「アレルギー疾患・自己免疫疾患などの発症機構と治療技術」
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実績報告

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# IL-17 ファミリー分子、C 型レクチンを標的とした自己免疫・アレルギー疾患の発症機構の解明と治療薬の開発

## §1. 研究実施体制

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②研究項目

1. IL-17 ファミリー遺伝子の機能解析
2. C 型レクチンファミリー遺伝子の機能解析
3. 新規関節炎発症関連遺伝子の解析

## §2. 研究実施内容

(文中に番号がある場合は(3－1)に対応する)

### 研究のねらい・概要

本研究は、IL-17 ファミリー分子及び C 型レクチンを標的とした自己免疫疾患・アレルギー疾患の発症機構を解明し、最終的に治療薬の開発に結びつけることを目的としている。これまでに、IL-17F ノックアウト(KO)マウスと IL-17A/F ダブル KO マウスを作製し、自己免疫疾患やアレルギー応答と粘膜における細菌感染防御にはそれぞれ異なる IL-17 ファミリー分子が機能発揮していること、Dectin-2 が Th17 細胞の分化を誘導し真菌感染防御に重要な役割を担っていること、などを明らかにした。

### 研究進捗状況・成果

### 1. IL-17 ファミリー遺伝子の機能解析

1−1. 関節炎誘発性の IL-17 産生性γδT 細胞の性状解析

我々が開発した関節炎動物モデルである IL-1 レセプターアンタゴニストノックアウトマウス(IL-1RaKO)マウスの病態解析から Th17 細胞よりγδT 細胞が主要な IL-17A 産生細胞である

ことが明らかとなった。しかしながらγδT 細胞が IL-17A を産生することは既に知られているが疾患との関係は明らかではない。これまでに IL-1RaKO マウスはヌードマウスとの交配で関節炎を発症すること、抗γδTCR 抗体で発症が抑制されることを明らかとしγδT 細胞が病態形成に深く関与していることが示された。さらにγδT 細胞は抗原非依存的に IL-23 と IL-1 により IL-17A を産生することを示し、γδT 細胞特異的な IL-17A 産生メカニズムを明らかにした。今後、IL-17A 産生細胞の病原性を調べるために IL-17A 産生細胞を分離・移植し、関節炎発症時の各細胞サブセットの役割を明らかにしていきたい。

1−2. IL-1 に依存した Th17細胞分化機構の解析

IL-1RaKO マウスでは Th17 細胞が少ないながら存在するが、 IL-6 を欠損させても Th17 細胞が IL-1RaKO と同等数存在する事が分かり, 過剰な IL-1 シグナルの下では IL-6 非依存的に Th17 細胞分化が可能であることが示唆された。このメカニズムを解析したところ, IL-1 単独では Th17 細胞分化を誘導することはできないが、IL-21 存在下では IL-21 が IL-1R の発現を増加させる事によって IL-1 と協調的に Th17 分化を促進させる事を明らかにした。この際、IL-1 は Th17 細胞分化誘導因子の発現を上げるとともに、Foxp3 発現を抑制することで Th17 細胞分化を制御していることを明らかにした。Th17 細胞が関節炎に関与することが知られているが、過剰なサイトカイン産生が生じている炎症性疾患時の Th17 細胞分化機構の一端を明らかにし関節炎の病態形成理解につながった。

## §3. 成果発表等

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