

論文要旨等報告書

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授与した学位	博士
専攻分野の名称	歯学
学位授与の番号	博 甲 第 3 8 1 8 号
学位授与の日付	平成 2 1 年 3 月 2 5 日
学位授与の要件	医歯薬学総合研究科病態制御科学専攻(学位規則第4条第1項該当)
学位論文題名	Stromal cells promote bone invasion by suppressing bone formation in ameloblastoma (エナメル上皮腫間質細胞の骨形成機能抑制による骨吸収促進)
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学位論文内容の要旨

Background: Ameloblastoma is the most frequently encountered benign but locally invasive odontogenic tumor. Typical ameloblastoma begins insidiously as a central lesion of bone, which is slowly destructive, and ultimately growth expansively within the bone. Radiological examination shows multilocular, soap bubble or cystic type appearance. This feature suggests that in ameloblastoma along with enhanced bone resorption may be mineralization is also impaired. Bone remodeling is a normal process that involves the resorption of bone by osteoclasts and the synthesis of bone matrix by osteoblasts. The mechanism responsible for tumor growth in bone is complex and involved tumor stimulation of the osteoclast and the osteoblast as well as the response of the bone microenvironment. The importance of the interaction between stromal and epithelial cells is well established in tumorigenesis. Tumor cells live in a complex microenvironment that includes extracellular matrix (ECM), diffusible growth factors, cytokines and a variety of non-epithelial cell types.

Objectives: Ameloblastoma exhibit a variety of histological patterns, a great infiltrative potential and a high recurrence rate with tumor cells lying on abundant stroma. There is no report for the stromal and tumor cell interaction and their subsequent role in bone invasion resulting to tumor progression in ameloblastoma. In this study, we focused on the stromal variation and role of stromal-tumor cell interaction in impaired bone formation as well as enhanced bone resorption in ameloblastoma.

Materials and Methods: 22 blocks from 17 cases were used for this experiment. 54 areas from these 22 blocks were chosen based on the presence of bone tissue, stroma and tumor nests. The type of stroma near the bone interface and around the tumor nest was categorized based on their histological characteristics and four different groups were made. Osteoblasts and osteoclasts were identified according to their histological characteristics. The counting process was performed along the bone surface adjacent to the tumor stroma using H&E sections and immunohistochemistry with CD68. The measurement of bone length at the interface was done using Image J program. Both cell count and measurement processes were repeated three times and the average was calculated. The differences in the number of osteoblasts, osteoclasts and CD68 positive cells at the different type stroma were subjected to statistical analysis. Primary antibodies used for immunohistochemical staining were sFRP-2, TGF- β 1, RANKL, BMP-2, OPG and IL-6.

Results: Histologically four types of stroma were observed; fibrous, desmoplastic, myxoid and myxoid with hyalinization. After counting the total cell number, the number of osteoclasts and CD68 positive cells were observed to be more abundant in myxoid type stroma. However, statistical analysis showed no significant difference between fibrous type and desmoplastic type as well as between myxoid type and myxoid with hyalinization type stroma. Finally, fibrous and myxoid types of stroma were distinctly identified. sFRP-2 and TGF- β 1 revealed a strong expression in myxoid type compared to the fibrous type stroma. RANKL showed positive but BMP-2 and IL-6 showed negative immunoreactivity in both types of stroma. In this study, myxoid stroma showed strong immunoexpression in all of these molecules comparing to fibrous type stroma. This finding suggests that bone destruction without proportional bone formation is more remarkable in myxoid type stroma. And the tumor cells only induce a favorable microenvironment for tumor invasion by secreting sFRP-2, RANKL and IL-6.

Conclusion: In ameloblastoma, stroma acts on both suppression of new bone formation and bone resorption, might play a crucial role in bone invasion of ameloblastoma.

論文審査結果の要旨

エナメル上皮腫は、生物学的には良性とされているが、顎骨侵襲能が高く、再発率も高い。そのため、臨床的に準悪性として取り扱われ、顎骨離断を含む広範な切除が求められる事も多い。

近年、多発性骨髄腫においてsFRP-2を介した骨芽細胞分化抑制因子による骨形成の抑制が、骨吸収を進行させることが報告された。しかし、エナメル上皮腫では多発性骨髄腫と異なり腫瘍胞巣と骨組織との境界に豊富な間質が介在し、顎骨吸収への腫瘍間質の関与が推察される。

そこで本研究では、エナメル上皮腫における骨吸収のメカニズム、特に腫瘍間質の関与を明らかにすることを目的とし、骨界面における腫瘍間質の性状と腫瘍間質における骨吸収および骨形成関連因子の局在を免疫組織化学的に検索している。

エナメル上皮腫17例を用いた組織学的観察と骨界面上の骨芽細胞、破骨細胞数の計測およびCD68免疫染色結果から、腫瘍間質はfibrousとmyxoid typeに分類された。

骨吸収および骨形成関連因子 (sFRP-2, TGF- β 1, RANKL, IL-6, OPG, BMP-2) の免疫組織化学的検索により、エナメル上皮腫の腫瘍間質においてsFRP-2, TGF- β 1, RANKLの局在を認めた。特にmyxoid typeではfibrous typeと比べsFRP-2, TGF- β 1が強陽性を示し、顎骨吸収との関連性が示唆された。

以上のことから、エナメル上皮腫における顎骨吸収には腫瘍間質の性状が深く関与し、骨吸収促進因子のみならず骨形成抑制因子の活性化により顎骨侵襲を促進することが示唆された。

これらの知見は、エナメル上皮腫における顎骨吸収メカニズム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(歯学)の学位授与に値すると判定した。