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) Vα14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

Vα14 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．Vα14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（Vα14 Jα281）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：

(ｲ) 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。

(ﾛ) 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（pTαと Vβ8）とリンパ球には発現していないと考えられていたGMCSF 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Vα14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．Vα14抗原受容体リガンドの発見：Vα14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) Vα14 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

Vα14 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

Vα14 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．Vα14 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

Vα14 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

Vα14 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

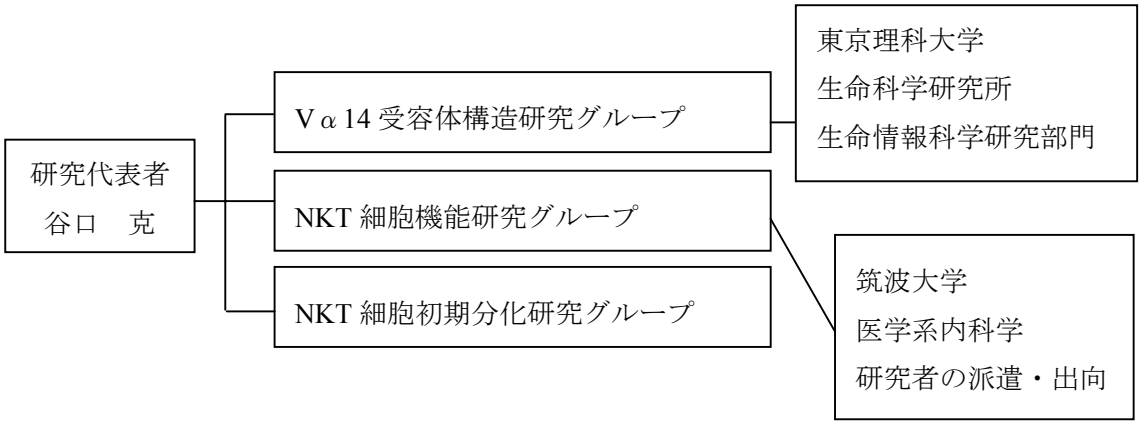
平成 13 年度

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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(3) 特許出願（国内　　件、海外　1件）

① 国内

② 海外

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(5) その他特記事項

なし