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研究課題名（和文）膵嚢胞性腫瘍の病態予測における包括的ゲノム解析の応用

研究課題名（英文）Molecular characterization of IPMN using comprehensive genome analysis

研究代表者
多田　稔（TADA, Minoru）

東京大学・医学部附属病院・講師

研究者番号：８０３０２７１９

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研究成果の概要（和文）：25例のIPMNについてKras, Braf, PIK3CAの変異と、p16, smad4の欠失、p53蓄積を検討した。Kras変異はgastric-typeに多く、PIK3CA変異はintestinalの一例に認めた。smad1/5/8のリン酸化がintestinal-typeで多いことを見出し、報告した(J.Gastroenterol. 2012 47(2):203-13)。さらに、膵がん細胞株および臨床検体で増幅を認めた遺伝子のうち、ノックダウンの結果から上皮間葉転換を促進する分子を見出した。この分子のIPMNにおける関与を解析中である。

研究成果の概要（英文）：We characterized the molecular signature of IPMN in this project. 11 gastric, 11 intestinal, one pancreatobiliary, and two oncocytic types were included in this study. We compared the molecular characteristics of two major subtypes, gastric-type and intestinal-type IPMN. Gastric-type showed a higher incidence of KRAS mutations (9/11, 81.8%) compared with intestinal type (3/11, 27.3%). The intestinal type (9/11, 81.8%) demonstrated more frequent SMAD1/5/8 phosphorylation compared with gastric-type IPMN (3/11, 27.3%).In addition, we identified a molecule that accerelated epithelial- mesenchymal transition in pancreas cancer cells. The gene was amplified in pancreas cancer cells and human pancreatic tumors. We now examine the significance of the molecule in IPMN as well as in pancreatic cancers.

研究分野：　医歯薬学

科研費の分科・細目：　内科系臨床医学・消化器内科学

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１．研究開始当初の背景

膵癌では Kras 遺伝子変異がほとんどすべてに検出されることが特徴的である。しかし、膵液レベルの解析では、膵癌のない症例の膵液から Kras 遺伝子変異が検出されることがある。当研究室の研究により、膵嚢胞が存在すると膵液中に変異 Kras 遺伝子が多く検出されることを明らかとした (Tateishi, Tada et al. Gut 1999)。IPMN (Intraductal Papillary Mucinous Neoplasm)は膵のう胞性腫瘍の一病態で、元来は良性と診断される場合が多い一方、時に悪性化する症例がある。そこで当科では IPMN を含め、膵に嚢胞を有する症例について、画像による経過観察を行ってきた。その結果、膵癌発症が年率 0.9%と高率に認められ、膵嚢胞は膵癌の高危険群であることを突き止めた（Tada M, et al. Clin Gastroenterol Hepatol 2006;4:1265-1270、Tada M. Clin Gastroenterol Hepatol 2007;5:522.）。

その膵嚢胞性腫瘍の一つ IPMN は膵前がん病変である PanIN とも類似する病態と考えられるが、PanIN が微小膵管における変化であり基本的に画像診断では捉えられないのに対し、IPMN は嚢胞性病変として捉えられるため、膵癌の早期診断につながる可能性がある。近年、IPMN にも複数のタイプがあることが明らかになり、臨床形態的には主膵管型と分枝型に分類される。また IPMN の組織亜型は 4 種あり、大部分が gastric type と intestinal type に分類される。悪性頻度が高く原則として手術が検討される主膵管型はほとんど intestinal type であることが最近報告され、そのがん化の経過は adenoma-carcinoma sequence に類似すると考えられている。主膵管の intestinal type IPMN の悪性化例はいわゆる近接した部位に生じる IPMN 由来膵がんであることが多いが、一方で分枝膵管型は IPMN と離れた部位に PanIN を介する通常型膵癌が合併する場合がみられる。つまりがん化に至るメカニズムも両者で全く異なる可能性がある。それぞれの特有な分子マーカーがあれば IPMN 病変から浸潤するがん発生に留意すべきなのか、あるいは異所性に生じるがんの確率が高いことに留意すべきか、というような経過予測の上で有効な情報となる可能性もありうる。

癌細胞のゲノムでは、特定の遺伝子領域で増幅や欠失が起こることが知られている。近年、大規模 SNP タイピングを目的として開発された高密度オリゴヌクレオチドアレイが、染色体コピー数変化および LOH を同時に解析できるということがわかった(下図・例)。そこで、当研究室ではこのアレイを用いて膵癌細胞株 25 種類のゲノム異常の網羅的解析を行ってきた。解析の結果、24 のホモ欠失領域と 23 の増幅領域を認め、それぞれ 8 領域は今回初めて指摘された部位であった。L0H は 9p,18q,17p,8p,13q,6q,3p,6p,22q,9q と 12q において 50%以上の細胞株に認めた。その後、この新規に増幅および欠失あるいは LOH を認めた領域に関して、膵癌手術検体を用いた解析を行い、細胞株と同様の異常を認めることを確認した（Lin LJ,et al. Oncology. 2008;75(1-2):102-12.）。

２．研究の目的

intestinal type の IPMN に特有の分子マーカーを同定し、早期の治療法決定と発がん予防、また分枝型 IPMN の悪性例の予測にも役立てることを目標とする。

３．研究の方法

IPMN の組織はマイクロダイセクションを活用して選択的に採取し、DNA を抽出する。以前に膵がん検体を用いて同定された遺伝子領域の増幅・欠失といったコピーナンバー異常について定量的 PCR を用いて評価する。またコピーナンバー異常に伴う遺伝子発現変化についても定量的 RTPCR にて評価する。発現異常を認めた遺伝子については膵発がんにおける生物学的役割を検討するために、過剰発現およびノックダウン膵がん細胞を樹立して増殖能、遊走能、浸潤能、腫瘍形成能などについてアッセイを行う。

４．研究成果

25例のIPMNについて*Kras, Braf, PIK3CA*の変異と、*p16, smad4*の欠失、p53蓄積などについて検討を行ってきた。*Kras*変異はgastric-typeに多く、*PIK3CA*変異がintestinalの一例のみに認められた。その他の分子の異常については亜型によって有意に差を認められなかった。ただしsmad1/5/8のリン酸化がintestinal-typeで有意に認められることを見出し、報告した(J.Gastroenterol. 2012 47(2):203-13)。

さらに、膵がん細胞株およびヒト膵がん検体を用いた検討で、遺伝子増幅を認めた遺伝子のうち、そのノックダウン細胞を用いた実験の結果から膵がん細胞において上皮間葉転換を促進する分子を見出した。現在はこの分子が上皮間葉転換を誘導する分子機構を明らかにし、膵がんのみならずIPMNの生物学的特性における関与について臨床検体での解析も行って検討を続ける。

５．主な発表論文等

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６．研究組織

(1)**研究代表者**

多田　稔（TADA Minoru）

東京大学・医学部附属病院・講師

研究者番号：80302719

(2)**研究分担者**

立石　敬介（TATEISHI Keisuke）

東京大学・医学部附属病院・講師

研究者番号：20396948

毛利　大（MOHRI Dai）

東京大学・医学部附属病院・特任臨床医

研究者番号： 20582513