

千葉大学大学院医学研究院 教授

谷口 克

「自己免疫制御の分子基盤」

1. 研究実施の概要

基本構想：

研究の目的は免疫制御系の新しい細胞系列として同定された NKT 細胞の(1) 分化機構、(2) 生理機能、(3) NKT 細胞機能の分子基盤、(4) $V\alpha 14$ 受容体のリガンド同定を行うことによって、免疫制御の分子機構を明かにし、(5) 自己免疫疾患発症の分子的理解を可能にする事である。

この目的を達成するために次のプロジェクトを遂行することとした。

NKT 細胞前駆細胞の同定

NKT 細胞の分化機構

$V\alpha 14$ NKT 細胞抗原受容体のリガンド同定

NKT 細胞機能発現のメカニズム

NKT 細胞療法の基盤技術開発

実施・研究成果のまとめ：

平成 8 年から平成 13 年までに支援された戦略的基礎研究費で得た成果の要約は次のとおりである。

1. $V\alpha 14$ 抗原受容体遺伝子の発見と NKT 細胞分化：

NKT 細胞の抗原受容体は、多様性の無いただ一種類の受容体 ($V\alpha 14 J\alpha 281$) で、T 細胞では使われておらず、NKT 細胞に特徴的である事が明らかとなった。

2. NKT 細胞が新しいリンパ球系列であることの証明：

(i) NKT マウスと NKT 欠損マウスの作成：NKT 細胞だけが出現し、通常のリンパ球が無い NKT マウスおよびすべての組織から NKT 細胞のみが欠失し、他の免疫系は正常のマウスを作成することに成功した。

(ii) NKT 細胞前駆細胞の証明：NKT 細胞にのみ分化する前駆細胞の存在を証明した。この細胞は幼若型受容体 ($pT\alpha$ と $V\beta 8$) とリンパ球には発現していないと考えられていた GM-CSF 受容体を発現し、細胞内には遺伝子再構成に必要な酵素 RAG を持つ。さらに GM-CSF 受容体からの刺激で $V\alpha 14$ 遺伝子再構成を起こし成熟型 NKT 細胞に分化した。以上の事実を総合して、NKT 細胞は免疫系の新しいリンパ球系列であると考えられた。

3. $V\alpha 14$ 抗原受容体リガンドの発見： $V\alpha 14$ 受容体はクラス Ib 分子である CD1d と共に抗原を認識するが、それが α -ガラクトシルセラミド (α -GalCer) という糖脂質であることを証明した。

4. α -ガラクトシルセラミドと CD1d 分子の相互作用：CD1d に結合する α -ガラクトシルセラミドの結合様式を明らかにすることができた。すなわち、ガラクトースの 3-OH 基が CD1d アルファヘリックスの Arg79 と Glu83 に結合し、2-OH 基は Arg79 と Asp80 に結合し、スフィンゴシン 3-OH 基が Val149 に、Amide nitrogen が Asp153 と結合し安定化する。

5. NKT 細胞の生理機能：

NKT 細胞はこれまで未解決であった様々な免疫現象、たとえば免疫寛容の維持、がんの免疫学的監視、I 型糖尿病などの自己免疫疾患発症制御などの免疫制御のみならず、エンドトキシンショック、ウイルス肝炎モデルである ConA 誘導肝炎、結核肉芽腫形成などの感染症に必須であることが NKT 細胞欠損マウスを用いて証明された。

6. リガンドによる活性化 NKT 細胞の機能：

(イ) がんの臓器転移阻止、(ロ) マラリア感染防御、(ハ) 流産に活性化 NKT 細胞が関与することが明かとなり、臨床応用へ期待されている。

このように、これまで未解決であった免疫現象の多くが、この新しい免疫系によって担われていることがわかった。この NKT 細胞系の発見は、免疫現象の基本的理解、制御、免疫疾患の発症機序解明に新しい道を開くものと考えられる。

2. 研究構想

免疫制御系の新しい細胞系列として同定された NKT 細胞の(1) 分化機構、(2) 生理機能、(3) NKT 細胞機能の分子基盤、(4) $V\alpha 14$ 受容体のリガンド解析を行うことによって、免疫制御の分子機構を明らかにし、自己免疫疾患発症の分子的理解を可能にするため、次のような年次計画を実行した。

平成 8 年度

- NKT 細胞前駆細胞の同定・解析
- $V\alpha 14$ NKT 細胞抗原受容体のリガンド同定
- NKT 細胞機能発現のメカニズム

平成 9 年度

- NKT 細胞前駆細胞の同定
- $V\alpha 14$ NKT 細胞抗原受容体のリガンド解析
- NKT 細胞機能発現のメカニズム

平成 10 年度

1. NKT 細胞前駆細胞の同定
2. $V\alpha 14$ NKT 細胞抗原受容体のリガンド解析
3. NKT 細胞機能発現のメカニズム
4. NKT 細胞の分化機構

平成 11 年度

- V α 14 NKT 細胞抗原受容体のリガンド解析
- NKT 細胞機能発現のメカニズム
- NKT 細胞療法の基盤技術開発
- NKT 細胞の分化機構

平成 12 年度

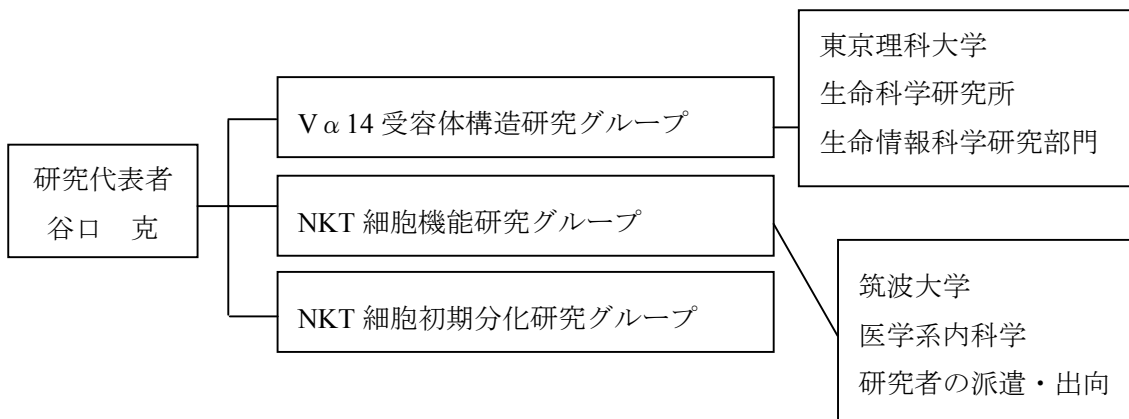
- V α 14 NKT 細胞抗原受容体のリガンド解析
- NKT 細胞の分化機構
- NKT 細胞機能発現のメカニズム
- NKT 細胞療法の基盤技術開発

平成 13 年度

- NKT 細胞の分化機構
- NKT 細胞療法の基盤技術開発

3. 研究実施体制

(1) 体制



4. 研究期間中の主な活動

- (1) ワークショップ・シンポジウム等
なし

5. 主な研究成果

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① 招待、口頭講演 (国内 8件、海外 17件)

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(3) 特許出願 (国内 件、海外 1 件)

① 国内

② 海外

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(4) 新聞報道等

① 新聞報道

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(5) その他特記事項

なし