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学位論文題目	Intratumoural heterogeneity of intestinal expression reflects environmental induction and progression-related loss of induction in undifferentiated-type gastric carcinomas （未分化型胃癌での腸発現の腫瘍内多様性は環境からの誘導と癌進展に伴う誘導の喪失を反映している）
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別紙様式３

論 文 内 容 要 旨

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学位論文題目	**Intratumoural heterogeneity of intestinal expression reflects environmental induction and progression-related loss of induction in undifferentiated-type gastric carcinomas** (未分化型胃癌での腸発現の腫瘍内多様性は環境からの誘導と癌進展に伴う誘導の喪失を反映している) Histopathology, 2008, in press		

Background and aim:

Gastric carcinomas (GCs) have been morphologically classified into differentiated-type and undifferentiated type in Japan. Genetic lineage analyses have shown that undifferentiated type gastric carcinomas (UGCs) derive not only from signet ring cell carcinoma (SIG) but also from dedifferentiated tubular adenocarcinoma (TUB). UGCs deriving from SIG are characterized by the presence of a layered structure (LS), in which smaller progenitor cells of signet ring cells are distributed in the middle level of the mucosa and vertical mucosal polarity of gastric differentiation is retained, reflecting a gastric-type carcinogenesis. However, intestinal expression is also frequently detected in UGCs, though its significance as a marker of tumor progression remains controversial. Recently, it has been shown that tissue environment regulates the expression of Cdx2, the critical transcription factor that regulates intestinal expression. To demonstrate environmental regulation of tumor phenotypes in UGCs and to assess whether this regulation is lineage-specific, in the present study, we examined intratumoral heterogeneity of intestinal expression in UGCs with and without LS.

Methods:

We immunohistochemically examined intestinal expression by anti-Cdx2, MUC2 antibodies and gastric expression by anti-MUC5AC, MUC6 antibodies in 39 intramucosal and 49 extramucosally invasive UGCs. We analyzed detailed maps of staining results in each tumor.

Results:

1. Presence of LS^- part in intramucosal tumors correlated with the size of mucosal spread ($P = 0.043$). Predominance of LS was significantly more common in intramucosal tumors than extramucosally invasive LS^+ tumors ($P = 0.020$).
2. In LS, MUC5AC is expressed in the superficial part of the mucosa. Loss of this polarity (deep expression of MUC5AC) was independent of intestinal expression and associated with extramucosal invasion ($P = 0.0266$).
3. In LS^+UGCs, intestinal expression was enhanced as the tumor spreads in the mucosa in LS^+ part of intramucosal tumors (presence of Cdx2/MUC2 expression:

$P = 0.0362/0.0336$) and in LS^- part of $LS^\pm$ extramucosally invasive tumors (predominance of Cdx2 expression: $P = 0.0177$), and was reduced as the tumor invaded deeper (presence of Cdx2/MUC2 expression: $P < 0.0001/P = 0.0005$), whereas, in LS^-/TC^+UGCs, intestinal expression was common and predominant irrespective of tumor size and was insignificantly reduced as the tumor invaded deeper.

4. Analyses of individual tumors have confirmed the average trends that intestinal expression in the mucosa was more common in LS^- part than in LS^+ part and that intestinal expression reduced as the tumor invaded deeper.

5. The tubular differentiation in LS^+UGCs was accompanied by enhanced Cdx2 expression and reduced MUC2 expression, whereas that in LS^-/TC^+UGCs was often not accompanied by any changes in Cdx2 or MUC2 expression.

Discussion:

1. Though LS^- parts are often accompanied by intestinal expression, the intestinal expression and the loss of LS are different phenomena. It was the latter that was related to tumor progression (loss of polarity of gastric expression and extramucosal invasion).

2. The UGCs of different genetic lineages (LS^+ and LS^-/TC^+UGCs) showed different modes of regulation in intestinal expression; in LS^+UGCs, intestinal expression showed dynamic alteration (increase of expression during mucosal spreading and reduction of expression in extramucosal invasive part) probably reflecting environmental induction and loss of the induction, whereas it was relatively stable in LS^-/TC^+UGCs. Analyses of individual tumors confirmed the above average trends in LS^+UGCs and demonstrated the stability of intestinal expression in LS^-/TC^+UGCs with tubular differentiation as well as with tissue environmental changes.

3. The stable intestinal expression in LS^-/TC^+UGCs might be fixed genetically, reflecting a genetic lineage of intestinal-type carcinogenesis. Accordingly, Wnt activation and *TP53* mutation were reportedly common in LS^-/TC^+UGCs as in colorectal tumors.

4. The LS^-/TC^+UGCs conform morphologically to the mixed-type GC that reportedly carries the worst prognosis in GCs. This link between the intestinal expression and poor prognosis contradicts the recent reports that intestinal phenotype suggests better prognosis. This conflict suggests that intestinal expression, itself, may be regulated by many factors and not related closely to the prognosis of GCs.

Conclusion:

Intestinal expression in UGCs is affected not only by tumor progression but also by environmental factors and genetic lineage, and is not useful as a marker of tumor progression.

（備考） １．論文内容要旨は、研究の目的・方法・結果・考察・結論の順に記載し、２千字程度でタイプ等で印字すること。

２．※印の欄には記入しないこと。

別紙様式８（課程・論文博士共用）

学位論文審査の結果の要旨

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（学位論文審査の結果の要旨）

進行期の未分化型胃癌には印環細胞癌に由来するものと分化型腺癌に由来するものとがあり、種々の程度の腸発現があることが知られている。

本研究は、未分化型胃癌における腸発現に対する癌の由来や組織環境の影響を知るために、腸型発現の腫瘍内多様性を粘液コア蛋白と転写因子の両面から検討した。その結果、分化型腺癌に由来するものでは腸発現は腫瘍全体に安定して見られるのに対して、印環細胞癌に由来するものでは、粘膜内では腫瘍径の増大とともに腸型発現が増加するが、粘膜外では深部に浸潤するほど腸発現が減少することを明らかにした。後者の粘膜外浸潤部近傍の粘膜でよくみられたのは、胃型分化の極性の乱れと増殖細胞の分布の乱れであり、腸発現の分布はランダムであった。

以上のように本研究は、未分化型胃癌における腸発現に及ぼす腫瘍の由来や組織環境の影響を初めて明らかにし、腸発現を腫瘍進展の指標として用いるさいにはその影響を十分考慮する必要があることを示したものであり、本論文は、博士（医学）の学位論文に値するものと認められる。

（平成 20 年 08 月 30 日）