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免疫アレルギー疾患予防・治療研究事業

免疫疾患に対する免疫抑制療法等先端的新規治療法に関する研究

平成１４年度～１６年度　総合研究報告書

主任研究者　山　本　一　彦

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Ⅰ．総合研究報告書

厚生労働科学研究費補助金（免疫アレルギー疾患予防・治療研究事業）
総合研究報告書

免疫疾患に対する免疫抑制療法等先端的新規治療法に関する研究

主任研究者　山本　一彦　東京大学大学院医学系研究科アレルギーリウマチ学　教授

研究要旨　　免疫難病に対する治療法は現在のところ満足するものがなく、欧米では政府、大学、企業ともに積極的な研究が推進されているが、我が国ではかなり遅れている。この現状を打開する目的で、我が国から発したオリジナルな概念である、CD25 陽性 CD4 陽性制御性 T 細胞、NKT 細胞の制御法、T 細胞レセプター遺伝子導入をはじめとして、欧米でホットに研究開発が展開されている末梢血幹細胞移植、CD20 に対する抗体療法、抗原変異ペプチド、細胞増殖に関する細胞内シグナルなどについて、それぞれの第一人者を集め、世界的に高いレベル研究を推進した。３年間でかなりの進展が見られたが、実際の臨床応用に結びつけるためにはさらなる研究の推進が必要である。

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A. 研究目的

全身性自己免疫疾患を中心とした免疫難病についての現在の治療法は、副腎ステロイドや免疫抑制薬が中心であり、一定の効果はあるものの、免疫系全体に対する抑制作用などの副作用が患者にとって不利に働くことが少なくない。したがって、より選択的、特異的で副作用の少ない治療法を開発することは緊急の課題となっている。しかし、我が国ではベンチャー企業の立ち後れ、基礎免疫と臨床免疫の相互交流の少なさなどから、この方面の研究が進んでいないのが現状である。そこで、本研究は、我が国で確立されつつあるオリジナルな概念を中心に、近未来的に実際の患者に応用可能な先端的新規治療法について、ヒト及びモデル動物での治療法を確立する事を目的とした。

B. 研究方法

山本は、全身性エリテマトーデスや関節炎などの動物モデルについて、病変臓器に浸潤している T 細胞クローンの動きを、独自に開発したクローン解析法で解析し、種々のパラメーターから病変特異的であると判定出来るクローンについて、その一つの細胞に発現している T 細胞レセプターの２つの鎖の全長 cDNA をクローニングする技術の改良を続けた。さらに複数の遺伝子を効率よくリンパ球に導入出来るベクターの開発を進め、自己のリンパ球に２つの T 細胞レセプター遺伝子に加えて３つ目の機能遺伝子を導入することで、人工改変による抗原特異的機能的 T 細胞を作成する技術の完成を目指した。これにより種々の免疫疾患に対する免疫細胞療法の適応が可能であることを示すことを目指した。

坂口はマウスの系で、自身が発見した CD25 陽性CD4陽性の制御性T細胞自体を制御する分子の検索と同定を行った。特に IL-2 および IL-2 レセプターの役割を調べるとともに、ヒトにおいて制御性 T 細胞を作成する為に、Foxp3 遺伝子に注目して、レトロウイルスベクターにて CD4 陽性細胞に遺伝子導入してその機能を調べた。山村は、すでに Nature 誌に発表している免疫制御物質 OCH のヒト NKT 細胞に対する影響を詳細に検討した。

これによりNKT細胞が産生するサイトカインのバランスを調節することで、免疫疾患を制御する方法の確立を目指した。

住田はヒトや動物モデルで既に同定してきた病因T細胞が認識するエピトープについて、その配列を一部改変することで病因T細胞の機能を修飾する方法を検討した。具体的にはコラーゲンタイプIIのエピトープの検索とそれを改変したアナログペプチドを作成し、T細胞株の反応を検討した。またα－アミラーゼ，Glucose-6-phosphate isomerase (GPI)などのT細胞エピトープをリコンビナント蛋白や合成ペプチドで決定した。

上阪は病態形成に関わるCD8陽性T細胞に注目し、その細胞増殖の速さの原因を追及した。特にJAKやSTATなどの細胞内シグナル分子に注目しCD4陽性T細胞との差異を検討した。

田中は、B細胞に注目し、既に欧米では癌や一部の自己免疫疾患の治療に用いられている抗CD20抗体の全身性自己免疫疾患治療への適応を検討した。小池は、強皮症患者への自己骨髄幹細胞移植の治療を続けるとともに、抗リン脂質抗体症候群の発症機構について詳細に検討するため、抗リン脂質抗体で刺激された単核球内のシグナル伝達を検討し、さらにそのシグナルの阻害による治療法の開発を試みた。

(倫理面への配慮)

動物モデルでの研究は指針に従った。ヒトの培養細胞を用いた研究はインフォームドコンセントを取得した後に行った。患者への治療に関しては各施設の倫理委員会の承認を得た。以上のことで倫理上問題ないと考える。

C. 研究結果

山本は昨年度の全身性エリテマトーデスモデルのNZB/W F1マウスにおける、ヌクレオソームに対するT細胞レセプター遺伝子と抑制性のCTLA4Ig分子をコードする遺伝子の導入による抑制実験の研究を続けた。さらにコラーゲン誘導関節炎の病変局所に集積しているT細胞のT細胞レセプターを解析したところ、Vβ8.1/8.2陽性のT細胞レセプターにはDXGGという共通モチーフが存在することを見いだした。そこでVβ8.1/8.2陽性のCD4陽性T細胞をシングルセルソーティングを行うことで、1つの細胞から2つのT細胞レセプター遺伝子をクローニングすることに成功した。さらにこれを用いて関節炎を制御するT細胞を作成した。以上の成果により、このような制御性T細胞による治療法が可能であることが判明した。

坂口は自らが発見し世界的に注目されているCD25陽性CD4陽性制御性T細胞の生存・増殖に、IL-2が重要であることを見いだした。さらにFoxp3遺伝子が発生、分化を司るマスター遺伝子であることを見いだし、Foxp3遺伝子導入により、ヒトにおいても制御性T細胞を作成出来ることを示した。山村は自己免疫疾患の制御で注目されているNKT細胞を刺激する変異ペプチドOCHについて、ヒトのNKT細胞に対する影響を調べたところ、CD4陽性NKT細胞において、マウスと同様にTh1/Th2バランスをTh2に偏向させる能力があることを示した。

住田はコラーゲンタイプIIのT細胞エピトープを決定し、アナログペプチドを作成しT細胞株の反応を検討した。またGPI、α－アミラーゼ、ムスカリン作動性アセチルコリン受容体のエピトープの決定を進めた。上阪は増殖の速いCD8陽性T細胞とCD4陽性T細胞を比較し、JAK1, JAK3およびその下流のSTAT5、ERKおよびAktのリン酸化がより強く認められることを示した。小池は、強皮症患者への自己骨髄幹細胞移植の治療を継続し、皮膚の軟化など臨床的な改善をみた。一方、抗リン脂質抗体の作用機序に関しての研究では、抗体を単核球に作用させたところ、凝固のイニシエーターである組織因子（TF）の発現にMAPK経路が関わっていることを見いだした。さらにこの中でもp38が重要であることが判明し、特異的p38阻害薬（SB203580）がTFの発現を抑制することを示した。

田中はCD20抗体を用いた重症SLE患者5例のパイロットスタディを行い、重篤な副作用を認めず5例全例で1年以上の長期寛解状態を得ていることを示した。

D. 考察

欧米では、免疫担当の細胞や分子に対するモノ

クローナル抗体療法、小分子の阻害薬、遺伝子療法、細胞療法など、多くの分野の技術・資源を動員して、免疫疾患に対する種々の治療法の開発が進められている。しかし、実際には少数の抗体療法を除いて未だに世界的に認められたものは多くないことから、さらに研究を進める必要性が提言されている。

一方、我が国では基礎免疫学は世界的なレベルにあるが、基礎免疫学と臨床免疫学を結ぶいわゆる応用免疫学の領域の発展が種々の理由で十分ではない。従来個々の研究室レベルからは、それぞれ新しい治療法の可能性についての検討の報告は散見されているが、研究者の組織または領域として新規治療法開発を推進するような土壌がほとんどなかったのが現状である。そこで、本研究は我が国で独自の新規治療法の開発に積極的な一流の基礎免疫学者と一定のレベル以上の基礎的な研究を行いつつ疾患研究を進めている臨床免疫学者を比較的少数集め、近未来的に応用可能であることに焦点を絞り、お互いに情報・技術を交換しながら、それぞれが独自の治療法を目指した。3年間の成果としては、かなりの達成度であると考える。

E. 結論

これまで我が国から発したオリジナルな概念である、CD25 陽性 CD4 陽性制御性 T 細胞、NKT 細胞の制御法、抗リン脂質抗体症候群、T 細胞レセプター遺伝子導入をはじめとして、抗体療法、変異ペプチド, シグナル伝達分子などについて、それぞれの第一人者を集め、世界的に高いレベル研究を推進できた。また臨床への応用に関してはすでにヒトでの治療を始めているものから、マウスでの治療法の開発の段階までの種々の段階のものがある。今後は近未来的に応用可能なことを目指して、各段階での実際的な問題点を明らかにして、各プロジェクトがスムーズに開発に向けられるようにする必要があると思われる。

F. 健康危険情報

特になし

G. 研究発表

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H. 知的所有権の出願・取得状況

1. 特許取得
   - Foxp3 発現リンパ球による免疫病の治療法（特許出願中・坂口）
   - 新規単クローン性抗体による制御性 T 細胞の操作（特許出願中・坂口）
2. 実用新案登録
   特になし
3. その他
   特になし

Ⅱ. 研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻・頁・出版名
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