

論文要旨等報告書

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学位論文題名	Frequent deletion of ING2 locus at 4q35.1 associates with advanced tumor stage in head and neck squamous cell carcinoma (頭頸部扁平上皮癌進行期におけるING2遺伝子の欠失)
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学位論文内容の要旨

Background: Head and neck squamous cell carcinoma (HNSCC) is a heterogenous disease with complex molecular abnormalities, including genetic alterations either in tumor suppressor genes (TSG) or oncogenes. Recent studies examined the relationship of allelic loss at chromosomal locations with clinicopathological data. Some of these studies focused on the identification of a reliable and easily applicable marker, which can diagnose cancer early during carcinogenic stage. Other studies performed molecular analysis, which would guide the clinician for the prognosis and behavior of tumor such as metastatic capacity, recurrence, response to therapy, and survival of the patient.

The ING family proteins are recently identified tumor suppressors containing a plant homeodomain (PHD) finger, a motif common to many chromatin-regulatory proteins. So far, five members of the ING family (ING1-ING5) have been identified in humans. Analysis of these genes showed that they function either in cooperation with p53 or in a p53-independent manner to induce cell growth arrest and/or apoptosis.

Objectives: Loss of heterozygosity (LOH) in the ING family members has been shown in HNSCC except for ING2. Like all the other members of ING family, ING2, which is located at chromosome 4q35.1, is a promising TSG. In this study, we performed LOH analysis of ING2 in HNSCC and compared its deletion with TP53 mutation status as well as clinicopathological variables.

Materials and methods: We performed LOH analysis in DNAs from 80 paired of normal and HNSCC tissues, by designing a microsatellite marker on chromosome 4q35.1, which specifically detects allelic loss of ING2 locus. TP53 mutation analysis and its relationship with ING2 chromosomal deletion were also performed in available 68 of the samples. The correlation between LOH status and clinicopathological characteristics was evaluated by using statistical methods. The overall survival (OS) and disease free survival (DFS) were also determined.

Results: LOH was detected in 54.6% (30/55) of the informative samples. TP53 mutations were identified in 26 out of 68 (38.2%) cases. Although high percentage of ING2 LOH and TP53 mutations were simultaneously observed, no statistically significant association was detected. This finding suggests that ING2 LOH occurs independently of TP53 status. Statistical significance was obtained between LOH and tumor size (T stage) ($p= 0.02$), application of radiotherapy ($p= 0.02$) and chemotherapy ($p= 0.03$). A near significant relationship was shown between ING2 LOH and DFS ($p= 0.11$). These results suggest that allelic loss at 4q35.1 is likely to be a late event and might also provide prognostic significance in HNSCC. Finally, positive node status (N) appeared to be the only independent prognostic factor for both OS ($p= 0.031$) and DFS ($p= 0.044$).

Conclusions: Our study showed allelic loss of 4q35.1 in HNSCC. The high percentage of LOH suggests ING2 as a candidate TSG in HNSCC. High LOH frequency was statistically associated with advanced T stage, suggesting that ING2 LOH might occur in late stages during HNSCC progression.

論文審査結果の要旨

癌は、癌遺伝子および癌抑制遺伝子と呼ばれる複数の遺伝子異常が生じることにより発生する。特に癌抑制遺伝子の機能低下は癌の発生に重要であり、新規癌抑制遺伝子の発見・機能解析は癌病態解明において重要な意義を有する。

Loss of Heterozygosity(LOH)解析は、相同染色体にコードされている一方の遺伝子の欠失状態を検索する方法である。癌組織においてLOHがみられる遺伝子は癌抑制遺伝子である可能性が高いと考えられる。これまでの頭頸部扁平上皮癌における解析から ING familyが癌抑制遺伝子として癌化に密接に関与していることが報告されているが、ING2遺伝子に関してはその詳細は不明である。

本研究は、頭頸部扁平上皮癌におけるING2遺伝子のLOH解析を行うとともに、その欠失とTP53遺伝子変異および臨床データとの関連を検討したものである。

頭頸部扁平上皮癌80症例において、ING2特異的プライマーを用いてLOH解析を行った結果、55症例中30症例と高頻度(54.6%)のLOHが認められた。TP53のmutation解析では、検索可能であった68症例中26症例(38.2%)においてmutationを認めた。統計学的解析からING2のLOHとTP53遺伝子変異の間には明らかな相関は認められなかった。ING2のLOHと臨床病理データとの比較から、TNM分類のT因子、放射線治療の有無、化学療法の有無との間に相関を認め、進行期(Late T, T3-T4)において有意に高いLOHを認めた。また、LOHを認めた患者は無疾患生存率が短い傾向を示した。

以上のことから、ING2は頭頸部扁平上皮癌における新規癌抑制遺伝子である可能性が示唆され、癌の病期と関連することが示唆された。

これらの知見は、頭頸部扁平上皮癌における病態解明の一端を担う基礎研究として価値のある研究業績である。よって本論文は博士(学術)の学位論文として価値があるものと判断した。