

論文要旨等報告書

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学位論文内容の要旨

Background: Oral squamous cell carcinoma (OSCC) is the most common cancer of the oral cavity and have an incidence of about 500 000 new cases in the world each years. Despite progress in therapy, the cure rate does not exceed 50% and improvement of our knowledge of the carcinogenesis of OSCC is needed. It is known that tumor suppressor gene (TSG) inactivation is a major event in carcinogenesis and that the 1p36 region is suspected to harbor many TSG implicated in various type of cancer. In cervical SCC, some studies suggest that damages in 1p36 region could be a frequent and early event and it is also suggested that OSCC carcinogenesis could be correlated with inactivation of TSG located in this region. So, we have chosen to investigate 1p36 region in patient with OSCC.

Objectives: Identification of TSG is an important step for establishing new markers of cancer progression and improves the treatment of the disease. As TSG involved in OSCC carcinogenesis are potentially located in 1p36 region, we have chosen to examine this region. Our objective is to identify areas of the 1p36 region susceptible to harbor such TSG. Identification of such regions could be used as a strong basis for further studies to identify and characterize new TSG involved in OSCC. This will allow establishing new markers for cancer progression and helping to diagnosis the status of the cancer and provide a treatment adapted to the patient. Such data will be also useful for elaborating new and more effective therapies which could target these genes.

Materials and Methods: Paired samples of DNA extracted from 27 Japanese patients with OSCC were used. The samples were amplified by polymerase chain reaction (PCR) with 9 microsatellite markers selected from the literature which covers the 1p36 region. The amplified samples were subject to polyacrylamide gel electrophoresis, stained with silver staining and used for loss of heterozygosity (LOH) analysis.

Results: LOH was found at least in one locus in 85% of the investigated cases. The markers which gave the higher rates of LOH were D1S228 (38%), D1S199 (28%), D1S243 (25%), D1S450 (25%), D1S1676 (23%) and D1S468 (22%). We have identified 3 regions which are frequently deleted. They are region 1 (D1S468-D1S243), region 2 (D1S450-D1S228) and region 3 (D1S199-D1S1676). All of these regions harbor genes which could be candidate TSG as RIZ, p73, UBE4B, Rap1GAP, EPHB2 or RUNX3. Moreover, in region 2, LOH only with the marker D1S228 was obtained in 22% of the case, so TSG located in region 2 are of special interest as they could be involved in early events of OSCC carcinogenesis. At the opposite, the markers D1S199 and D1S1676, which delimit the region 3, do not shown LOH alone at the exception of 1 case, so it is possible that TSG of this region are related with later event of carcinogenesis in this type of cancer.

Conclusions: We have localized 3 areas in 1p36 region which are frequently deleted in OSCC patients. All these regions possess genes which could be candidate TSG involved in OSCC carcinogenesis. Further studies are needed for the clarification of the role of these genes in OSCC.

論文審査結果の要旨

口腔扁平上皮癌は発生頻度が高い悪性腫瘍である。その発生に関与する癌遺伝子・癌抑制遺伝子については不明な点が多いが、癌化に関わる癌抑制遺伝子を特定できれば、病態の理解と新規治療法の開発に大きく貢献することができる。癌抑制遺伝子の抑制・機能低下の原因のひとつとして、同染色体にコードされている一方のアレルの欠失

(Loss of Heterozygosity : LOH) が挙げられる。癌組織においてLOHが高頻度に存在する領域を検索すれば、癌抑制遺伝子の同定に寄与できると考えられる。

本研究では、多種類の癌で高頻度に欠失が報告されている染色体1p36領域に注目し、LOH解析によって、口腔扁平上皮癌の発生に関わる新規癌抑制遺伝子候補を検討することを目的としたものである。

実験の対象には、27症例の口腔扁平上皮癌患者の正常組織と癌組織からゲノムDNAを抽出したペアサンプルを用いた。染色体1p36領域について9種類のマイクロサテライトマーカーを用いて詳細なLOH解析を行った結果、22%~38%と高頻度にLOHを示す3領域を同定した。各LOH欠失領域にはp53、UBE4B、RIZ1(PRD2)、Rap1GAP、EPHB2の新規癌抑制遺伝子候補と考えられる複数の遺伝子が存在していた。特にRIZ1遺伝子は最もLOHの検出頻度が高い領域に存在し、また、症例間でのLOHの出現パターンから、RIZ1遺伝子が口腔扁平上皮癌の癌化に深く関与する可能性を示唆した。

以上のように、口腔扁平上皮癌において染色体1p36に高頻度にアレルの欠損を有する領域を認め、複数の新規癌抑制遺伝子候補の存在が示唆された。

これらの知見は、口腔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)の学位授与に値するものと判断した。