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Area tematica

Tumour biology and pathology

Titolo

The role of microRNAs in driving EGFR-TKI resistance in NSCLC cell lines

Testo

Background: the inhibition of EGFR kinase activity by tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib, can result in improved response and prolonged progression-free survival (PFS) in NSCLC patients harboring sensitizing exon 19del and exon 21 L858R mutations. Unfortunately, almost all patients will develop resistance to EGFR-TKI, in particular T790M is the most frequent mutation. Nowadays, new methods are urgently needed for a rapid, cost-effective and non-invasive identification of biomarkers as a valuable tool for obtaining the genetic follow-up data during the course of the disease. Circulating microRNAs might represent a new precious biomarker for patients' monitoring. The study aimed to verify the association between microRNAs expression and EGFR mutational status in adenocarcinoma wt and EGFR-TKI sensitive mutated (del19) cells.

Methods: EGFR wt and mutated adenocarcinoma cells (A549, HCC827), were cultured in RPMI1640 and incubated at 37C in 5% CO_2. Cell viability before treatment was evaluated by MTT assay and then cells were treated with Erlotinib at growing concentration. MicroRNAs were extracted by using miRNeasy mini kit (QIAGEN). Nucleic acids quantity and quality was evaluated through the NanoDrop ND-2100 Bioanalyzer whereas integrity through the 2100 Bioanalyzer. MicroRNAs after retrotranscription were profiled through TaqMan Array Human MicroRNA Cards v2.0.

Results: microRNAs extracted from A549 (wild-type) and HCC827 (del19) were profiled and differential expression analyzed at basal conditions (no treatment) using the wt cell as control. The miRNAs analysis highlighted that among the up-regulated microRNAs (miR-7, miR-18a, miR-106b, miR-200b, miR-505, miR-625), the miR-7 expression levels were 10 times higher, whereas among the down-regulated miRNAs (let-7f, miR-10b, miR-192, miR-193, miR-194, miR-767, miR-801), let-7f was 12 times lower. This signature may represent a valid start point for studying variations of the aforementioned miRNAs levels during TKIs treatment in order to demonstrate their involvement in inducing resistance.

Conclusions: to outline molecular mechanisms responsible for resistance onset as consequence of TKIs treatment, the hypotetical role of miRNAs has been studied. The preliminary data, obtained so far only in cultured cell lines at basal conditions, would acquire higher relevance, if their involvement may be confirmed also in TKI-treated cells.

Parole Chiave

1. microRNA
2. NSCLC
3. TKI resistance

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