constitutively activated mainly by the loss of Keap1 or gain of Nrf2 functions due to point mutations in the key interacting domains of these two proteins. Beside of genetic lesions, Keap1/Nrf2 epigenetic abnormalities, as aberrant Keap1 promoter methylation and regulation by microRNAs were reported as emerging mechanisms of deregulation. Here we investigated the contribution of miRNA machinery on the modulations of Keap1/Nrf2 activity in lung tumors by analyzing panels of NSCLC and SCLC cell lines.

Methods: We searched for candidate miRNAs interacting with Nrf2 and Keap1 by using a combination of published data and in silico analyses performed by multiple bio-informatics tools (miRTarBase for known miRNAmRNA interactions; TargetScan, MiRanda, microRNA.org, miRBase also for predicted interactions). After this preliminary analysis we selected a list of 11 miRNAs that are experimentally validated in other tumors and/or predicted to be associated to NRF2 or KEAP1 and profiled their expression levels by real-time PCR in lung cancer cell lines and tissues.

Results: miR-27 family (miR-27a and miR-27b) was found to be significantly downregulated in NSCLC and SCLC cell lines. Conversely, miR-200 family (miR-200a and miR-141) was found to be significantly upregulated. Afterward, the expression data for miR-27 family and miR-200a was validated on an available training set of 29 tumor/normal paired tissues from NSCLC patients. As expected, miR- 200a was significantly up-regulated ($p < 0,01$, t-test), whereas miR27a and miR-27b significantly downregulated ($p < 0,001$, t-test) in tumors compared to normal tissues.

Conclusions: Since the obtained results refer to currently un-investigated miRNAs related to Keap1/Nrf2 axis in lung cancer, we plan to extend our analysis and confirm their role and impact on KEAP1/NRF2 modulation by in vitro studies. Our preliminary results suggest that redoxi-miRNA in lung cancer should add a new order of complexity to the regulation of the Nrf2/ARE pathway and will need to be more deeply explored in the future.

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17P REDOXI-miRNA of Keap1/Nrf2 axis in lung tumors

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Background: Oxidative and electrophilic changes in cellular redox balance are mainly coordinated by the Keap1/Nrf2 axis and is strongly related to tumor progression, chemo- and radio-therapy resistance of cancer cells. In lung tumors this system is