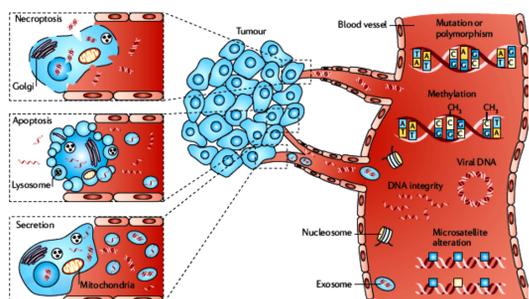
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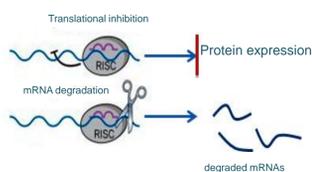
### Introduction

During the growth of a tumor, DNA, mRNA, and microRNAs are released into the blood circulation of cancer patients. Changes in the levels of these circulating nucleic acids are associated with tumor burden and malignant progression. Circulating cell-free nucleic acids may therefore be used as liquid biopsy to predict tumor development.



Due to various physiological events, such as apoptosis and necrosis, nucleic acids from a tumor are released as cell-free molecules into the bloodstream. They are also released by active secretion and then, they circulate in exosomes in the blood. Cell-free and exosomal DNA, RNA and microRNAs can be isolated from plasma or serum, and quantified. Cell-free DNA can be used for screening of mutations, methylation, integrity, and microsatellite alterations.

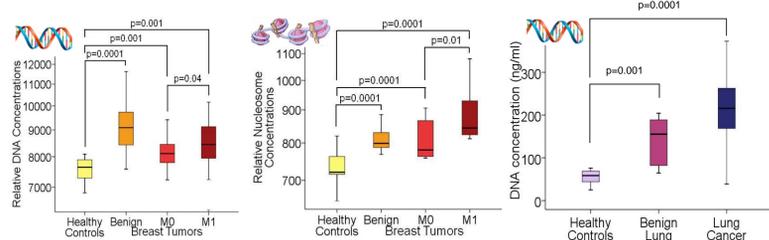
MiRNAs are a family of evolutionary conserved, small non-coding RNA molecules consisting of approximately 22 nucleotides. They inhibit gene expression post-transcriptionally by specifically binding to the 3' untranslated-region (3'UTR) of their target mRNA.



They regulate approximately 50% of all protein-coding genes, and have binding affinity to hundreds of different mRNAs. Hence, microRNAs are involved in the regulation of various cellular processes such as development, differentiation and proliferation.

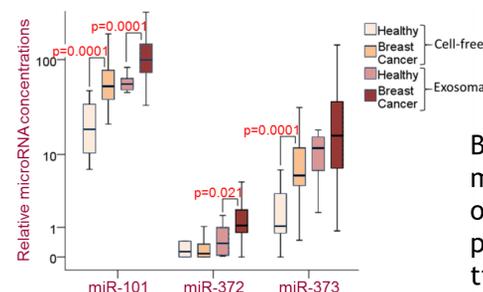
### Results

Increased levels of circulating cell-free DNA in blood of breast and lung cancer patients



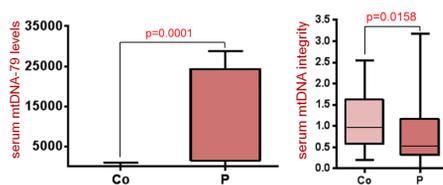
Box plots showing the distribution of DNA and nucleosome concentrations in serum of healthy women and patients with breast (M0, primary cancer, M1 metastatic cancer) or lung tumors, quantified by using Quant-iT™ PicoGreen dsDNA Reagent and Circulating nucleosomes Cell Death Detection ELISA.

Increased expression levels of circulating cell-free and exosomal microRNAs in blood of breast cancer patients

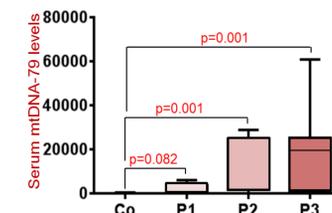


Box plots showing the distribution of microRNA concentrations in serum of healthy women and breast cancer patients, quantified by using real-time TaqMan PCR.

Circulating mitochondrial (mt) DNA as biomarker linking environmental chemical exposure to carcinogenic halo-alkane-based pesticides to early preclinical lesions



Exposure to halo alkanes enhances relative serum levels of mtDNA. Box plots showing the distribution of mtDNA-79 and the mtDNA integrity (mtDNA-230/mtDNA-79) in controls (Co) and exposed (P) groups, measured by real-time PCR.



Time related increase in serum mtDNA after exposure to halo-alkanes. Exposed subjects are grouped in P1 with confirmed current intoxication, P2 with short-term (20-120 days) past exposure and P3 with long-term (>5 months) past exposure.

### Conclusions

- Deregulation of circulating nucleic acids in blood of cancer patients and exposed individuals.
- Diagnostic relevance of circulating nucleic acids in blood of cancer patients and exposed individuals.
- Circulating nucleic acids are a promising class of potential liquid biomarkers.
- Extraction of circulating nucleic acids from blood plasma and serum can be performed in real-time.
- Quantification of circulating nucleic acids can facilitate decisions in the treatment of cancer patients and disposed individuals.

### Outlook

We aim at identifying blood markers that are correlated with the exposure in high risk patients. The results of our study may provide a new diagnostic tool that can be performed regularly on high risk subjects without the use of expensive imaging technology.

### References

Eichelser C, Müller V, Milde-Langosch K, Wikman H., Pantel K, Schwarzenbach H. *Oncotarget* 2014, 5:9650-9663.  
Schwarzenbach H, Nishida N, Calin GA, Pantel K. *Nat. Rev. Clin. Oncol.* 2014, 11:145-156.  
Budnik LT, Kloth S, Baur X, Preisser AM, Schwarzenbach H. *PLoS ONE* 2013, 8(5):e64413.