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Upregulation of miR-202-3p reduces Icotinib resistance in lung carcinoma A549/Ico cells.

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Abstract

Icotinib exerts a good anti-tumor efficacy on non-small cell lung cancer (NSCLC), while Icotinib resistance has become an important limiting factor in the clinical application. Studies have certified that a great quantity of microRNAs are involved in the development of cancer. Here we found that miR-202-3p was observably down-regulated in A549/Ico cells, which is a kind of Icotinibresistant lung cancer cells. Transfection of A549/Ico cells with miR-202-3p reversed the Icotinib resistance and increased cell apoptosis. Subsequently, we examined the expression of ADP-Ribosylation Factor-like 5A (ARL5A), the functional target of miR-202-3p, as well as the multi-drug resistant (MDR) related genes glutathione s transferase π (GST-π), Multi Drug Resistance 1 (MDR1), multidrug resistance-associated protein 1 (MRP1) and breast cancer resistance protein (BCRP), which were down-regulated following the upregulation of miR-202-3p in A549/Ico cells. Our study demonstrated that miR-202-3p transfection reduced Icotinib resistance in human lung cancer A549/Ico cells by modulation of its downstream target ARL5A and MDR-related genes expression. These findings suggest that miR-202-3p may function as a novel therapeutic candidate in patients with MDR lung cancer.

Keywords: Icotinib resistance, miR-202-3p, Lung carcinoma, A549/Ico cells.

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Introduction

MicroRNAs (miRNAs) are a class of endogenous RNAs which contain 18–25 nucleotides in noncoding single-stranded [1]. The number of verified miRNAs has grown rapidly since their discovery in 1993 [2]. Over the past few years, studies have shown that miRNA regulate up to one third of human genes at the posttranscriptional level [3]. As miRNAs involve in biological development, as well as cell proliferation, differentiation and apoptosis, dysregulation of miRNAs plays a crucial role in the pathologic processes of tumorigenesis [4,5]. Although miRNAs perform vital functions in regulation of developmental gene expression, their role in tumor progression remains poorly understood. MiR-202-3p is located within a chromosomal fragile site in 10q26 [6]. Related reports have clarified that miR-202-3p is downregulated in colorectal cancer [7], breast cancer [8] and cervical squamous cell carcinoma [9], it also can inhibit cell proliferation in neuroblastomas [10]. Furthermore, overexpression of miR-202-3p can suppress cell proliferation and induce cell apoptosis in cancer cells.

Nowadays, NSCLC has been one of the leading causes of cancer-related mortality in the world, accounting for about 80% of all lung cancer cases [11]. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have proven to be an indispensable method in the treatment of advanced NSCLC [12], due to its exact curative effect, mild adverse reactions and oral administration convenient [13]. Icotinib is a kind of EGFR-TKIs, developing entirely by Chinese scientists independently, exerts an excellent anti-tumor efficacy on NSCLC [14]. However, although the treatment of Icotinib can prolong the life of patients with NSCLC, the majority of patients develop an acquired resistance to Icotinib 8–10 months following the initiation of treatment [15].

Usually, tumor cells undergo self-adaptation through contacting with chemotherapeutic drugs in MDR [16]. MDR-related protein and lung resistance-related protein can reduce drug absorption while increase drug efflux, along with the enhancement of cellular detoxification capability. ARL5A is a Protein Coding gene which belongs to the ARF family of GTP-binding proteins, and studies have explored that MiR-202-3p can inhibit cell proliferation by directly targeting ARL5A in colorectal cancer [2]. GST-π is an important cell detoxifying enzyme [17], MDR1, MRP1 and BCRP are important drug resistance genes, upregulation of these genes is a signal for the emergence of drug resistance [18].

In the present work, we aimed to explore the effect of miR-202-3p expression on Icotinib resistance in human lung cancer A549/Ico cells. We confirmed that the expression of miR-202-3p was downregulated in A549/Ico cells, and transfection of miR-202-3p reversed Icotinib resistance and increased cell apoptosis relatively. Furthermore, upregulation of miR-202-3p decreased ARL5A and MDR gene expression