The Current Stream and Prospect of Glycoscience Application —Therapeutic Antibodies—

糖鎖に関わる応用研究の潮流と展開—抗体医薬—

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Abstract

Many therapeutic antibodies have been approved since the late 1990s, and these agents represent a major new class of drugs. However, there still remains room for improvement in the clinical effect and cost of therapeutic antibodies licensed on the market. Most therapeutic antibodies, which currently have been developed as medical agents, are human IgG1 whose molecular weight is approximately 150 kDa. Human IgG1 is a glycoprotein bearing two N-linked oligosaccharides bound to the antibody constant region (Fc), and exercises its effector functions of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) through the interaction of the Fc with either lymphocyte receptors (FcγRs) or complements. Recently, therapeutic antibodies have been shown to improve overall survival as well as time to disease progression in a variety of human malignancies such as breast, colon and haematological cancers (1–4), and genetic analysis of FcγR polymorphisms of cancer patients has demonstrated that ADCC is a major anti-neoplasm mechanism responsible for the clinical efficacy of anti-CD20 antibody Rituxan[®] (rituximab) and anti-Her2 antibody Herceptin[®] (trastuzumab) (5–9). Thus, there are currently numerous efforts to improve ADCC of therapeutic antibodies. We have found that the removal of fucose residues from the biantennary complex-type oligosaccharides attached to the Fc dramatically enhances the ADCC of the IgG due to improved FcγRIIIa binding (10–17), and have developed the technology, designated as Potelligent[™], to control the fucosylation of therapeutic antibodies (18, 19). Application of this technology has now started for the development of the next generation of more effective therapeutic antibodies.

要 約

1990 年後半から抗体医薬品が次々と認可され、これら認可された多くの抗体医薬は新しい医療として定着しつつある。しかし、現行の抗体医薬の臨床効果は必ずしも充分なものではなく、また、投与量が多いため薬剤費が高いといった課題が残されている。医薬として開発されている抗体のほとんどは分子量約 150kDa のヒト IgG1 であり、その Fc 領域に 2 本の N-グリコシド結合複合型糖鎖が結合する糖タンパク質である。Fc 領域は Fc 受容体や補体などが結合する領域であり、この部分を通じて抗体依存性細胞傷害活性 (antibody-dependent cellular cytotoxicity; ADCC) や補体依存性細胞傷害活性 (complement-dependent cytotoxicity; CDC) といったエフェクター活性が発揮される。最近の抗体医薬の臨床成績では、乳癌、大腸癌、血液癌といった多くのヒト悪性腫瘍において、延命や病態悪化に至るまでの期間延長といった効果が観察されている (1–4)。また、癌患者 Fc 受容体の多型解析から、非ホジキンリンパ腫治療薬抗 CD20 抗体 Rituxan[®] (リツキシマブ) や乳癌治療薬抗 Her2 抗体 Herceptin[®] (トラスツズマブ) の主たる抗腫瘍メカニズムの一つは ADCC 活性であることが明らかにされ (5–9)、医薬開発に応用可能な ADCC 活性増強技術の開発が次世代抗体技術として注目されている。我々は、抗体の Fc 領域に結合している N-グリコシド結合複合型糖鎖からフコースを除去することで Fc 受容体 IIIa に対する親和性を向上させ ADCC 活性を大幅に高められることを見出し (10–17)、このフコース修飾を制御する技術を開発した (18, 19)。現在、次世代抗体医薬の開発のため、Potelligent[™] と名付けたこの技術の応用を精力的に開始している。

A. Introduction

Progress has been made in antibody engineering technology in the last decade, which has enabled the

A. はじめに

近年の抗体工学の進歩により、ヒトに対する抗原性が低く、臨床応用可能な遺伝子組換え抗体の作製が可能となった。

production of recombinant monoclonal therapeutic antibodies such as humanized antibody and human antibody, both of which are of sufficiently low immunogenicity for clinical applications. Mouse/human chimeric antibody and complementarity determining region (CDR)-grafted antibody have been generated as humanized antibodies by gene engineering technology (20–24), and fully-humanized antibodies have been generated from either transgenic mice capable of producing human antibody or phage libraries of human immunoglobulin (25–31). Human genome has been sequenced and almost all information of protein antigens is now available for generation of molecular-target base medicines, which is stimulating strong competition in the development of therapeutic antibodies (32). Numerous trials using therapeutic antibodies are currently underway, including 100 clinical and more than 300 pre-clinical studies. Thus, 17 types of recombinant monoclonal therapeutic antibodies have already been approved in the USA, and these agents represent a major new class of drugs (Table I). Each of the world sales of anti-CD20 IgG1 Rituxan^R (rituximab) for non Hodgkin's lymphoma and of anti-TNF- α IgG1 Remicade^R (infliximab) for chronic rheumatoid arthritis and Crohn's disease reached approximately 2 billion dollars in 2004. In the near future, rituximab will be administered to far more patients than currently treated patients as it has been reported that clinical efficacy of rituximab for chronic rheumatoid arthritis was observed in phase III clinical study. Moreover, it becomes the most conspicuous topic of therapeutic antibodies that anti-VEGF IgG1 Avastin^R (bevacizumab) licensed in late 2004 has demonstrated statistically significant improvement in overall survival of patients with metastatic cancers of

具体的には、マウス/ヒト型キメラ抗体やヒト型相補性決定領域(complementarity determining region; CDR)移植抗体などのヒト化抗体作製技術の開発や(20–24)、ヒト抗体産生トランスジェニックマウスやファージライブラリーを利用した完全ヒト抗体作製技術の開発が(25–31)、モノクローナル抗体治療を医薬として可能ならしめたと言える。抗原となるヒトのゲノム情報が完全に解読された今日、抗体医薬は分子標的医薬の代表として熾烈な競争時代に入っている(32)。現在、世界では、100を超える臨床試験と300を超える前臨床試験が行われていると言われている。米国では、既に、17種類の抗体が医薬品として承認販売されており、抗体は新しい医療分野を開拓しつつある(表I)。これら認可された抗体医薬の中でも、癌領域では非ホジキンリンパ腫適応の抗CD20キメラ抗体Rituxan^R(リツキシマブ)が、炎症領域では慢性関節リュウマチ及びクローン病適応の抗TNF- α キメラ抗体Remicade^R(インフリキシマブ)が、それぞれ、およそ2000億円という売り上げを2004年度に記録した。リツキシマブは、さらに、慢性関節リュウマチ適応への適応拡大を狙った第3相試験においても有望な治療効果が報告されており、今後より多くの患者さんの治療に用いられる可能性がある。また、2004年下期に認可された抗VEGFヒト化抗体Avastin^R(ベバシズマブ)は、それまで多くの薬剤が試されたが有効な治療効果が得られなかった大腸癌において、化学療法との併用で有意な延命効果を示し話題となった(33–35)。ベバシズマブは、米国において、発

Table I. Recombinant therapeutic antibodies on the market USA.

Trade	Company	Type	Antigen	Indication	Approval Date
Reopro ^R	Centocor/Lilly	Chimera	gpIIb/IIIa	Thrombosis	12/24/1994
Rituxan ^R	IDEC/Genentech/Roche	Chimera	CD20	NHL	11/26/1997
Zenepax ^R	Roche	Humanized	IL-2R	Transplantation	12/10/1997
Simulect ^R	Novartis	Humanized	IL-2R	Transplantation	05/12/1998
Synagis ^R	MedImmune/Abott	Humanized	RSV	RSV Infection	06/19/1998
Remicade ^R	Centocor/J&J	Chimera	TNF- α	RA, Crohn's	08/24/1998
Herceptin ^R	Genentech/Roche	Humanized	Her2	Breast Cancer	09/25/1998
Mylotarg ^R	Celltech/AHP	Drug-conjugate	CD33	AML	05/17/2000
Campath ^R	ILEX/Schering	Humanized	CD52	B-CLL	05/05/2001
Zevalin ^R	IDEC/Schering	⁹⁰ Y-conjugate	CD20	NHL	02/19/2002
Humira ^R	Abott/CAT	Fully human	TNF- α	RA	12/31/2002
Xolair ^R	Genentech/Novartis/Tanox	Humanized	IgE	Allergic asthma	06/20/2003
Bexxar ^R	Corixa/SKB	¹³¹ I-conjugate	CD20	NHL	06/27/2003
Raptiva ^R	Genentech/Xoma	Humanized	LFA-1	Psoriasis	10/27/2003
Erbitux ^R	ImClone/BMS/Merck	Chimeric	EGFR	Colon Cancer	02/12/2004
Avastin ^R	Genentech	Humanized	VEGF	Colon Cancer	02/26/2004
Tysabri ^R	Biogen-IDEC/Elan	Humanized	Integrin α 4 β 1	MS	12/23/2004

RSV: respiratory syncytial virus, NHL: non-Hodgkin lymphoma, AML: acute myeloid leukemia, B-CLL: B-cell chronic lymphocytic leukemia, RA: rheumatoid arthritis, MS: Multiple sclerosis.

the colorectum in combination with standard chemotherapy regimens (33–35). The first year sales of bevacizumab in the USA, indeed, recorded 0.5 billion dollars. The clinical efficacy of bevacizumab for both breast and lung cancers in phase III study has been also reported at the American Society of Clinical Oncology (ASCO) held in 2005. Thus, it is thought that the indication of therapeutic antibodies will be expanded, and we have to face a severe problem of the expensive cost of therapeutic antibodies.

B. The Need for Next-generation Therapeutic Antibodies

Although various antibody therapies are currently recognized as novel medicines that confer great benefits to patients, these agents also bring up an issue referred to as “economical toxicity”. The drug costs alone of treatment with anti-tumor therapeutic antibodies of rituximab, trastuzumab or bevacizumab can amount to over 10–20 thousand dollars due to a significant amount of drug needs for clinical efficacy. The world sale of currently licensed recombinant therapeutic antibodies in 2005 is estimated to exceed 10 billion dollars. As mentioned above, the indication of therapeutic antibodies will be further expanded in the near future. This economic situation is not viable, and is at risk of collapse. Moreover, there still remains the need to improve the efficacy of many antibody therapeutics such that they can be used to achieve not only remission, but complete recovery from disease; many of the currently approved antibody therapies remain unable to induce more than remission. Therefore, the development of the next-generation therapeutic antibodies with enhanced clinical efficacy is expected.

C. Physiological Mechanism of Therapeutic Antibodies

Physiological action of therapeutic antibodies is based on two mechanisms of antibody; the efficacy of therapeutic antibody is the result of target antigen specificity and biological activities referred to as antibody effector functions, and which are activated by the formation of immune complexes shown in Fig. 1. We can classify therapeutic antibodies into two types, one of which is therapeutic antibodies functioning as neutralizing agents of the molecular target causative of aggravated disease. Both infliximab and bevacizumab are known as typical such neutralizing therapeutic antibodies. Neutralization of the specific antigen function is mediated by the antigen-binding region of the antibody (Fab). Therapeutic antibodies can also mediate the effector functions of antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and the direct induction of apoptosis via the constant region of the antibody (Fc) (36–39). Rituximab and anti-Her2 antibody Herceptin[®] (trastuzumab) are known as typical therapeutic antibodies showing their clinical efficacy through

売初年度 600 億円を超える売り上げを記録している。さらに、非小細胞肺癌、乳癌に対する第3相試験でもベバシズマブによる良好な治療結果が2005年の米国臨床癌学会(American Society of Clinical Oncology; ASCO)で報告されており、今後の開発動向が非常に注目されている。このように、抗体医薬が適応される疾患はより広がるものと思われるが、一方で高い薬剤費の問題が深刻さを増してきている。

B. 次世代抗体医薬開発の必要性

新たな医療として認知され始めた抗体医薬ではあるが、多くの患者さんに恩恵をもたらすと同時に、“economical toxicity”と揶揄される新たな課題を我々に突きつけ始めた。リツキシマブ、トラスツズマブ、あるいはベバシズマブといった抗癌抗体医薬の薬剤費は、薬効発現のために多くの量の抗体投与が必要となるため、100～200万円と高額なものにならざるを得ない。現在認可されている遺伝子組み換え抗体医薬品の2005年の総売上は1兆円を超えると見積もられている。さらに、上述のごとく、抗体医薬の適応は近い将来より広がるであろう。このままでは、医療保険制度の維持は難しく医療経済の破綻は免れない。また、現行の抗体医薬において癌患者さんの顕著な延命効果が報告されているものの、完治に向けて一層の治療効果の改善が求められている。このような背景から、より治療効果の高い次世代抗体医薬の開発が求められている。

C. 抗体医薬の薬効メカニズム

抗体医薬の薬効メカニズムは抗体が有する2つの生物活性に基づいている。すなわち、標的抗原特異的な結合活性とエフェクター活性と呼ばれる抗体の生物活性によってその薬効は発揮されており、これら活性の発現には図1に模式的に示した抗原抗体複合体の形成が必要である。抗体医薬品は、標的抗原分子に対する中和活性を有しているか否かで2つのタイプに分類することができる。病態形成に重要な役割を担っている標的分子に対する中和活性が薬効発現に必要な抗体医薬としてはインフリキシマブやベバシズマブが代表的な例として挙げられる。標的抗原分子の機能の中和は抗体の抗原結合領域であるFabを介して発揮される。一方、抗体医薬はFcと呼ばれる抗体定常領域を介して、抗体依存性細胞傷害活性(antibody-dependent cellular cytotoxicity; ADCC)や補体依存性細胞傷害活性(complement-dependent cytotoxicity; CDC)あるいはアポトーシスの直接誘導といったエフェクター活性を発揮することができる(36–39)。このエフェクター活性を利用して薬効を発現する抗体医薬としてはリツキシマブや抗Her2抗

Fig. 1. Schematic drawing of ADCC. IgG-antibody-coated tumor cells are efficiently killed by monocytes or NK cells, which have Fc receptors able to bind to the Fc region of IgG molecules. The binding of the antibody-covered tumor cells to these Fc receptors activates the cytotoxic process ADCC.

the effector functions. There are currently numerous ongoing efforts mainly to improve the effector functions of therapeutic antibodies (40–42).

D. Importance of ADCC on Clinical Efficacy of Therapeutic Antibodies

ADCC, a lytic attack on antibody-targeted cells, is triggered upon the binding of lymphocyte receptors (FcγRs) on specialized killer cells of natural killer (NK) cells and macrophages to the antibody Fc region. Although the nature and importance of effector functions of ADCC, CDC, and the direct induction of apoptosis in influencing physiological activity of therapeutic antibodies have long been recognized, the most important function in terms of the clinical efficacy has remained a matter of debate. Among these functions, ADCC in particular is considered to be an important mechanism of clinically effective antibodies (43). Recently, therapeutic antibodies have been shown to improve overall survival as well as time to disease progression in a variety of human malignancies such as breast, colon and haematological cancers (1–4). Genetic analyses of FcγR polymorphisms, in the case of both non-Hodgkin's lymphoma and breast cancer patients, have clearly demonstrated that ADCC is one of the critical effector functions responsible for the clinical efficacy of these agents (5–9). A superior clinical response of patients with the FcγRIIIa allotype (FcγRIIIa-158Val), which has high affinity for rituximab, has been observed, in contrast to the results obtained from patients with the low-affinity allotype (FcγRIIIa-158Phe) (5–8). Breast cancer patients who responded to trastuzumab with complete or partial remission were found to have a higher capability to mediate *in vitro* ADCC when treated with trastuzumab than the non-responders (9). These facts have demonstrated the importance of ADCC in the development of antibody therapies that are clinically

体 Herceptin[®] (トラスツズマブ)が代表的な例として挙げられる。現在、抗体医薬の薬効を高める研究としてエフェクター活性を向上させる研究が盛んに行われている(40–42)。

D. 抗体医薬の臨床効果における ADCC 活性の重要性

ADCC 活性とは、標的細胞に結合した抗体が NK 細胞やマクロファージなどのエフェクター細胞上の Fc 受容体と結合することで、抗体依存的に誘導される標的細胞傷害活性である。抗体医薬の薬効発現のメカニズムとして、ADCC 活性や CDC 活性あるいはアポトーシスの直接誘導といったエフェクター活性の重要性が古くから指摘されているが、臨床上的どのメカニズムが最も重要なものか明らかとなっていなかった。現在では、これらメカニズムの中では、特に、ADCC 活性が重要なメカニズムの一つであると考えられつつある(43)。最近になり、多くの抗体医薬の臨床成績が明らかになるにつれ、乳癌、大腸癌、血液癌といった多くのヒト悪性腫瘍において、延命や病態悪化に至るまでの期間延長といった抗体医薬の臨床効果が明確となってきた(1–4)。そして、非ホジキンリンパ腫及び乳癌の癌患者さんの Fc 受容体多型解析が行われ、リツキシマブ及びトラスツズマブいずれにおいても、その主たる抗腫瘍メカニズムの一つは ADCC 活性であることが明らかにされてきている(5–9)。ヒトの Fcγ 受容体 IIIa には、158 番目のアミノ酸がバリンであるタイプ(FcγRIIIa-158Val)とフェニルアラニンであるタイプ(FcγRIIIa-158Phe)の遺伝子多型が存在する。治療抗体リツキシマブに対して高い親和性を示す Fc 受容体 FcγRIIIa-158Val を有する非ホジキンリンパ腫患者は、低親和性を示す Fc 受容体 FcγRIIIa-158Phe を有する患者に比べてより優れた臨床効果を示した(5–8)。トラスツズマブによる乳癌治療においても、完全寛解あるいは部分寛解した患者さんでは治療効果が観察されなかった患者に比べて、末梢血をエフェクター細胞として用いたインビトロ ADCC 活性測定において、トラスツズマブによる有意に高い活性が検出されている(9)。これらの結果は、臨床的に効果のある抗体医薬を

effective. ADCC enhancement technology applicable for clinical applications is expected to a key technology in the development of next-generation therapeutic antibodies with enhanced clinical efficacy.

E. Defucosylated Antibodies as Next-generation Therapeutic Antibodies

As the shortcomings of currently licensed therapeutic antibodies, especially for the treatment of cancer patients, is also recognized, there are numerous challenges to improve the efficacy of therapeutic antibodies. These challenges have included both the effector function enhancement of antibody and co-administration of adjuvants such as cytokines and CpG (44–47). Among these efforts, ADCC enhancement strategy is attracting recent attention as the importance of ADCC on clinical efficacy of therapeutic antibodies is widely recognized. There are two types of approach to enhance ADCC of therapeutic antibodies; both the introduction of point mutations into the Fc region of antibody (48, 49) and the modification of *N*-linked oligosaccharides attached to the Fc region of the antibody (50) are available. Therapeutic antibodies have two *N*-linked oligosaccharide chains bound to the Fc region as shown in Fig. 2. The oligosaccharides are of the complex biantennary type, composed of a mannosyl-chitobiose core structure with the presence or absence of core fucose, bisecting *N*-acetylglucosamine (GlcNAc), galactose, and terminal sialic acid, which gives rise to structural heterogeneity (51–53). Human IgG is primarily employed as therapeutic agent, and both human serum IgG and therapeutic antibodies are well known to be heavily fucosylated (54, 55). Human IgG has a unique oligosaccharide structure in which multiple, non-covalent interactions between the oligosaccharides and the protein portion of the C_H2 domains results in reciprocal influences of each on the conformation of the other (56–58). Although the influence of the refined Fc oligosaccharide structures on ADCC of IgG has long

開発するには、ADCC 活性が重要であることを示唆している。臨床応用可能で、かつ既存抗体の ADCC 活性を増強することができる技術の開発が臨床効果を高めた次世代抗体医薬の開発の鍵を握ると言われる所以である。

E. 次世代抗体医薬としてのフコース非修飾抗体

現行の抗体医薬の課題が明らかになるにつれ、抗体医薬の臨床効果を増強させる多くの試みが開始されている。これら試みの中には、抗体自身のエフェクター活性を増強させようとする試み以外にも、抗体医薬と併用してその効果を高めようとするサイトカインや CpG を用いたアジュバント療法開発といった試みも含まれている(44–47)。中でも、抗体自身のエフェクター活性を増強させようとする試みは、抗体医薬の臨床効果発現に ADCC 活性が重要であるという認識が広まるにつれ、大変注目を集めるようになった。抗体医薬の ADCC 活性を増強させる手段としては2つのアプローチが知られている。その一つは、抗体の Fc 領域のアミノ酸配列を改変するものであり(48, 49)、もう一つのアプローチは抗体の Fc 領域に結合している糖鎖の構造を制御するものである(50)。図2に示すように、抗体は2つの *N*-グリコシド結合糖鎖を Fc 領域に有している。この抗体の *N*-グリコシド結合糖鎖は、Mannosyl-chitobiose Core 構造を基本構造とする複合型2本鎖糖鎖であり、非還元末端側ではガラクトース、バイセクティング *N* アセチルグルコサミン及びシアル酸の有無について、還元末端ではフコースの有無について多様性が存在している(51–53)。抗体医薬はヒト IgG が用いられて開発されており、ヒト血中 IgG も抗体医薬もいずれも高度にフコース修飾されていることが知られている(54, 55)。ヒト IgG では、糖鎖部分と C_H2 ドメインのタンパク質部分が非共有結合的に相互に影響し合って三次構造の維持に関わっている(56–58)。そのため、大変ユニークな糖鎖構造を有していると言う事ができる。抗体糖鎖の微細な構造が ADCC 活性に及ぼす影響につ

Fig. 2. Schematic drawing of human IgG1 oligosaccharide structure. The *N*-linked biantennary complex-type oligosaccharide is attached to the C_H2 domain of the Fc region of human IgG1: GlcNAc (○), mannose (□), bisecting GlcNAc (●), fucose (☆), galactose (■), sialic acid (△).

been a matter of debate, research groups of Genentech and Kyowa Hakko Kogyo Co., Ltd. have found that the most important carbohydrate structure in terms of the enhancement of ADCC is the fucose attached to the innermost GlcNAc of the biantennary complex oligosaccharides (10, 11). The removal of fucose residues from the biantennary complex-type oligosaccharides attached to the Fc dramatically enhances the ADCC of the antibodies due to improved FcγRIIIa binding without altering either antigen binding or CDC activity (10–19). Defucosylated antibodies achieve high effector activity at low doses, inducing high cellular cytotoxicity against tumor cells that express low levels of antigen (12), and triggering high effector function in NK cells with the low-affinity FcγRIIIa allotype (FcγRIIIa-158Phe) for currently licensed therapeutic antibodies (13). The superior *in vivo* efficacy of defucosylated antibody has also been demonstrated using a human PBMC-engrafted mouse model (14). IgG bearing the Fc biantennary complex type of oligosaccharides lacking core fucosylation is a normal component of natural human serum IgG, as mentioned above, and therefore there is little concern regarding its intrinsic immunogenicity. Thus, the application of defucosylated antibodies is expected to be among the most powerful and elegant approaches to the development of the next generation of therapeutic antibodies.

F. Future Directions

Recombinant protein expression technology in mammalian cell culture is the principal means of commercial production of therapeutic antibodies. Mammalian cells such as Chinese hamster ovary (CHO) cell lines or the mouse myeloma cell lines NS0 or SP2/0 have produced all therapeutic antibodies that are currently licensed on the market. However, these cell lines are not available for production of defucosylated therapeutic antibodies because they retain intrinsic α -1,6-fucosyltransferase (*FUT8*) responsible for core fucosylation of the Fc oligosaccharide of the products. Thus, we have developed production methods of stably producing defucosylated therapeutic antibodies; *FUT8*-knockout cell lines have been established as ideal host cell lines to give stable yields of completely defucosylated therapeutic antibodies, irrespective of the production system (18), and small siRNAs against the *FUT8* gene have been identified as convenient reagents capable of converting the established antibody-producing cells to more desired cell lines that produce highly defucosylated antibodies with improved ADCC (19). Clinical trials using defucosylated antibody therapeutics are currently in preparation.

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いは長い間議論があったが、我々及び Genentech のグループが、Fc 領域に結合する *N*-グリコシド結合複合型糖鎖還元末端の *N*-アセチルグルコサミンへのフコースの付加修飾こそが抗体の ADCC 活性に最も大きな影響を与えることを明らかにした(10,11)。抗体 Fc 領域に結合する *N*-グリコシド結合複合型糖鎖還元末端の *N*-アセチルグルコサミンからフコース残基を除去すると Fc 受容体 IIIa に対する親和性が上がり ADCC 活性が 100 倍以上と劇的に向上する(10–19)。この際、抗原結合活性や CDC 活性には変化は観察されない。フコース非修飾抗体は低い用量で高いエフェクター活性を示す能力を有しており、癌抗原を低いレベルでしか発現していない癌細胞に対しても高い殺細胞活性を示し(12)、現在認可されている既存の抗体医薬に対して低い親和性しか示さない Fc 受容体 Aロタイプである FcγRIIIa-158Phe を発現する NK 細胞に対しても強いエフェクター機能を惹起する(13)。フコース非修飾抗体の優れたインビボの効果は、ヒト末梢血単核球を移植したマウスを用いた腹水癌モデルにおいて示されている(14)。フコース修飾のないコア構造を持つ *N*-グリコシド結合複合型糖鎖が付加した IgG はヒトの血液中にも観察されており、その抗原性を心配する必要はない。従って、フコース非修飾抗体を次世代抗体医薬の開発に応用することは最もエレガントな方法の一つとして期待されている。

F. 今後の展開

抗体医薬の商業生産は哺乳類細胞を用いた遺伝子組換え法により行われている。現在上市されている抗体医薬の全ては、チャイニーズハムスター卵巣細胞由来の CHO 細胞株か、あるいはマウス骨髓腫由来の NS0 あるいは SP2/0 細胞株を用いて製造されている。しかしながら、これら細胞株は内在性の α -1,6- フコース転移酵素を有しているため、生産した抗体の糖鎖のコア構造にフコースが修飾されてしまう。そのため、フコース非修飾抗体を製造する宿主細胞としては用いることができない。そこで、我々は、安定にフコース非修飾抗体を製造する方法を開発した。すなわち、製造方法に影響されず、完全にフコース修飾のない抗体医薬を製造する理想的な宿主細胞として α -1,6- フコース転移酵素をノックアウトした細胞株を樹立している(18)。また、既存の抗体医薬の生産株といった既に樹立済みの抗体生産細胞を、高い ADCC 活性を有する低フコース修飾抗体生産株へ簡便に変換することが可能な、 α -1,6- フコース転移酵素に対する RNA 干渉低分子も見出した(19)。現在、フコース非修飾抗体医薬を用いた臨床試験の準備が開始されている。

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