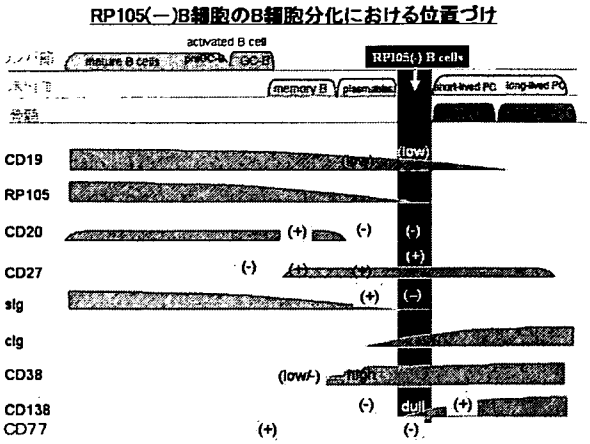

図1

B 細胞の恒常性の維持には、BAFF や APRIL の液性因子やその３つの受容体 BAFF-R、BCMA、TACI が重要な役割を果たしていることが報告されている。そこで、SLE 由来の RP105 陰性Ｂ細胞が BAFF や APRIL などの液性因子により誘導されるか、あるいは、その生存が維持されるかを in vitro で検討した。BAFF 存在下では RP105 陰性Ｂ細胞の生存率の増加が誘導されたが、RP105 陽性Ｂ細胞や健常者由来の RP105 陰性Ｂ細胞では、生存率の増加はほとんど誘導されなかった(図２)。

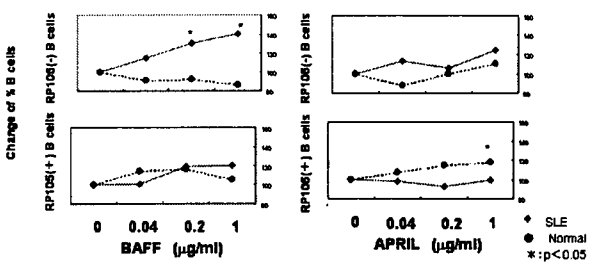

図2

つぎに、CD40L シグナルの RP105 陰性Ｂ細胞への影響についても検討を行った。in vitro における RP105 陰性 B 細胞相対比率の増加は単量体 sCD40L では誘導されなかったが、３量体 sCD40L の強い刺激で誘導された(図３)。

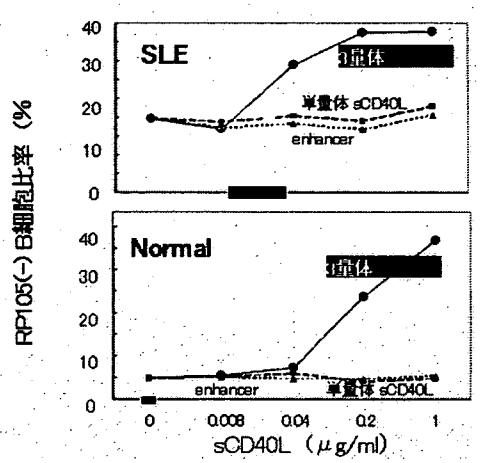

図3

RP105 陰性Ｂ細胞特異的抗体の作成と治療戦略を企図した。現在は RP105 陰性 B 細胞に特異的に発現する新規分子の同定と、その分子に対する特異的抗体を作成しているところである。タンパク質レベルでの RP105 陰性 B 細胞特異的分子の発現、および標的細胞に対する抗体による細胞傷害活性の測定も施行中である。また、既知分子としては、BCMA が RP105 陰性 B 細胞に特異的に発現していることを認めており、標的となる候補分子の１つとして有力である(図４)。

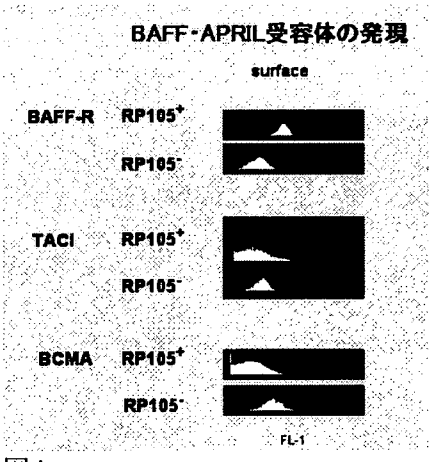

図4

D.考察

Ｂ細胞恒常性維持にかかわる RP105 が欠損した場合、B 細胞の異常活性化が持続し自己免疫病態に寄与する可能性が考えられる。RP105 陰性Ｂ細胞は自己抗体産生Ｂ細胞であり、B 細胞分化の過程で新たなヒト B 細胞サブセットを形成している。このような自己抗体産生Ｂ細胞サブセットの末梢での病的集積が自己免疫病態に大きく寄与している可能性がある。

RP105 陰性 B 細胞を制御する方法として、RP105 陰性 B 細胞の除去が挙げられる。そのために、RP105 陰性 B 細胞に特異的に発現する抗原を同定し特異的抗体を作成する方法が考えられる。RP105 陰性 B 細胞特異的分子の同定を試みるとともに新分子に対する抗体を開発中である。今後、これらの抗体を利用して生物学的製剤の臨床的開発にあたる。もう一つの方法として、RP105 陰性 B 細胞クローン拡大の制御がある。RP105 陰性 B 細胞数の拡大をきたすような要因であるサイトカイン、共刺激分子、感染因子、細胞因子、遺伝的素因などを解明し、それを抑制する方法である。RP105 陰性 B 細胞は、BAFF/３量体 sCD40L により生存が維持され、BCMA の発現が増強している。これらは治療標的として有用であると考えられる。

RP105 陰性 B 細胞特異的治療法により、自己反応性 B 細胞の除去・制御が可能となれば、自己抗体産生が抑制され、自己免疫疾患の治療に繋がると思われる。RP105 陰性 B 細胞を標的とした新規治療の開発上の利点として、治療標的のスペクトラムが狭い特異的治療であり、正常 B 細胞に対する影響が少ないために、安全性や副作用の面で優れている可能性が考えられる。しかし、ヒトにおける RP105 陰性 B 細胞には、未知の部分が多く、臨床応用に向けて今後も研究が必要である。

E.結論

自己免疫疾患において、自己抗体産生 RP105 陰性 B 細胞を標的とすることにより、病的細胞に限定した、より有効かつ安全な特異的治療法が開発できると考えられる。

F. 健康危険情報

なし

G.研究発表

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H.知的財産権の出願・登録状況

(予定も含む)

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

（4） 研究成果の刊行に関する一覧表

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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