Abstract

**Background:** The aim of this study was to confirm the role of nuclear pore membrane protein 121 (POM121) in oral squamous cell carcinoma and to explore the underlying mechanism.

**Methods:** POM121 mRNA and protein expressions were evaluated in OSCC tissues and normal oral tissues by quantitative real-time polymerase chain reaction (qRT-PCR) and immunohistochemistry. The relationship between POM121 expression and clinical characteristics was analyzed. Bioinformatics analysis was performed to explore the possible mechanisms how POM121 affected OSCC.

**Results:** We confirmed that POM121 mRNA expression in OSCC tissues was significantly higher than that in non-tumorous tissues, as was POM121 protein expression. POM121 expression was associated with distant metastasis and TNM stage. Multivariate analysis confirmed POM121 expression as an independent prognostic factor for OSCC patients. OSCC patients with high POM121 expression had a worse overall survival (OS) compared with patients with low POM121 expression. Bioinformatics analysis indicated POM121 may regulate OSCC through hedgehog and/or p53 signaling pathway.

**Conclusion:** Targeting of POM121 expression levels could provide new diagnostic and therapeutic strategies for OSCC patients.

Key words: POM121, oral squamous cell carcinoma, prognosis, tissue microarrays
Nuclear pore complexes (NPCs) are large protein cylinders composed of more than 30 nucleoporins (NUPs) that function as the only gateway in the nuclear envelope. NPCs control the communication between the cytosol and the nucleus, and regulate cellular signaling. It was reported that NPCs are involved in cell cycle regulation [10], heterochromatin reorganization [11], transcriptional regulation [12], and RNA processing [13]. Aberrant nucleocytoplasmic transport and the subsequent nucleoporin-associated mislocalization of proteins are responsible for tumorigenesis and proliferation [14]. NUP98, TPR and several other NUPs have been confirmed to have a close relationship with tumors [15-17], but the specific NUPs and underlying mechanisms connected with OSCC require further investigation.

In this study, we analyzed POM121 expression in OSCC tissues and in oral non-tumor tissues and confirmed that POM121 expression was related to tumor proliferation, metastasis, and poor prognosis in OSCC. Our results provide a new insight into the biological characteristics of POM121 in OSCC. Further studies are required to confirm POM121 as a potential biochemical marker for OSCC patients.

Materials and methods

Tissue specimens and patient data

Oral tissue was obtained from 298 patients who had undergone surgery or biopsy at the Affiliated Hospital of Nantong University between January 2003 and December 2012. The tissues consisted of 298 OSCC, 50 dysplasia, and 32 normal oral tissue. None of the patients had undergone any neoadjuvant therapy before sample collection. The patients included 134 males and 164 females, with a median age of 35 years (range, 40–75years). Clinical data was collected from patient medical records, and disease clinical stages of OSCC were determined according to the 7th AJCC Cancer Staging Manual. The study complied with the requirements of the Human Ethics Committee of Affiliated Hospital of Stomatology, Nanjing Medical University, and written consent was obtained from all patients.

Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA in frozen tissue was extracted using Trizol reagent (Invitrogen, Carlsbad, USA) according to the manufacturer’s instructions. cDNAs were synthesized using a Maxima First Strand cDNA Synthesis Kit (Invitrogen, Carlsbad, USA) according to the manufacturer’s protocol. Amplified reactions were performed with SYBR Select Master Mix (Applied Biosystems, USA) using an ABI Prism 7500HT Sequence Detection System (Applied Biosystems, USA). Primers were as follows: human POM121 forward, 5’-CAGACGCCACCGTGTGCT-3’, and reverse, 5’-GATCCCACCAATGGAAAATC-3’, and GAPDH forward, 5’-ACAACTTGTAT CGTGAAGGC-3’, and reverse, 5’-GCCATACAGGCC ACAGTTTC-3’. POM121 mRNA expression was normalized to GAPDH and calculated as 2^{ΔΔCt}(ΔCt = Ct_{POM121} − Ct_{GAPDH}). All experiments were performed three times.

Construction of tissue microarrays (TMA) and immunohistochemistry analysis (IHC)

TMAs were constructed in the Department of Pathology, Affiliated Hospital of Stomatology, Nanjing Medical University. Tissue cores (2 mm in diameter) were collected from donors and arranged in paraffin that was then made into new FFPE blocks. Sections of 4μm-thick were cut and attached to glass microscope slides. After deparaffinization and rehydration, tissues were heated in 0.01 M citrate buffer, pH 6.0 for antigen retrieval, and then incubated in 3% H2O2 to inhibit endogenous peroxidase activity [18]. POM121 was detected with a polyclonal rabbit anti-human POM121 antibody (dilution 1:200; GTX102128, GeneTex, USA) and EnVision peroxidase kit (Dako, Carpinteria, USA). IHC results were evaluated by two pathologists blind to patient data. Staining intensity for POM121 was determined as 0 (negative), 1 (weakly positive), 2 (moderately positive), and 3 (strongly positive) [19]. The final staining score = 3×percentage of strong staining + 2×percentage of moderate staining + 1×percentage of weak staining. The final staining score ranged from 0 (no staining) to 300 (100% of cells with strongly positive staining). The cutoff point of high and low or no POM121 expression was set as 110.

Gene set enrichment analysis (GSEA) and protein interaction network

The Cancer Genome Atlas (TCGA) database was searched to obtain RNAseq data of gastric cancer patients. GSEA v2.2.2 software was utilized to perform GSEA and analyze differences in biologic pathway. POM121 mRNA expression level was divided as low (<0.5) and high (>0.5) groups, and functional gene sets were defined according to KEGG gene sets in Molecular Signatures Database (MSigDB). p < 0.05 and FDR < 0.01 were recognized as differentially expressed threshold. STRING v10.5 was used to construct the putative protein interaction network of POM121.

Statistical analysis

All data were analyzed using the SPSS 18.0
were defined as statistically significant. To confirm the prognostic factors, the Kaplan–Meier method was used to analyze cumulative survival rate. The Cox proportional hazard regression model was constructed for univariate and multivariate analyses to confirm the prognostic factors. P values of < 0.05 were defined as statistically significant.

**Results**

**POM121 mRNA was overexpressed in OSCC tissues**

qRT-PCR was performed to detect POM121 mRNA expression levels in 22 cases of OSCC tissues and matched normal oral tissues. Results showed that POM121 mRNA expression in OSCC tissues was 3.312±2.143 fold higher than that in matched normal oral tissues (P<0.05, Figure 1).

**POM121 protein expression in OSCC tissues**

POM121 protein expression was detected by IHC assay in OSCC, dysplasia, and normal oral tissues. Results showed that POM121, which is embedded in the nucleus and nuclear envelope, was overexpressed in OSSC tissues (Figure 2). The occurrence rate of high POM121 expression in OSCC tissues was 59.73% (178/298), higher than that in normal oral tissues (18.75%, 6/32) and dysplasia (22.0%, 11/50) (Table 1).

| Characteristic | n  | POM121 expression (%) | χ²  | P     |
|---------------|----|-----------------------|-----|-------|
|               |    | Low or no (%)         | High (%) |      |
| Oral cancers  | 298| 120(40.27)            | 178(59.73) | 39.233 | <0.001* |
| Normal        | 32 | 26(81.25)             | 6(18.75) |       |
| Dysplasia     | 50 | 39(78.00)             | 11(22.00) |       |

**Correlation between POM121 expression and clinical characteristics in OSCC**

The correlation between POM121 expression and pathological parameters in OSCC was analyzed. High expression of POM121 was significantly connected with distant metastases (χ²=7.680, P=0.006) and TNM stage (χ²= 5.352, P=0.021). However, no significant difference was found between POM121 expression and sex, age, location, differentiation, tumor size, lymph node metastases, caries, or smoking (Table 2).

![Figure 1. POM121 mRNA expression in 31 OSCC tissue pairs.](http://www.jcancer.org)
**Table 3.** Univariate and multivariate analysis of prognostic factors for overall survival in oral cancer

|                      | Univariate analysis |                      | Multivariate analysis |                      |
|----------------------|---------------------|----------------------|-----------------------|---------------------|
|                      | HR                  | P-value              | 95% CI                | HR                  | P-value              | 95% CI                |
| POM121 expression    |                     |                      |                       |                     |                      |
| high vs low or no    | 1.903               | **0.000***            | 1.384 - 2.617         | 1.844               | **0.000***            | 1.321 - 2.575         |
| Gender               |                     |                      |                       |                     |                      |
| male vs female       | 1.124               | 0.433                | 0.839 - 1.505         |                      |                      |                       |
| Age(year)            | 1.119               | 0.449                | 0.836 - 1.498         |                      |                      |                       |
| ≤60 vs > 60          |                     |                      |                       |                     |                      |                       |
| Location             | 1.106               | 0.500                | 0.825 - 1.485         |                      |                      |                       |
| Tongue vs Others     |                     |                      |                       |                     |                      |                       |
| Differentiation      | 1.063               | 0.637                | 0.824 - 1.372         |                      |                      |                       |
| Distant metastasis   |                     |                      |                       |                     |                      |                       |
| TNM stage            |                     |                      |                       |                     |                      |                       |
| N0 vs N1 vs N2 vs N3 | 1.493               | **0.000***            | 1.223 - 1.823         | 1.322               | **0.016***            | 1.053 - 1.659         |
| Smoking              |                     |                      |                       |                     |                      |                       |
| yes vs no            | 1.289               | **0.039***            | 1.103 - 1.640         | 1.075               | **0.021***            | 1.090 - 2.891         |
| yes vs no            | 1.775               | **0.021***            | 1.140 - 2.891         | 1.167               | **0.028***            | 1.017 - 1.331         |
| yes vs no            | 0.690               | 0.075                | 0.458 - 1.038         |                      |                      |                       |
| yes vs no            | 0.571               | 0.071                | 0.310 - 1.048         |                      |                      |                       |

HR, hazard ratio; CI, confidence interval; T4b, invasion of adjacent area.

**Association between POM121 expression and prognosis in OSCC patients**

Univariate and multivariate analyses were performed to confirm prognostic factors for OSCC patients. Univariate analysis indicated that POM121 expression (P<0.001), tumor size (P=0.039), lymph node status (P<0.001), distant metastasis (P=0.021), and TNM stage (P<0.001) were significantly associated with OS of OSCC patients. Multivariate analysis showed that high POM121 expression (HR, 1.844; 95% CI, 1.321 - 2.575; P<0.001) was an independent prognostic factor for OS, as well as lymph node metastasis (HR, 1.322; 95% CI, 1.053 - 1.659; P=0.016) and TNM stage (HR, 1.163; 95% CI, 1.017 - 1.331; P=0.028) (Table 3). Kaplan-Meier survival curves confirmed that high POM121 expression, lymph node metastasis, distant metastases, and TNM stage were associated with poor OS and disease-free survival (Figure 3).

**The main enriched KEGG pathways and interacting proteins of POM121**

To explore the role of POM121 in OSCC proliferation and metastasis, an integrative analysis of OSCC microarray was carried out on the base of TCGA database. In the results of GSEA, high POM121 expression group is significantly enriched in adherens junction, axon guidance, cell cycle, hedgehog signaling, lysine degradation and mismatch repair (Figure 4A). We constructed a putative protein interaction network using the STRING interactive database. Each node in the network represented a protein that interacted with POM121, and different colors represent different degrees of closeness. The results showed that NUP62, NUP98, and some other proteins had interactions with POM121 (Figure 4B).
Figure 3 Survival curves of OSCC using the Kaplan-Meier method and the log-rank test. (A) Overall survival curves of POM121 (blue line low, green line high). (B) Overall survival curves of TNM stage, TNM 0 and I (blue line), TNM III and IV (green line). (C) Overall survival curves of location, tongue (blue line), gingival and buccal mucosa (green line). (D) Overall survival curves of tumor size, between 0 and 2 cm (blue line), between 2 and 4 cm (green line), greater than 4 cm (gray line). (E) Overall survival curves of lymph node metastases, N0 (blue line), N1 (green line). (F) Overall survival curves of distant metastases, M0 (blue line), M1 (green line).

Figure 4 The main enriched KEGG pathways and protein interaction network. (A) The GSEA results showing the correlation of POM121 levels and OSCC related gene sets in MSigDB. Gene sets “adherens junction”, “axon guidance”, “cell cycle”, “hedgehog signaling”, “lysine degradation” and “mismatch repair” were enriched in POM121 high expression phenotype. (B) Using the STRING online database, total of 47 proteins (13 in Orange centring on POM121, 6 Red centring on E2F1, 22 in green centring on MYC, and 3 in purple connected with POM121, E2F1 and MYC) were filtered into the protein interaction network.
Table 4. The main enriched KEGG pathways of POM121

| Term                                      | ES  | NES | P-value | FDR q-value |
|-------------------------------------------|-----|-----|---------|-------------|
| KEGG_ADHERENS_JUNCTION                    | 0.54| 1.83| 0.006   | 0.268       |
| KEGG_AXON_GUIDANCE                        | 0.38| 1.51| 0.037   | 0.365       |
| KEGG_CELL_CYCLE                           | 0.48| 1.66| 0.040   | 0.298       |
| KEGG_HEDGEHOG_SIGNALING_PATHWAY           | 0.42| 1.51| 0.049   | 0.329       |
| KEGG_LYSINE_DEGRADATION                   | 0.51| 1.69| 0.014   | 0.318       |
| KEGG_MISMATCH_REPAIR                      | 0.62| 1.63| 0.044   | 0.297       |

ES: enrichment score; NES: normalized enrichment score; FDR: false discovery rate.

Discussion

POM121 is a 121 kDa transmembrane NUP that anchors the NPC to the mammalian nuclear membrane and is less conserved than two other vertebrate membrane NUPs, NDC1 and GP210 [20, 21]. POM121 has an important role in NPC assembly, nuclear transport, and cytoplasmic membrane stacks [22-24]. It was reported that the N-terminally-truncated POM121C blocks HIV-1 infection after completion of reverse transcription and before integration [25]. Guo et al. further confirmed that full-length POM121 enables efficient HIV-1 pre-integration complex nuclear import by KPNB1-dependent classical cargo nuclear transportation [26]. Interestingly, POM121 was also found to be involved in the propagation of nuclear apoptosis, which is related to tumorigenesis [27]. POM121 was found to promote proliferation, aggressiveness, and therapeutic resistance in prostate cancer [28]. However, little is known about the relationship between POM121 and oral cancer.

In this study, bioinformatic analysis revealed that POM121 and SEC13 were hub genes in OSCC tissues, with POM121 upregulation the greatest. To confirm the conclusions acquired from microarray analysis, POM121 mRNA expression was detected in fresh frozen OSCC tissues and matched non-tumorous oral tissues by qRT-PCR. The result showed that POM121 mRNA levels in OSCC tissues were significantly higher than in normal oral tissues. According to IHC analysis, POM121 was found to be located in the nuclear envelope and nucleoplasm. High POM121 expression was detected more frequently in OSCC tissues (59.73%) than in normal oral tissues (18.75%), similar to the observed mRNA expression patterns. We also detected POM121 expression in oral dysplasia tissues and confirmed that high POM121 was expressed in OSCC tissues but not dysplasia (22.00%). Interestingly, the positive expression rates of POM121 in dysplasia did not show a significant difference with normal oral tissues. Insufficient patient samples may account for this phenomenon.

We analyzed 298 samples of OSCC tissues and their associated clinical information to explore the association between POM121 and clinicopathological features. Our findings showed that POM121 expression was significantly connected with distant metastases and TNM stage. High POM121 expression was more common in patients with distant metastases and TNM (III + IV) stage. These results indicated that POM121 was associated with the development and progression of OSCC. Moreover, the correlation between POM121 protein expression and distant metastasis indicated POM121 may be involved in OSCC metastasis.

Univariate Cox regression analysis showed that POM121 expression, tumor size, lymph node status, distant metastasis, and TNM stage were associated with survival of OSCC patients. Multivariate analysis further confirmed that POM121 expression, lymph node metastasis, and TNM stage were independent prognostic factors for OSCC patients. Kaplan-Meier survival curves also supported the importance of POM121 in patient prognosis. These results suggested that high levels of POM121 in patients predicted poor OS and disease-free survival.

Little is known about the molecular mechanisms of POM121 in OSCC development and progression. The results of GSEA showed that the expression of POM121 influences adherens junction, axon guidance, cell cycle, hedgehog signaling, mismatch repair and lysine degradation. Mismatch repair is well-known biological activity involved in cancer, and the role of mismatch repair and relevant proteins in oral carcinogenesis and development has grown [29]. Adherens junction refers to the feature of all epithelial sheets and apical adhesive structures, regulating cancer invasion and metastasis [30]. Hedgehog signaling is reported to modulate the tumor microenvironment in several cancers, associated with tumor cell growth, invasion, and metastasis [31, 32]. Hence, we presumed POM121 may participate in tumorigenesis, invasion and metastasis.

Our protein interaction network revealed close connection between POM121 and a large group of proteins, including NUP62, MYC and so on. POM121 may participate in tumor progression through these proteins. The protein network also showed POM121 interacted with NUP62. Interestingly, NUP62 is confirmed to regulate squamous cell carcinoma
POM121 regulates nuclear import of oncogenic MYC through importinβ to promote prostate cancer [28]. Some studies demonstrated MYC is involved in tumorigenesis and progression in OSCC [34-36]. Furthermore, it has been confirmed that soluble POM121 has a role in NUP98-mediated gene regulation by colocalizing and interacting with the transcriptional regulator NUP98, which has been found to participate in the pathogenesis of several hematological malignancies [37, 38]. NUP98 is required for full expression of p21, a critical effector of the p53 pathway, which is associated with OSCC progression [39, 40]. Further studies should be undertaken to explore if POM121 regulates the expression of MYC and/or p53 signaling pathways.

Conclusion

The expression of POM121 in OSCC tissues is higher than that in normal oral tissues. High POM121 expression is associated with poor overall survival in OSCC patients. Our results show that POM121 has the potential to be considered as an independent prognostic biomarker in OSCC.

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Ethical statement

This study was performed in accordance with medical ethical standards and was approved by the Ethics Committee of Nanjing Medical University. Written informed consents were obtained from all study participants.

Competing Interests

The authors have declared that no competing interest exists.

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