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ORIGINAL ARTICLE

Identification of key genes involved in nasopharyngeal carcinoma☆

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KEYWORDS
Nasopharyngeal carcinoma;
Differentially expressed genes;
Enrichment analysis;
Regulatory network

Abstract
Introduction: Nasopharyngeal carcinoma (NPC) is the most common cancer originating from the nasopharynx.
Objective: To study the mechanisms of NPC, we analyzed GSE12452 microarray data.
Methods: GSE12452 was downloaded from the Gene Expression Omnibus database and included 31 NPC samples and 10 normal nasopharyngeal tissue samples. The differentially expressed genes (DEGs) were screened by ANOVA in the PGS package. Using the BiNGO plugin in Cytoscape and pathway enrichment analysis in the PGS package, functional and pathway enrichment analyses were performed separately to predict potential functions of the DEGs. Furthermore, Transcription Factor (TF)-DEG pairs were searched, and then the TF-DEG regulatory network was visualized using Cytoscape software.
Results: A total of 487 genes were screened as DEGs between the NPC samples and the normal nasopharyngeal tissue samples. Enrichment analysis indicated that PTGS2 was involved in the regulation of biological process and small cell lung cancer. ZIC2 and OVOL1 may function in NPC through targeting significantly up-regulated genes (such as PTGS2, FN1, CXCL9 and CXCL10) in the TF-DEG regulatory network (e.g., ZIC2→PTGS2 and OVOL1→CXCL10).
Conclusion: PTGS2, FN1, CXCL9, CXCL10, ZIC2 and OVOL1 might play roles in NPC.
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PALAVRAS-CHAVE
Carcinoma nasofaríngeo;
Genes diferencialmente expressos;
Análise de enriquecimento;
Rede reguladora

Identificação dos principais genes envolvidos no carcinoma nasofaríngeo

Resumo
Introdução: O Carcinoma Nasofaríngeo (CNF) é o câncer mais comum originário da nasofaringe.
Objetivo: Estudar os mecanismos de CNF; dados do microarranjo GSE12452 foram analisados.
Método: GSE12452 foi baixado da base de dados Gene Expression Omnibus e inclui 31 amostras de CNF e 10 amostras de tecido nasofaríngeo normal. Os Genes Diferencialmente Expressos (GDE) foram analisados por ANOVA no pacote PGS. Usando o plugin BiNGO no Cytoscape e análise de enriquecimento da via no pacote PGS, análises de enriquecimento funcional e da via foram realizadas separadamente para prever as potenciais funções dos GDE. Além disso, os pares Fator de Transcrição (TF)-GDE foram pesquisados e em seguida a rede reguladora de TF-GDE foi visualizada usando o programa Cytoscape.
Resultados: Um total de 487 genes foram analisados como GDE entre as amostras de CNF e amostras de tecido nasofaríngeo normal. A análise de enriquecimento indicou que PTGS2 estava envolvido na regulação do processo biológico e câncer pulmonar de pequenas células. ZIC2 e OVOL1 podem funcionar no CNF almejando-se de maneira significativa os genes suprarregulados (como o PTGS2, FN1, CXCL9 e CXCL10) na rede reguladora de TF-GDE (p.ex., ZIC2→PTGS2 e OVOL1→CXCL10).
Conclusão: PTGS2, FN1, CXCL9, CXCL10, ZIC2 e OVOL1 podem desempenhar alguns papéis no CNF.
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Introduction

As the most common cancer originating from the nasopharynx, nasopharyngeal carcinoma (NPC) caused approximately 86,700 new cases and 50,800 deaths globally in 2012.[1] NPC is extremely common in Southeast Asia and southern China, with more than 50,000 new cases each year.[2,3] NPC can be induced by multiple factors including heredity, viral factors and environmental influences.[4] Most cases of NPC are correlated with Epstein–Barr Virus (EBV) infection, which is a B-lymphotropic herpesvirus possessing growth-transforming properties.[5] Therefore, it is of great importance to study the mechanisms of NPC.

Many studies investigating the mechanisms of NPC have been published. There are several genes (such as C-myc, AKT1, p53, MDM2, LMP1 and PTEN) implicated in the pathogenesis of NPC because they are often amplified or altered in patients with this disease.[6–8] Disabled 2 (DAB2) is frequently down-regulated by promoter hypermethylation and may be a potential tumor suppressor in NPC.[9] Previous studies show that the potential tumor suppressor gene A disintegrin-like and metalloprotease domain with thrombospondin type 1 motifs 9 (ADAMTS9) is closely related to lymph node metastases, and it can inhibit tumor growth by suppressing angiogenesis in NPC.[10,11] The transcription factor (TF) adaptor-related protein complex 1 (AP-1) activated by the EBV-encoded Nuclear Antigen 1 (EBNA1) can target hypoxia-inducible factor-1α, interleukin 8 and Vascular Endothelial Growth Factor (VEGF), which promotes microtubule formation in NPC cells.[12] The TF Forkhead Box M1 (FOXM1) is involved in tumor development, and the adenovirus vector AdFOXM1shRNA, which expresses FOXM1-specific short hairpin RNA, may be used as a therapeutic intervention for the treatment of patients with NPC.[13] By down-regulating the expression of Secreted Protein, Acidic and Rich in Cysteine (SPARC), TF sex determining region Y-box 5 (SOX-5) functions in the progression of NPC and may be used as a predictor for poor NPC prognosis.[14,15] Although these studies have been performed to investigate NPC, the mechanisms of NPC still remain unclear.

In 2006, Sengupta et al. analyzed the expression of all latent EBV genes between NPC samples and normal nasopharyngeal epithelium samples, and obtained a panel of differentially expressed genes (DEGs).[3] Using the same data that was used by Sengupta et al.,[3] we not only screened the DEGs but also performed a comprehensive bioinformatic analysis to identify key genes associated with NPC. The potential functions of the DEGs were predicted by functional and pathway enrichment analyses. In addition, a TF-DEG regulatory network was constructed to investigate the regulatory relationships between TFs and DEGs.

Methods

Microarray data

The GSE12452 expression profile data deposited by Sengupta et al.[3] was downloaded from the Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) database, which was based on the platform of the GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array. The specimens included 31 NPC samples and 10 normal nasopharyngeal tissue samples collected from patients from Taiwan with informed consent. The samples were resected, fast frozen and then stored in liquid nitrogen.

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