To the Academic Board of the doctoral program in Molecular Medicine

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Introduction

Malignant pleural mesothelioma (MPM) is predominantly caused by asbestos exposure and is an aggressive cancer with poor prognosis. MPM is extremely resistant to chemotherapy drugs and other treatments. The goal of my project is to detect novel genes playing a role for the maintenance of the malignant phenotype of MPM, providing new molecular targets for novel therapies. In the original project, we used the strategy to evaluate all published transcriptome studies on MPM and we showed that at least 60 LDEGs (literature deregulated genes) were deregulated in MPM compared to normal pleura and to other cancer types. We selected from this list five interesting genes for verifying the gene silencing. If these genes are important in driving the malignant phenotype, appreciable results should be seen. During the year we started from the scratch with a new search adding the novel information available on the website of TCGA (The Cancer Genome Atlas), where 85 MPM specimens were analyzed for transcriptome. We integrated the TCGA data with the RNA-seq-data from normal lung samples cohort, available on the Gene Expression Omnibus (GEO). We ran differential expression analysis on raw-data from TCGA and GEO, identifying the deregulated genes (DEGs). It would be necessary to compare them with the transcriptomes derived from healthy pleural tissues and other cancer type, so we updated the original list of LDEGs with the newly published manuscripts. We filtered the DEGs with LDEGs. With a bioinformatic approach we analyze this new list of genes, identify 14 genes over-expressed in MPM tissues and associated with the prognosis of MPM patients.

Methods

We evaluated the protein expression of the selected LDEGs and DEGs in the cell lines (Mero-14, 41, 95, ZL-55, REN, MSTO, and control pleura line Met-5A) through western blot and SiRNA transfection for gene silencing. We used commercial kits for the functional analyses. Bioinformatics analysis was carried out using the R language.

Results

The western blots of the LDEGs reveal that expression data in the cell lines has only a partial overlap of genes expression. Only LAMC1 protein shows a clear over-expression in the malignant cell lines, but from the functional point of view LAMC1 is not indispensable for the malignant phenotype. The functional experiment for the gene silencing on the other genes are ongoing. In the new elaboration of the project, we have identified three gene signatures with prognostic value for MPM patients. We started a western blot screening for those genes, showed that only some cell lines could represent the patients group with the worst prognosis from which we selected the DEGs. The siRNA transfection of the DEGs and the functional analysis is underway. Other bioinformatics analysis on the validation of the signature is ongoing.