MicroRNA-128-3p-mediated depletion of Drosha promotes lung cancer cell migration

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Alteration in microRNAs (miRNAs) expression is a frequent finding in human cancers. In particular, widespread miRNAs down-regulation is a hallmark of malignant transformation. In the present report, we showed that the miR-128-3p, which is up-regulated in lung cancer tissues, has Drosha and Dicer, two key enzymes of miRNAs processing, as the main modulation targets leading to the widespread down-regulation of miRNA expression. We observed that the miRNAs down-regulation induced by miR-128-3p contributed to the tumorigenic properties of lung cancer cells. In particular, miR-128-3p-mediated miRNAs down-regulation contributed to aberrant SNAIL and ZEB1 expression thereby promoting the epithelial-to-mesenchymal transition (EMT) program. Drosha also resulted to be implicated in the control of migratory phenotype as its expression counteracted miR-128-3p functional effects. Our study provides mechanistic insights into the function of miR-128-3p as a key regulator of the malignant phenotype of lung cancer cells. This also enforces the remarkable impact of Drosha and Dicer alteration in cancer, and in particular it highlights a role for Drosha in non-small cell lung cancer cells migration.

1. MiR-128-3p expression is up-regulated in NSCLC tissues

2. MiR-128-3p expression triggers a global down-regulation of miRNAs

3. The miRNA processing enzymes Drosha and Dicer are novel targets of miR-128-3p

4. Ectopic expression of miR-128-3p promotes migratory phenotype in lung cancer cells

5. MiR-128-3p-mediated miRNAs down-regulation promotes EMT program

6. Drosha depletion in lung cancer cells mimics miR-128-3p effects on cell migration and EMT

Conclusions

In lung cancer cells, the oncogenic miR-128-3p directly binds to Drosha and Dicer 3'UTR determining the inhibition of their expression. The consequence is a significant alteration in miRNAs biogenesis, characterised by a global down-regulation in miRNAs expression, a feature known to promote tumorigenesis. Among the down-regulated miRNAs by miR-128-3p, there is a group of miRNAs that target SNAIL and ZEB1, two of the major players of EMT. This event leads to an up-regulation of SNAIL and ZEB1 and to a consequent induction of EMT that promotes metastatic potential of lung cancer cells. MiR-128-3p levels might be kept high through alternative processing mechanisms that are Drosha/Dicer independent.