

肝内胆管細胞の heterogeneity(多様性)についてのプロテオーム解析

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はしがき

PBC の標的細胞は胆管上皮細胞であるが、同細胞の解析は遅れており、最新の手法を用いて、その多様性(heterogeneity)や、病的分子の表出を検討することにより、新たな治療法の標的となる分子の探索を行うことを目的とした。

A. 研究方法

平成16年度は主に生体肝移植の摘出肝および正常動物より分離された胆管細胞を用いて、μアレイ、プロテオミクス法といった最新の技術を用いて、胆管細胞特異的に発現される蛋白の探索を行った。人組織からの分離は、手術件数の減少のため、基礎条件設定に難渋したが、それを補うべく動物モデルを用いて、基礎検討を進めた。特に胆管細胞の多様性に寄与する分子に着目し、そのうちの一つとして ephrin が挙げられることを明らかにした。また、μアレイ法によりレトロウイルスのエントリーに関与する蛋白が小葉間胆管特異的に発現されることを見出したため、逆転写酵素阻害剤を用いた二重盲検試験を組織し、実際の PBC 患者に投与した。平成17年度は、AMA 産生を伴う胆管炎動物モデルから胆管細胞を分離し、AMA の産生と関連する蛋白の探索を行った。

B. 研究結果

平成16年度の研究より小型胆管により優位に発現される蛋白の一つとして、 EphA5 が見出された。膜蛋白である Eph 受容体 family はリガンドである ephrin 刺激 によるチロシンキナーゼの活性化を介する系と、非刺激下で Eph 受容体に結合する RhoGEF 等を介する系によるRhoファミリーの調節を経て、アクチンの構築を制御して いると考えられており、神経突起、血管新生、細胞の malignant transformation に関 与している。NMC-S、NMC-L 上の EphA member の発現と局在を検討し、細胞運動、 形態に与える機能を検討するために、小型、大型肝細胞上の EphA 発現を RT-PCR, direct sequence で確認し、免疫染色、共焦点レーザー顕微鏡で局在を検討した。 EphA の機能の検討にはリガンドである ephrinA5-Fc キメラを用い、糸状仮足の形態 を観察した。糸状仮足の形成を膜透過性の cyclic AMP analogue である N6, 2' -O-dibuityryladenosine 3': 5'-cyclic (dcAMP)刺激下で検討した。その結果、EphA8 は大型、小型の胆管細胞双方に認められたが、EphA5 は小型胆管細胞に強く発現が 認められた。EphrinA5 は糸状仮足を有意に退縮させた(p<0.01)。EphA5 の発現は主 に糸状仮足に局在し、細胞質にも一部認められた。さらに EphA8 は細胞質と葉状仮 足に認められた。dcAMP 刺激により、EphA5、EphA8 の membrane 上への translocation が認められ、小型胆管細胞の糸状仮足の伸展が認められたが、大型胆 管細胞には認められなかった。さらに、今回新たに開発した胆管細胞の分離法が、純 度の高い胆管細胞を得る方法として有望であることを確認した。

また、今回用いた手法を応用して、胆管細胞の多様性や、細胞特性についての共同研究をまとめて発表した。

研究組織

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研究成果 (次頁以降)

Abstract

It is remarkable that microarray technologies have nearly reached a pinnacle. Establishment of further analysis and management of enormous data derived from microarray technology is currently the highest priority. The heterogeneous functions of cholangiocytes regulate the pathophysiology of the biliary epithelium regarding secretory, proliferative and apoptotic activities. Distinct expression profiles of two murine cholangiocytes lines, termed small and large were revealed by microarray analysis. The features of the two cholangiocyte cell lines, categorized partly according to gene ontology, indicate the specific physiological role of each cell lines. Namely large cholangiocytes are characterized as "transport" and "immune/ inflammatory responses". In contrast to large, small cholangiocytes are associated with properties of limited physiological functional ability and proliferating/migrating potential with specific molecules like Eph receptors, comparable to mesenchymal cells. 'Omic study will be of great help to understanding the heterogeneiety of cholangiocytes.

Introduction

Several research avenues have established novel scientific theories. We initially examined phenotypic manifestations of various forms of induction, analogy and abduction. Subsequent preliminary studies resulted in a firm-working hypothesis. We then tested this hypothesis in order to establish our theoretical groundwork. However, recent advances in the field of bioinformatics have become routine, especially in regards to the initial speculative step in designing a rational approach. Since the initial DNA microarray analysis experiment1, microarray has developed rapidly and is now well established, with manufacturers meeting market demand2. The number of scientific papers with "microarray" as a key word steadily increased on PubMed from 2001 to 2004, reaching a total of 8603 papers. Moreover, an enormous quantity of raw data potentially contained in "microarray" papers is anticipated in the near future, and the estimate is based on the number of the genes analyzed in each paper (e.g. 30000-40000 genes expressed in mammalian cells). Therefore, it is essential for future advances to reliably preserve a database containing all of the raw data. establishment of the data analysis system as well as data mining and data sharing, is anticipated to be the highest priority in this field. We will focus on such issues pertaining to general microarray experiments as well as the methods and the results of microarray analyses designed to the characterize cholangiocytes in this chapter.

Microarray analysis

We will simply give an overview of the current status, analytic method and data-sharing aspects of microarray analysis, partly in accordance with the description of Knudsen3. One of the currently popular microarray systems is the Affymetrix DNA Chip®, which employs in situ oligonucleotide synthetic technology as well as mass-production compatible to that of silicon chips. Several microarrays and expression analysis services are commercially available from several companies including Amersham, Clontech (TAKARA), Invitrogen and so on. As in other experiments, the quantity of RNA samples should be standardized, otherwise correction steps will be necessary for the evaluation of the results by "scaling" generally employing internal controls. Moreover, verification of the linearity of spot intensity-sample quantity curves for all applied spots is also necessary in microarray experiments. The companies supplying ready-made products have overcome these problems and established quality control, making their products popular with researchers applying commercial products to limited numbers of samples. Although array technologies at the bench have nearly reached a zenith during the past several years, there are some in silico systems under The parametric t-test and non-parametric Wilcoxon's rank-sum/ Mann-Whitney tests are the most popular methods applicable to test the significance of

differences between pairs of samples. The normality of each spot intensity for the samples becomes an issue if the t-test or ANOVA is used with a routine microarray having thousands of spots. The most conservative statistical method, Bonferroni's correction, which defines the level of significance more strictly according to the number of tested items, might be applicable even to microarray experiments4. Even if we employ other less conservative approaches5, we may need to verify the differential expressions of the specific molecules by other methods in some cases. Several software available. including some that are free (http://rana.lbl.gov/EisenSoftware.htm)6, for analysis of microarray data. Cluster analysis categorizes each gene into distinct clusters according to Euclidian distance based on the variation among the samples at multiple time-points or under the different conditions. Each gene in a cluster shows a similar expression pattern under different conditions, which may indicate a common transcription pathway, RNA degradation process, and/ or similarities of gene function in a cluster. In other words, microarray technology holds promise for elucidating the complex regulatory mechanisms of RNA transcription as well as unknown gene functions. Every gene is currently being defined, allowing organization according to (http://www.geneontology.org/). The gene ontology project was originally designed to create a thesaurus-like hierarchy of gene properties, based on molecular function, biological processes and cellular components, in order to integrate databases in a The combination of raw microarray data and this unified classification will greatly facilitate developing the speculative groundwork for our experiments. This approach differs from the usual methodology based on molecular properties including domain structure, 3D structure, evolution or expression patterns. raw microarray data can be a source of new hypotheses, regardless of the original aim of This may make it difficult to share raw microarray data. The unified the experiment. approach, termed MIAME (http://www.mged.org/Workgroups/MIAME/miame.html), for submission of microarray data is described in the guidelines of each paper contributing of data to be shared and for peer review. The statement that "MIAME is neither a dogma, nor a legal document - it assumes a cooperative data provider and a fair reviewer" suggests a potential difficulty in data sharing, probably stemming from the complexities of ownership and intellectual property rights to data. Microarray data is clearly precious, even in the current era of non-sharing, and should be carefully stored by each lab, organization or government. Such data should be viewed as common property, with potential future benefits to mankind.

Features of cholangiocytes

Bile flows from canalicular spaces, encircled by hepatocytes, through the canals of Hering, interlobular bile ducts (branches of which are 20-100µm in diameter and lined by cuboidal epithelium), and septal bile ducts (which are more than 100µm in diameter and lined by a simple tall columnar epithelium) to hilar intrahepatic bile ducts7. The cholangiocytes that line the interlobular and bolder bile ducts7 also contribute to bile The mechanism underlying this phenomenon, described elsewhere in secretion^{8, 9}. detail, is explained briefly by out-intraluminal vectorial passive transport of water caused by the osmotic gradient which is formed by active transport of several substrates driven by cholangiocytes 10, 11. This physiological function, conserved even in cultured cell lines, characterizes the specialized cholangiocytes. Isolated rat cholangiocytes are classified as large or small, depending on their size. Large cholangiocytes, regarded as representative functional biliary epithelial cells in vivo, respond to secretin with increased choleresis¹². In contrast, little is known about the properties of small Cholangiocytes are sometimes altered in a disease-specific manner. cholangiocytes. For example, primary biliary cirrhosis (PBC), a potentially fatal cholestatic disorder due

to ductopenia, is a representative disease characterized by specific destruction of interlobular bile ducts. CD8+ cytotoxic T cells were suspected to play a major role in this type of destruction. Tetramer technology revealed the existence of an E2 subunit of the pyruvate dehydrogenase complex (PDC-E2)159-167-specific to autoreactive cytotoxic T cells in PBC13. Hypothetically, there are several specific properties (e.g. adhesion molecules, MHC antigens 14, specific autoantigens, variations in apoptosis and so on) of cholangiocytes lining interlobular bile ducts, which make them vulnerable to attack by cytotoxic lymphocytes. A novel disease etiology was proposed by Gershwin et al. 15, who demonstrated that IgA class anti-mitochondrial antibodies, transported via transcytosis from the basolateral to the apical surface co-localize with PDC-E2 in cholangiocytes. Moreover, molecules that bind PDC-E2 monoclonal antibody are expressed on the apical membranes of PBC cholangiocytes¹⁵. These observations indicate the cytotoxicity associated with functional impairment of cholangiocytes to be caused by interaction In this regard, the mechanism of transcytosis may specifically with IgA-PDC-E2. dictate the underlying disease process. Such a hypothesis could be explained by cholangiocytes heterogeneity based on the recognition that large and small cholangiocytes are derived from bile ducts of corresponding diameters16. susceptibility of bile ducts to pathological conditions (e.g. chronic ductopenic rejection 17, GVHD¹⁸, ischemic cholangitis¹⁹, PBC or ductopenia resulting from other pathologies) is due not only to the specific destruction of cholangiocytes but also to the difficulty of regenerating the bile ducts i.e. with normal structures, in contrast to the rapid regeneration of hepatocytes in cases with acute liver injury. The proliferation of cholangiocytes that potentiates the regeneration of bile ducts occurs in a characteristic manner, i.e. secretin, somatostatin or bile duct ligation results in proliferation of large cholangiocytes²⁰, whereas chemical injury of bile ducts with CCl₄ increases the numbers of small cholangiocytes^{21, 22}. Therefore, to clarify the mechanisms sustaining cholangiocyte growth is essential to understanding the regulation of bile ducts regeneration. We identified an Eph receptor, a membrane bound-type tyrosine kinase, as one of the key molecules for reorganization/ proliferation of cholangiocytes, and a subtype of this family, which is expressed mainly in small cholangiocytes²³. Thus, the heterogeneous expression profiles of cholangiocytes are expected to facilitate further study of these cells.

Analysis of heterogeneous cholangiocytes

For the evaluation of genes that are expressed by small and large cholangiocytes see Several liver diseases, including non-alcoholic fatty liver disease24, liver $cirrhosis^{25}$, hepatocellular carcinoma $^{26,\ 27}$ and cholangiocellular carcinoma 28 have been studied extensively using microarray techniques. Some studies have examined whole liver samples, consisting of various cell types, probably for the purpose of disease Sample size is critical for the detection of subtle changes in the expression of meaningful genes²⁹, a possible problem in assessing rare diseases. Another problem in the study of biliary diseases like PBC by microarray is that cholangiocytes account for only 3% of the cell population even in the normal liver³⁰. Over 75% of the cell population is regarded as necessary to test the significance of differences in expression levels2. Therefore, for the purpose of analyzing chlangiocytes, isolation³¹ or microdissection³² is necessary prior to analysis. Our study goals were to characterize the physiological role of biliary epithelia in the mouse and to analyze cholangiocyte heterogeneity. Due to the complexities of the isolation steps, maintaining quality control or reproducibility was possible when obtaining a large scale of sample RNA from freshly isolated cholangiocytes. Moreover, given the necessity of conducting further functional assays, we immortalized and subcloned the isolated Balb-c mouse cholangiocytes by introducing the SV40 large T antigen³³.

established large and small cholangiocyte cell lines were evaluated by their morphologies and responsiveness to secretin. We revealed 230 genes (4.74%) showing different expression patterns in the two cells lines, among 4800 genes tested by combining two types of ready-made microarrays34. Our large cholangiocyte line was characterized by gene ontology, transport and immune/inflammatory responses, which were apparent, even without the statistical tests presented in the table. The term "transport" includes movement of anions, water and bile acids, and thus represents the physiological functions of bile ducts. These observations indicate a special feature of large cholangiocytes which presumably play a role in local immune reactions. contrast, our small cholangiocytes are categorized into a subgroup characterized by rapid cell cycle turnover of as well as poor physiological functional ability. In addition to these fundamental properties, our small cholangiocytes are characterized by abundant expressions of actin and vimentin and poor expression of E-cadherin. Together with rich spindle-type cell processes, small cholangiocytes have a feature in common with mesenchymal cells probably originating from epithelial-mesenchymal transition35. This remains controversial issue. Another measure feature of cholangiocyte is the capability of the responsiveness to hormones and neuropeptides. Specifically, estrogen receptor³⁶ and receptor for IGF-1(insulin like growth factor 1)³⁷, NGF(nerve growth factor)38 and acetylcholine (M3)39 have been shown to play a major role in modulating cholangiocyte proliferation. Estrogen receptor expresses at minimal level in amount in both types of cell lines. In contrast, IGF receptor was preferentially expressed in large cholangiocyte line in our microarray study. expression of estrogen receptor inducible under pathological conditions like bile duct injury40 may explain the discrepancy between the experiments results. Predominant expression of IGF receptor in large cholangiocytes may be a marker of differentiated biliary epithelial cells as well as a proliferating effector of maturated cholangiocytes.

Concluding remarks

Microarray is a powerful tool for elucidating functional cholangiocyte heterogeneity. Although the evaluation of some crucial biological regulatory processes like protein modification requires methodologies other than microarray, the potential of microarray technology is anticipated to grow with the development of data analysis theory for the comprehension of complex networks.

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Legends of the table

Differences in cDNA expression between small and large cholangiocyte lines
The entire dataset obtained from the Atlas Glass Array mouse (Clontech, Takara Bio
Inc., Shiga, Japan) was analyzed by ArrayGauge software (Fuji Photo Film Co., Ltd.,
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AND THE PROPERTY OF HE AND PROPERTY FINANCES AND ADDRESS OF THE PARTY	aquagoum 1 aquagoum 2 aquagoum 2 aquagoum 3 aquagoum 3 schare carrier family 10 (soutum/bile acid cotrarreporter ramily, member 1 G-protein coupled purinerylc receptor P2Y1 (P2RY1) packweylc screenter P2X. Aquati-grized inn channel 4 Detection of Stimulus fall-like receptor 5 toll-like receptor 5 toll-like receptor 5 toll-like receptor 6 Cell arretteration FAIS-like hyrodise interes 1 (FLT1); vascular andothellal growth factor receptor 1 (VEGF21) agricular arretteration (VEGF21) interes insert domain receptor (VCRF); vascular permentility factor (VPF) interes insert domain receptor (VCRF); vascular permentility factor (VPF) interes insert domain receptor (VCRF); vascular permentility factor (VPF) interes insert domain receptor 3 (FCFRI); imparts- binding growth factor receptor 3 (FCFRI); imparts- binding growth factor receptor 3 (FCFRI); imparts- binding growth factor receptor 1 (TGF-beta 1; TGFB1) transforming growth factor beta 1 (TGF-beta 1; TGFB1) transforming growth factor beta receptor 1 (TGF-beta receptor 1; TGFRI; ESK2	MML 071694 MML 071895 MML 0713797 MML 007472 MML 000099 MML 076689 MML 076689 MML 0767474 MML 0713847 LUZZR29 MML 0713847 LUZZR29 MML 071805 MML 071805 MML 071805 MML 071805 MML 071804 L07297 J00386 X70842 MMS20643 AMS1342 MMS20643 AMS1342 MMS3777 D25540	CO-000000001	1111 87 76 76 77 76 78 78 78 78 78 78 78 78 78 78 78 78 78	146 627 114 245 275 278 204 222 8728 402 652 2229 114 569 23 116 58 152 152 485	1.32 0.71 1.50 0.95 1.36 0.95 1.46 0.95 4.04 1.93 1.99 3.13 0.72 0.85 1.32 0.85 1.32 0.85 1.32 0.85 1.32 0.85 1.32 0.85 1.32 0.85 1.32 0.85 1.32 0.85 1.32 0.85 1.33 1.34 0.85 1.35
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