Title: Chemo-resistant associated genes in esophageal squamous cell carcinoma identified by RNA sequencing



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ABSTRACT

Esophageal cancer (EC) represents the sixth leading cause of cancer deaths worldwide. Although many reports have indicated that patients who receive chemoradiation therapy had a significantly better 5-year survival rate, it is unclear why certain patients respond better than others to chemotherapy. Unambiguous molecular markers are needed to identify which patients are likely to respond best to particular treatments. To identify potential genes and miRNAs associated with chemo-resistance in chemo-sensitive and chemo-resistant esophageal squamous cell carcinoma (ESCC) cell lines, a variety of ESCC cell lines were treated with different kind of chemotherapy drugs. By comparison of IC50, the chemo-sensitive and chemo-resistant cell lines were obtained and subjected to RNA sequencing analyses. In total of 238 candidate genes including two well-known chemo-resistant related genes (MDR1 and ZEB2) and some novel chemo-resistant related genes (such as PHF15, MYO15B, FAM84B, DSEL) were upregulated in chemo-resistant cell lines with more than 5 fold compared to that of chemo-sensitive cell lines. KEGG Pathway analyses showed these genes involved in tumor angiogenesis, tumor occurrence, tumor development, and metabolism process control. Moreover, 224 of novel chemo-resistant related miRNA were identified via small RNA-seq (>5 fold). Of which, 27 of miRNA, which involve in Notch and cell cycle pathways, showed statistical significance between chemo-resistant and chemo-sensitive cells ($P<0.0001$). miR-140-3p is one of the miRNAs with dramatically statistical significance among three resistant/sensitive cells (>20 fold, $P<0.0001$) and its potential target gene (NFYA) were also identified as one of significant different genes between chemo-resistant and chemo-sensitive cells by RAN-seq. Further study demonstated that overexpression of miR-140-3p downregulated the NFYA mRNA level. Collectively, our study identified a set of key genes and miRNAs associated with chemo-resistance in ESCC. Of note, miR-140-3p may play critical roles via regulate its target gene NFYA in chemo-resistance in ESCC.