（書式１２）

氏　　名	サマネ　　ヤズダニキビ Samaneh Yazdanikivi
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学位論文題目	Implication of angiogenesis and progesterone receptor A expression in cell proliferation of neuroendocrine tumor（神経内分泌腫瘍の細胞増殖における血管増生とプロゲステロン受容体 A 発現の関与）
論文審査委員	主査　教授　笹野　公伸 教授　伊藤　潔　　教授　高橋　和宏

論文内容要旨

Variable molecular pathways are considered to play important roles in cell growth of neuroendocrine tumor (NET). Angiogenesis is considered one of the most pivotal features, because NET has been well-known as a highly vascularized tumor and its inhibition could be one of the most important therapeutic strategies of the patients. The pancreatic NET (PNET) has been also reported to express progesterone receptor (PR) and its expression also demonstrated as an important prognostic factor in these patients. The correlation of these two pivotal treatment targets, angiogenesis and PR, has been previously reported in other tumors in which higher level of angiogenesis was correlated with adverse PR expression but not in NET. Therefore, in order to understand the mechanisms of cell proliferation in NET, we first examined the process of cell proliferation and structural alterations of intratumoral blood vessels in human NET during tumor development and progression. We then examined the status of PR isoforms and their association with cell proliferation of the tumor cells. We also evaluated the correlation between angiogenesis and PR status of the patients. Microvessel density was evaluated using the endothelial cell markers vasohibin-1 (VASH-1) and CD31 in 135 NET cases. Double immunohistochemistry staining was performed to localize endothelium (CD31 and VASH-1) and pericytes (nestin) on the same vessels. Quantitative RT-PCR and proliferation assay were also performed following the treatment of cells with progesterone (P4) as PR agonist and RU486 as PR antagonist in empty vector pcDNA3.1(-) and PRA transfected cells of NET cell line, QGP-1. PRA, PRB and cyclin D1 (CCND1) were also immunolocalized in the cases examined. The ratio of Ki-67/CD31 was significantly positively correlated with that of VASH-1/CD31 positivity (P= 0.001), indicating that the ratio of VASH-1/CD31 reflects the status of neovascularization in NET. This ratio tended to be higher in NET than in its nonneoplastic counterpart (P= 0.10) and to increase according to World Health Organization (WHO) grade, although the differences did not reach statistical significance (P= 0.32). The ratio of VASH-1/nestin-positive vessels, representing the maturation of neovessels, was also significantly higher in NET than in its nonneoplastic counterparts (P= 0.003). PRA and PRB immunoreactivity was detected more frequently in PNET than in other gastroenteropancreatic NET (P< 0.001, P< 0.001; respectively). PRA immunoreactivity was significantly lower in higher than lower grade PNET (P= 0.04) whereas CCND1 significantly elevated in higher grade PNET (P= 0.035). Significant difference was also confirmed in immunohistochemical analysis of PRA-CCND1 status among nonneoplastic and different WHO grades (P= 0.004). No significant correlation was detected between PRA and VASH-1/CD31 (P= 0.94). The proliferative activity of QGP-1

cell line with PRB expression, increased after administration of P4 (P= 0.006) whereas no significant changes detected in PRA transfected cells (P= 0.42). Results of my present study demonstrated that angiogenic activity was significantly increased with the vessel maturation decreased in NET with higher WHO grade. These structural changes in the vessels were considered to play an important role in inducing tumor-cell proliferation of NET. In addition, PRA could play an inhibitory role in cell proliferation in PNET by PRB inhibition under the presence of P4, which then probably decreased CCND1 expression. Results of my present study demonstrated that angiogenic process and PR expression were involved in independent pathways of NET biology in contrast to different neoplasms such as breast cancer, which could provide important information as to the development of potential therapeutic targets in the patients with NET.

【所定様式⑬No.1】大学院の課程による者（課程博･医学）

審　査　結　果　の　要　旨

博士論文題目　Implication of angiogenesis and progesterone receptor A expression in cell proliferation of neuroendocrine tumor（神経内分泌腫瘍の細胞増殖における血管増生とプロゲステロン受容体A発現の関与）

所属専攻・分野名　医科学専攻　・　病理診断学　分野

氏名　Samaneh Yazdanikivi

ヒト腫瘍において組織中における腫瘍血管の増殖機序や腫瘍血管の分化はその生物学的動態を考えるに際しては極めて重要である。 神経内分泌腫瘍はその頻度こそ高くはないが種々のホルモンを合成、分泌する事からその血管密度は極めて高い事は知られているが、その血管新生動態に関しては不明のままであった。 今回ヤズダニは膵・消化管神経内分泌腫瘍における腫瘍血管の増殖が有する臨床病理学的意義や、治療標的臓器としての意義について検討を行い、Vasohibin-1の発現で検討した腫瘍新生動態が腫瘍細胞の増殖能力と正相関をすることを初めて示した。更にヤズダニは腫瘍血管のpericytesの発現動態から 神経内分泌腫瘍においての腫瘍血管成熟についても初めて検討成果を示した。 一方神経内分泌腫瘍では従来プロゲステロン受容体(PR)が高率に発現し臨床予後に関連する事は知られていたが、今回ヤズダニはその生物学的動態や治療標的としての意義についても研究を行った。 特にPRのsubtypesであるPRAを介するプロゲステロンの作用がPRBを抑制する事で神経内分泌腫瘍の細胞増殖を抑制する事を初めて細胞モデルを用いて示した。 そしてヤズダニは乳癌他で提唱されているプロゲステロンと血管新生との相互関係にも着目し、神経内分泌腫瘍ではこの両者は別々な独立した経路で腫瘍細胞の増殖制御に関わっている事を初めて示した。

以上は神経内分泌腫瘍患者の特異的治療を含めて今後の更なる発展が期待される優れた研究成果であるとも考えられる。

よって，本論文は博士（医学）の学位論文として合格と認める。