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COORDINATOR: PROF. EMANUELE ALBANO

SCUOLA ALTA FORMAZIONE

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First year

STUDENT: **GIUSEPPE MANCUSO** CYCLE: **XXIX** YEAR: **2013-2014**

TUTOR: **PROF. RENZO BOLDORINI**

Title

Analysis of microRNA expression in carcinomas of the lung and mesothelioma and their prognostic-predictive

Lung cancer is the leading cause of cancer-related deaths worldwide. An estimated 1.82 million new cases and 1.59 million lung cancer-related deaths occurred in 2012 (globocan.iarc.fr). In Italy, Lung Cancer is the most common cause of cancer death, with more than 38.200 new cases and more than 27.500 each year (ISTAT 2013).

Lung cancers are classified according to the histological types and this classification has important implications for the treatment and prognosis of the disease; there are two main categories: small cell lung cancer (SCLC) and non-small cell lung cancers (NSCLC).

SCLC comprises about 15-20% of all lung cancer and it is characterized by its rapid progression and frequent metastases. SCLC is sensitive to initial chemotherapy but most patients relapse rapidly and become resistant to chemotherapeutic agents, resulting in a poor prognosis and the 5-year survival rate only about 5%. Drug resistance is the most important reason for failure of SCLC chemotherapy; standard therapeutic interventions used today, which combine chemotherapy (etoposide plus platinum compounds) and radiation therapy, reflect the prevailing state-of-the-art from the early 1980s (Aisner et al. 1986; Amini et al. 2014).

NSCLC accounts for approximately 85% of all lung cancers and is further subdivided into three major histological subtypes: adenocarcinoma (40%), squamous cell carcinoma (30%), and large cell carcinoma (15%). NSCLC is characterized by a generally poor prognosis, whit a 5-year survival rate for advanced stage of about 5-20% and 60-70% in early stage. The treatment options are based mainly on the stage (extent) of the cancer; standard chemotherapy drugs include erlotinib (Tarceva), gefitinib (Iressa), crizotinib (Xalkori) and afatinib (Giotrif).

Malignant pleural mesothelioma (MPM) is a rare thoracic cancer that develops in the tissues that comprise the lining of the lung, and it is characterized by a long latency.

MPM includes three main histological subtypes: epithelioid (50-70%), biphasic (30%) and sarcomatoid (10-15%) (WHO classification); they are associated with a different prognosis. The epithelioid subtype is considered the less aggressive and most responsive to treatments, with the best prognosis (Boutin et al. 1998; Robinson et al. 2005). However prognosis is poor, the overall survival in no treated patients ranges from 4 to 12 months (Pass et al. 2001). There are no therapeutic standards for MPM and the treatment options depend on performance status, pulmonary function, stage, and age of the patient. The most commonly regimen used now includes the multitargeted antifolate drug (Pemetrexed) with a platinum drug such as Cisplatinum.

Lung cancer is characterized by multiple and heterogeneous genetic and epigenetic alterations, presence or absence of such mutations can heavily influence treatment outcomes in cases of targeted therapy. Targeted cancer therapies are drugs designed to interfere with specific molecules necessary for tumour growth and progression. Molecular targeted therapies are now included in the treatment regimen of lung cancers since they have been shown to extend progression free survival and improve overall survival.

The most frequently genetic abnormalities in SCLC are inactivation mutations in tumour suppressor genes such as TP53 and retinoblastoma gene (RB) (D'Amico et al. 1992; Yuan et al. 2013); other genetic alterations including overexpression of BCL-2 and only infrequent gain-of-function mutations in oncogenes such as PI3K3CA or MYC family members.

In NSCLC, driver genetic alteration occur in multiple oncogenes including, for adenocarcinoma (AD): K-RAS(26,9%), EGFR(9,4%), ALK (4%), MET(4%), PIK3CA(2,6%), RET (1,9%), ROS1(1,7%), BRAF(1,6%), HER2(0,9%). KRAS mutations are mutually exclusive with other driver events including EGFR, HER2 or BRAF mutations and ALK rearrangements (Sequist et al. 2011).

Whereas, FGFR1 (20%), PIK3CA (6,5%), PTEN (4-8%), DDR2 (3,8%) are oncogenic drivers for squamous cell lung (SCC) (Minuti et al. 2013).

MPM is characterized by a complex genomic alteration, with the loss of chromosomal loci encoding for tumour suppressor genes such as p16, p14, NF2 and TP53. The cyclin-dependent kinase inhibitor

2A/alternative reading frame (CDKN2A/ARF), neurofibromatosis type 2 (NF2) and BRCA1-associated protein-1 (BAP1) genes are the most frequently mutated tumour suppressor genes detected in MPM cells (Sekido et al. 2013).

The aberrant activation of multiple signal pathways, such as RAS/RAF/MEK,

PI3K/AKT/mTOR and STAT leads to the uncontrolled growth of cancer and impaired cell death signalling. Abnormalities of PI3K/PTEN/AKT/mTOR are more common in SCC than in AD, suggesting relevance on this pathway.

Evidence has shown that the poor prognosis of patients with NSCLC and therapeutic failure are associated with a number of abnormally activated signalling PI3K/AKT pathways. Aberrant AKT activation is a poor prognostic factor for NSCLC of all stages and contributes to resistance to first-generation single-agent targeting therapy such as Gefitinib, a tyrosine kinase inhibitor clinically used for patients with NSCLC with EGFR over-activation. One cause of therapeutic resistance is inactivation of cancer suppressor PTEN, which allows over-activation of the PTEN/PI3K/AKT pathway.

Some gene expression of markers of sensitivity to specific cytotoxic agents, such as ERCC1, BRCA1 for Platinum, RRM1 (Ribonucleotide reductase M1) for gemcitabine, or thymidylate synthase (TYMS) gene amplification, a Pemetrexed target, is associated with resistance to this drug. A high expression level of RRM1 has been found to be indicative of longer survival, independent of stage and performance status, and predictive power with regard to treatment with gemcitabine in advanced NSCLC. Low ERCC1 expression is predictive of better response to platinum-based chemotherapy (Su et al. 2010).

Recent evidence suggests significant roles that miRNAs play in the prognosis and diagnosis of lung cancer, increasing efforts are dedicated to the development of miRNA-based therapies.

MicroRNAs (miRNAs) are a class of evolutionarily conserved, small non-coding RNAs of 19-24 nucleotides in length that regulate gene expression mostly at the posttranscriptional level (Bartel et al. 2009). Initially, miRNAs were thought to be involved in the regulation of development and cell fate, but more recently it has been discovered that miRNAs participate in a broad range of processes including cell cycling, apoptosis, cell differentiation, tumour development, invasion, metastasis, and angiogenesis (Friedman et al. 2009).

In particular, miRNAs have been observed to be aberrantly expressed in many human cancers (Cortez et al. 2011) and they are a promising alternative biomarkers for detecting cancer, informing prognosis, and monitoring treatment response, as well as crucial players in cancer initiation, development and metastasis (Cortez et al. 2011; Nelson et al. 2008). From the biological point of view, miRNAs may be better predictive and prognostic markers than DNA or mRNA. A single miRNA, indeed, may regulate hundreds of target mRNAs, frequently grouped in a specific biological pathway. Consequently, a miRNA signature may provide comparable prognostic information several orders of magnitude greater than mRNAs. Besides miRNAs are more stable than other biomarkers during sample processing, thus more suitable for analysis in plasma, urine, stool and tissue (fresh or FFPE - Formalin-fixed, paraffin-embedded-) sample and this is a key point in the search for cancer markers.

Recent studies have indicated an emerging role for miRNAs, in addition to genetic and epigenetic changes (methylation/acetylation), in the anticancer-drug-resistant phenotype (Giovannetti et al. 2012), which opens up the possible application of miRNAs in evaluation of outcome and modification of response in known anti-tumour therapies (Hummel et al. 2010).

The possible applications of miRNAs in molecular prognostics, particularly in cancer, are provided by discovery of the role of miRNA in numerous pathological processes, and for cancer prognosis; miRNA can be complementary to other genomic and proteomic biomarkers (Cho et al. 2007).

The main mechanisms of resistance are: altered expression of the ATP-binding cassette family of transporters on cell membrane transporters, alterations in DNA repair pathways, resistance to apoptosis, and target modifications (Rodrigues et al. 2012).
Several recent studies have demonstrated how oncogenic miRNAs may interfere with DNA-repair pathways allowing cells to resist drugs that initially were effective against them (Giovannetti et al. 2012). To restore drug sensitivity via miRNAs, potential approaches include activation of tumour suppressor miRNAs or inactivation of oncogenic miRNAs and modulation of miRNA target genes, oncogenes, and tumour suppressor genes, through up- or down-regulation of miRNAs (Sarkar et al. 2010; Giovannetti et al. 2012).
Chemoresistance still remains the greatest difficulty to overcome in cancer therapy.
In this context, the research of potential prognostic power of miRNAs is still at an early stage.
In a recently study, an increased expression of miR-126 was shown to enhance the sensitivity of A549 cells to Adriamycin and Vincristine by down-regulation of VEGF-A (vascular endothelial growth factor A), multidrug resistance-associated protein 1, and suppression of AKT signalling (Zhu et al. 2012).
MiR-126 expression was down-regulated in lung cancer tissues compared to normal lung tissues and with an enhanced VEGF-A expression in lung cell lines (Liu et al., 2009). VEGF is a positive regulator of angiogenesis, and its expression is up-regulated in many cancers (Weekes et al., 2010; Salajegheh et al. 2013). Also, miR-126 can suppress lung cancer invasion by directly targeting CRK - CRK is known to elevate adhesion, invasion and migration (Crawford et al. 2008; Miller et al. 2003).
Furthermore, the activity of the PI3K-AKT pathway was suppressed by miR-126 as it targets the binding site of PI3KR2 mRNA in the 3′ UTR region (Yang et al., 2012)
This suggests that enhanced expression of miR-126 elevates sensitivity of non-small cell lung cancer cells to anticancer therapy via negative regulation of the VEGF/PI3K/AKT/MRP1 signalling pathway (Ebrahimi 2014).
Additionally, in MPM miR-126 is significantly down-regulated, its level is inversely correlated with that of the known target, SLC7A5 (Andersen M 2014).
While, miR-150 is aberrantly up-regulated in lung cancer tissue and specifically targets the 3'-UTR of p53 and regulates its expression. Down-regulation of miR-150 may contribute to tumour growth and proliferation, for affect of p53 expression through a direct or indirect pathway (Sun Y 2013; Zhang N 2013). The mechanism of the miR-150 effects on NSCLC cells is associated with alterations in the expression of human BRI1-associated receptor kinase 1 (BAK1). MiR-150 may function as an oncogene in NSCLC cells by directly targeting BAK1. Thus, these data highlight a novel molecular interaction between miR-150 and BAK1 and provide a novel strategy for NSCLC therapy via the down-regulation of miR-150 expression (Gu XY 2014).
A work showed that miR-192, miR-194 and miR-215 can target ZEB2, MDM2 and TYMS. MDM2 is a key inhibitor of p53. It activates hypoxia inducible factor 1 alpha and vascular endothelial growth factor activity (Patterson et al. 2011). Other studies demonstrated that p53 can regulate EMT through targeting ZEB2 by miR-192 family. (Kim et al. 2011; Khella et al. 2013).
There are evidences that miR-192 is another miRNA that is both regulated by p53 and capable of inducing cell-cycle arrest (Song et al. 2008; Georges et al. 2008; Braun et al. 2008). ERCC3 and ERCC4, two proteins involved in NER pathway, were down-regulated by miR-192, with consequent impairing of NER machinery (Xie et al. 2011). A recent study confirmed three novel miRNAs (miR-662, miR-192 and miR-192*) as prognostic for distant relapse in operable lung SCC (Skrzypski et al 2014).
Recent works investigated mir-200 family (mir-200b, mir-200a, mir-429, and mir-200c) and miR-205 its role in the promotion of EMT in NSCLC through regulation of ZEB1, ZEB2 and SIP1 (Gregory et al. 2008; Farshid et al. 2008).

Down-regulated of miR-200c in NSCLC restoration of expression increases sensitivity to Cisplatino. A chemoresistant phenotype along with tumour invasiveness in NSCLC cells was observed with loss of miRNA-200c expression and restoring its expression resensitized NSCLC cells to both Cisplatin and EGFR ablative therapy i.e., Cetuximab (Gibbons et al. 2009; Pacurari et al. 2009; Ceppi et al. 2010).
Recently Tejero and colleagues demonstrated that high levels of miR-200c are associated with shorter overall survival in a cohort of NSCLC patients with AD (Tajero et al., 2014).
While it has been reported that K-RAS is regulated by several tumour suppressor miRNAs, this is the first report on the direct regulation of K-RAS by miR-200c (Kopp et al. 2013).
Overexpression of miR-205 was detected in tissues from multiple subtypes of NSCLC that led to increased proliferation and angiogenesis (Cai et al., 2013).
Oncogenic miR-205, overexpressed in NSCLC cell lines and tissues, was shown to enhance cell growth, metastasis, and chemoresistance to Cisplatin of A549 cells by targeting PTEN (Lei et al., 2013).
Bi N et al. 2014 developed a prognostic miR-150/miR-886-3p signature and validated expression in an independent dataset of resectable SCLC. These preliminary results indicated that miRNAs may serve as promising molecular prognostic markers and new therapeutic targets for SCLC (Bi et al. 2014).
Lastly, miR-886-3p-PLK1/TGF-β1 nexus that modulates SCLC aggression suggests that both loss of miR-886-3p expression and hypermethylation of the miR-886 promoter are the promising indicators for poor outcome of as well as new therapeutic targets for SCLC (Cao J 2013).
Finally, there are very few studies on the expression of miRNA on cytological samples, following the report two examples. Fassina et al. develop a miRNA expression method for differentiating AD from SCC in cytologic specimens obtained by means of such a minimally invasive and safe technique as CT-guided TTNA (Fassina et al. 2011). Other study on cytologic specimens, Gilad et al. develop an assay based only on the expression of a small set of miRNAs that differentiates between the four main types of lung cancer. The assay displays high levels of accuracy in pathologic and cytologic samples. For the latter, fine-needle aspiration (FNA) and bronchial brushing and washing samples were tested, demonstrating the versatility of the assay (Gilad et al 2012).

	Target	SCLC	NSCLC	MPM	
Hsa-mir-126	PLK2, PI3KR2, CRK, EGFL7, SLC7A5	√	√	√	Sun Y 2010; Liu LY 2014; Andersen M 2014.
Hsa-mir-150	MYB, TP53, BAK1, ELK1, PLP2	√	√	-	Cohen-Armon 2007; Zhang J 2012; Gu XY 2014.
Hsa-mir-192	ZEB2, MDM2, TYMS, ERCC3, ERCC4	-	√	√	Patterson 2011; Xie 2011.
Hsa-mir-200c	ZEB1-2, KRAS	√	√	√	Gregory 2008; Kopp 2013.
Hsa-mir-205	ERBB3, E2F1, ZEB1-2, PTEN	√	√	√	Lei 2013; Cai 2013; Gregory 2008.
Hsa-mir-886-3p	PLK1, TGF-β1	√	-	-	Cao 2013; Bi 2014.

Table 1: Panel of MicroRNA, targets and the presence in the tissues examined.

Methodologies.

Patients and samples.

1) Cytological samples obtained from patients with a diagnosis of small cell and non-small cell lung carcinoma and with a minimum of 2-years follow-up will be retrospectively collected.

The samples were obtained by sputum, bronchial brushing or washing and by fine-needle aspiration biopsy during a routine procedure for diagnostic purposes. The samples are composed by cellular smears an/or by cell block and in all the cases the morphologic diagnosis was confirmed by a specific panel of immunohistochemistry. Before the inclusion in the present project, all the cases will be reviewed by an experienced pathologist.

We hypothesise that al least 30 cases of SCLC, 40 cases of AD and 30 cases of SCC will be included in the study.

Apart the SCLC that by definition is classified as high grade cancer, the other two group will be selected homogeneously for grading and staging, including a comparable number of grade 2 and 3 tumours with stage III (treated only by chemotherapy). For all the patients with NSCLC overall survival and disease-free survival will be evaluated, whereas for SCLC only overall survival will be considered and compared with the miRNA expression.

In all the cases, the neoplastic cellularity and the percentage of the tumour cells versus normal cells will be evaluated in order to establish a cut-off of expression. In analogy with our previous work on the analysis of EGFR in routine cytologic specimens of lung adenocarcinoma (Allegrini et al. 2012), we will also investigate the influence of the different types of fixative solution on the feasibility of miRNA expression in such samples.

2) Tissue samples of NSCLC, obtained by surgery from patients with stage I and II tumours will be evaluated in order to investigate miRNA expression from at least 50 cases, matched for grading and histological subtype. Also in these patients a minimum of 2-years of follow-up will be required and the disease-free survival will be compared with miRNA expression.

All the cases will be evaluated by an experienced pathologist and the area of interest will be selected, including a maximum number of cancer cells, avoiding necrotic areas.

miRNA Extraction, cDNA synthesis and miRNA expression analysis by real-time PCR.

Total RNA will be extracted from histological and cytological FFPE samples by miRNeasy FFPE Mini Kit (Qiagen) following manufactures instruction. RNA quantity will be tested by spectrophotometry, using NanoDrop (ThermoScientific), and then reverse transcribed to complementary DNA (cDNA) by means of TaqMan®miRNA reverse-transcription kit (Applied Biosystems) and using miRNA specific primer.

TaqMan® miRNA Assays (Applied Biosystems) will be used to quantify mature miRNA expression for the chosen candidate miRNAs: hsa-miR-126, hsa-miR-150, hsa-miR-192, hsa-miR-200c, hsa-miR-205, hsa-miR-886-3p and the reference non-coding RNAs RNU6.

Quantitative Real Time PCR will be carried out in triplicate on 7500 Fast Real-Time PCR Systems (Applied Biosystems) using a primer specific TaqMan® miRNA Assays (Applied Biosystems) for profiling miRNAs identified. Quantification of miRNA expression will be performed with the $2^{-\Delta\Delta Ct}$ method using normal lung tissue as calibrator.

Aims

Evaluate the feasibility of molecular analysis using cytological sample and small biopsies and the influence of the different types of fixative solution on miRNA expression in such samples.

The general aim of the study was to identify miRNAs related to prognosis, drug response, overall survival, disease free survival.

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Seminars 2014

Department of translational medicine.

PhD program in Sciences & Medical Biotechnology

The Borghese Sessions Steven R Ellis

08/09/2014

10:00 Clinical case - Skin as an organ

11:00 Layers of skin, cell types, developmental origins

09/09/2014

10:00 Cell-Cell Interactions - anchoring junctions

11:00 Cell-Cell Interactions - occluding junctions, tight junctions

10/09/2014

10:00 Cell Matrix Interactions - basal lamina

11:00 Epithelial-mesenchymal transition

11/09/2014

10:00 Angiogenesis

11:00 Innervation

15/09/2014

10:00 Basal layer stem cells, symmetric versus asymmetric divisions, transient amplifying cells

11:00 Solar radiation, nucleotide excision repair

16/09/2014

10:00 Basal and squamous cell carcinomas

11:00 Melanoma - biology

17/09/2014
10:00 Melanoma - treatment
11:00 Contact dermatitis

22/09/2014
10:00 Other skin disorders
11:00 Other components of skin

21/07/14 Dr Maria Giuseppina Miano "a functional link between arx and kdm5c genes linked to neuronal diseases defines a crucial epigenetic path"

16/07/2014 at 14.30 Prof. John F. McDonald "The potential of small regulatory RNAs for the treatment of ovarian cancer "

15/07/2014 ore 14.30-16 Prof.ssa Follenzi "applicazioni terapia genica"

30/06/2014 at 14-16 Dott. Cotella "the C-value paradox, junk DNA and ENCODE"

27/06/2014 at 14 Manuela Sironi "Has nature done the experiment for us? Evolutionary insights into infection susceptibility and autoimmunity"

26/06/2014 at 14 Prof Gianni Del Sal "Disarming mutant P53 in cancer"

19/06/2014 at 12-13.30 Prof.ssa Follenzi "terapia genica"

12/06/2014 at 14 Gianni Cesareni "Metformin rewires the signaling network of breast cancer cells and changes their sensitivity to growth and apoptotic stimuli"

11/06/14 at 14 Prof. Fabrizio Loreni "Ribosome alteration in cancer: effect or cause?"

9/06/2014 at 14 Dott Iacopo Baussano "Assessment of cervical cancer control in Rwanda and Bhutan"

5/05/2014 ore 12 Prof. Vittorio Colombo e Dr. Matteo Gherardi, “atmospheric pressure plasma sources ad processes for biomedical and surface treatment applications”

19/03/2014 14.30 Prof Emilio Hirsch “role of phosphoinositides-3-kinase C2-alph, a Class II PI 3-kinase, in development and cancer”

List of publications.

Tarallo S, Pardini B, **Mancuso G**, Rosa F, Di Gaetano C, Rosina F, Vineis P, Naccarati A. MicroRNA expression in relation to different dietary habits: a comparison in stool and plasma samples. Mutagenesis. 2014; 29(5):385-91.

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