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Sommario	Lamin A/C are essential components of the nuclear lamina. Together with B-type lamins and other structural components, they form the network which is located in the inner side of the nuclear membrane. It is now clear that lamins exert many different functions within the cell, most of them still largely unknown. Lamin A/C are absent in embryonic stem cells but are expressed in the majority of adult cell types, thereby suggesting their crucial role in differentiation. In addition, their expression is reduced or absent in several human malignancies, even though their role in the tumorigenesis has not been completely characterized yet. A down regulation of Lamin A/C could result in increased nuclear deformability thereby facilitating transit of cells through the capillaries and favouring cell invasive capacity. In a previous paper we demonstrated that LMNA gene knock-down inhibits differentiation in a cellular model of neuroblastoma and increases tumor progression. In this project I investigated some of the possible mechanisms by which Lamin A/C is down-regulated in neuroblastoma cells. As cellular models I employed two neuroblastoma cell lines showing different level of Lamin A/C expression (LAN-5 and SH-SY5Y cells). The analysis of the nascent transcripts of LMNA gene in both cell lines demonstrated that the transcriptional rate of this gene was reduced in the LAN-5

	cells, indicating that the protein is regulated at transcriptional level. In addition, I observed that there is a minor recruitment of Sp1 transcription factor on the LMNA promoter of LAN-5 cells, as evaluated by ChIP assay. Moreover, even though the chromatin configuration upstream the LMNA gene promoter is open in both cell lines, as evidenced by a similar enrichment of the H3K4me3 histone marker in both cell lines, we found a different configuration in the coding sequence region (CDS), as shown by a reduced enrichment in LAN-5 cells of the histone marker H3K36me3 which is associated with transcriptional activation. We then tried to exogenously express the LMNA gene in LAN-5 cells, in which the protein is not detectable. In spite of a very high upregulation of LMNA gene, I did not observed any detectable expression of Lamin A/C protein. I hypothesized that the protein could be regulated by a miRNA-mediated post-transcriptional mechanism. An in silico analysis of the miRNAs predicted by miRWalk database to significantly target LMNA transcripts, have evidenced a unique miRNA, the has-miR-539-5p. However, the inhibition of the expression of such miRNA was not able to rescue the expression of Lamin A/C protein in LAN-5 cells. At the moment I can conclude that the regulation of Lamin A/C protein in neuroblastoma cells is mainly to be ascribed to a transcriptional mechanism. However, I cannot exclude the existence of an additional regulation mechanism occurring at post-transcriptional and/or post-translation level that have to be further investigated.
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