論 文 内 容 の 要 旨

Synopsis of Thesis

氏 名 Name	鈴木 彩菜
論文題名 Title	Identification of invasive subpopulations using spatial transcriptome analysis in thyroid follicular tumors （甲状腺濾胞性腫瘍における空間トランスクリプトーム解析を用いた浸潤性亜集団候補の同定）

論文内容の要旨

〔目 的(Purpose)〕

Follicular tumors include follicular thyroid adenomas and carcinomas; however, it is difficult to distinguish between the two when the cytology or biopsy material is obtained from a portion of the tumor. The presence or absence of invasion in the resected material is used to differentiate between adenoma and carcinoma. If nodules that may be follicular thyroid carcinomas (FTC) are identified preoperatively, active surveillance of adenomas is possible. This reduces the risk of surgical complications and the expenses incurred during medical treatment. Spatial transcriptome analysis technology for formalin-fixed paraffin-embedded (FFPE) specimens has advanced considerably, and tumor heterogeneity can be detected. If invasive tumor subpopulations can be detected by spatial transcriptome analysis of FFPE specimens of FTC, new markers for assessing the invasiveness of FTC can be identified. The eligibility of the target tumors for resection can be determined during tissue biopsy and cytology. Therefore, we aimed to identify tumor subpopulations near the invasive area by spatial transcriptome analysis of FFPE specimens containing the invasive area of FTC and to perform immunohistochemical studies based on these results.

〔方法ならびに成績(Methods/Results)〕

We performed a spatial transcriptome analysis of a case of FTC using Visium CytAssist Spatial Gene Expression for FFPE (10x Genomics, CA, USA). Subsequently, we examined the dynamics of CD74 expression in 36 follicular thyroid carcinoma cases. The expression of CD74 was assessed using a visual grading system based on staining intensity under a light microscope. High intensity (++), low intensity (+), and no signal (-) were defined as strong, weak, and no staining, respectively. The invasive area was defined as a tumor lesion invading or over the capsule or an angioinvasive lesion. The periphery area of the tumor was defined as the tumor lesion within 1 mm of the tumor border.

We identified a subpopulation in a region close to the invasive portion, and this subpopulation expressed high levels of CD74. Immunohistochemically, CD74 was highly expressed in the invasive and periphery areas of FTC.

〔総 括(Conclusion)〕

CD74 is known to play an important role in antigen presentation by mediating the construction of MHC class II complexes and intracellular trafficking, and it has also been reported that CD74 is upregulated in malignant tumors and involved in increased growth and metastatic potential. Although high CD74 expression has been reported in papillary and anaplastic thyroid carcinomas, it has not been analyzed in FTC. Furthermore, the diversity of CD74 expression in thyroid tumors has not yet been reported.

The results of this study suggested that the staining score of the invasive area was significantly higher than that of the center area ($p<0.005$), revealing that the CD74-positive subpopulation might be used to predict the invasion of FTC.

Although this study was performed on resected material, it is expected that immunocytochemical staining for CD74 will be performed in the future on nodules suspected of having follicular tumors on cytological examination or biopsy tissue specimens to determine the possibility of invasion before surgery and contribute to reducing unnecessary resection of nodules with a low possibility of invasion.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

甲状腺濾胞性腫瘍には浸潤性の癌と非浸潤性の腺腫があるが、その一部を採取した細胞診・生検材料で両者の鑑別は形態学的に困難であり、切除材料にて鑑別される。そのため現状では、本来切除不要な腺腫まで切除しており、過剰診療が問題となっている。この回避には濾胞癌における浸潤性亜集団の同定が重要である。本研究では濾胞癌症例の空間トランスクリプトーム解析にて浸潤部に存在する亜集団を同定し、これらがCD74を高発現することを明らかにした。さらに多数例の濾胞癌症例を用いてCD74の発現動態を検討し、浸潤部でCD74が免疫組織学的に陽性を示すことを明らかにした。甲状腺腫瘍ではこれまで乳頭癌と未分化癌におけるCD74高発現の報告はあるが、濾胞癌では解析されていない。さらに甲状腺結節内でのCD74の発現多様性を解析した報告はない。本研究により明らかにされたCD74陽性亜集団は濾胞性腫瘍の浸潤予測に利用できる可能性があり、学位論文として相応しい。