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「DNAチップによる急性白血病の新規分類法提案」に関する研究

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総合研究報告書
「DNA チップによる急性白血病の新規分類法提案」に関する研究

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研究要旨：DNA チップを用いることで数千～数万の遺伝子に関する発現変化を比較的簡便に解析することが可能となり、これまでは鑑別診断が困難であった血液疾患の診断に役立つ新たな分子マーカーが同定されると期待される。しかし DNA チップはあまりに高感度な検査法であるため、異なった白血病患者の骨髄細胞全体を比べるような単純な解析を行うと、両患者の「骨髄中の構成細胞の違い」を反映した偽陽性結果を得ることになる。我々は広く患者さんの骨髄より造血幹細胞相当分画のみを純化し保存する「Blast Bank」を設立した。現在まで既に 600 例を越えるサンプルの保存に成功しており、本バンク細胞を用いた大規模 DNA チップ解析によって、遺伝子発現データおよび、各症例の臨床情報フォローアップデータより、初回寛解導入療法の成績にリンクする遺伝子、治療開始後 365 日の時点で寛解を維持できているか否かにリンクする遺伝子、など様々な臨床データに発現量が連関する遺伝子セットを抽出することに成功した。さらにこれら遺伝子の発現量を基に AML の新たなサブグループを定義可能なこと、またこれらサブグループが患者長期予後に連関することなども明らかにした。また白血病芽球で発現するマイクロ RNA についてもその網羅的発現解析を終了し、多くの新規マイクロ RNA を同定することに成功した。これら芽球の薬剤感受性について in vitro における耐性試験を行い、適切な薬剤の組み合わせ方の開発を行った。また遺伝子治療を目指した基盤技術の開発も行った。

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A　　研究目的

現在なお正確な診断が困難であり、かつ有効な治療法の存在しない白血病類縁疾患が数多くある。各患者の有効な治療法を選択する上でも正確な鑑別診断は必須であり、そのためには新たな分子診断マーカーの同定が最も重要であると考えられる。DNA チップは数千-数万の遺伝子発現変化を簡便に解析可能にする最新の研究システムであり、上述の目的に適したスクリーニング法であると期待される。

しかしこれまでのような正常組織と癌組織を単純に DNA チップで比較するような実験においては、両組織の構成細胞成分があまりに異なるため「偽陽性」遺伝子群の同定に終始することが殆どであった。例えば全く同じ白血病細胞が骨髄中に 5%ある患者と 90%ある患者の骨髄単核球を分離して、そこから得た mRNA を用いて DNA チップ比較を行えば、白血病細胞特異的な遺伝子の発現量は後者において 14 倍に増加しているため骨髄全体の遺伝子発現プロファイルは大きく異なってしまい、両患者が全く異なった疾患に罹患しているとの誤った結論が導かれるであろう。したがって真に臨床にフィードバック可能な精度の高い DNA チップ解析を行うためには、この様なポピュレーションの変化に影響されない新たなスクリーニング法の開発が必須と考えられる。

我々は白血病などの特発性血液疾患の多くが造血幹細胞（あるいはその近傍）の異常に起因することに着目し、これら疾患患者のフレッシュ検体より造血幹細胞相当分画のみを純化しストックするバンク事業「Blast Bank」をスタートした。本バンク細胞を用いて DNA チップ解析を行うことで、疾患の種類に拘わらず分化レベルがほぼ均一な細胞群を比較することが可能になり、疾患の病態解明に有用な知見が得られ

ると期待された。本システムを用いて、(1) 白血病の鑑別診断に有効な遺伝子マーカーの同定、(2) 白血病の薬剤感受性に関与する遺伝子マーカーの同定、(3) 病期が進行する白血病類縁疾患の病期特異的分子マーカーの同定、等を本研究計画で目指した。また同様な解析法を成人 T 細胞性白血病（ATL）などに対しても行った。これらの膨大な知見を元に、白血病関連疾患の診断用カスタム DNA チップの開発、および新規分指標的療法の開発を行う。

B　研究方法

1）造血幹細胞特異的マーカーである AC133 に対するアフィニティカラムを用いて、白血病を含む各種特発性血液疾患患者骨髄より造血幹細胞分画を純化保存し、これを Blast Bank と名付けた。平成 17 年 3 月現在で 600 例を越えるサンプルの保存に成功しており、これは純化細胞を用いたゲノミクスプロジェクトとしては世界最大級である。

2) ATL の病期進展機構解明を目的として、ATL 患者末梢血より CD4 陽性 ATL 細胞のみを純化保存する ATL Bank も行い 60 例を越えるサンプルの保存に成功した。またコントロールサンプルとして健常者末梢血より CD4 陽性 T 細胞分画を純化し、一部を PHA にて刺激した。

3）上記検体群を用いて以下のように DNA チップ解析を行った。細胞よりトータル RNA を抽出し、これを T7 RNA ポリメラーゼを用いてまず in vitro にて増幅した。さらにこれをもとに二本鎖 cDNA を合成し、ビオチン CTP の存在下で再び T7 RNA ポリメラーゼと反応させることで、ビオチン標識化した complementary RNA（cRNA）を作製した。このビオチン化 cRNA を DNA チップとハイブリダイズさせ、洗浄後、蛍光色素 PE 結合アビヂンと反応させた。この DNA チップ上の cRNA 結合スポットを Affymetrix 社の蛍光スキャナーで励起させ、各スポットの蛍光強度を測定した後統計処理を GeneSpring 7.0 (Silicon Genetics 社) にて行った。

4）ヒト白血病株化細胞として、U937 (AML)、HL-60 (APL)、TCC-S(CML myeloid crisis)を用いた。GO の併用薬として抗白血病剤の cytarabine 、 doxorubicin 、 daunorubicin, idarubicin 、 mitoxantrone 、 etoposide 、 6-mercaptopurine 、 methotrexate および vincristine を用いた。ヒト白血病株化細胞を GO と他剤の存在下で 4 日間培養し、MTT assay で dose-response curve を得、IC_{80} における併用効果を isobologram (Steel and Peckham)で分析した。

C　研究結果

1）我々は平成11年8月よりBlast Bankを立ち上げ既に600例を越えるサンプルのストックに成功した。現在本バンク中に130例を超える急性骨髄性白血病（AML）幹細胞サンプルが保存されており、世界的にも極めて貴重なリソースとなっている。これら Blast Bank分画を用いた解析が旧来の骨髄単核球全体を用いたものに比べ実際に偽陽性データが少ないこと、またバンクに用いるAC133陽性細胞がこれら疾患の責任クローンを含むことなども既に確認している

2）少量の検体よりマイクロRNA（miRNA）をクローニングする新規解析法mRAP法（miRNA Amplification Profiling）を開発した。本法を用いてマウスのmiRNA発現ボディマップを完成すると共に、白血病検体における解析を行った。その結果１００種類以上の新規miRNAを同定すると共に、癌化能を有するmiRNAを発見することが出来た。

3）骨髄異形成症候群のrefractory anemia with excess of blasts (RAEB)　11例を含む計99例のAML類縁疾患について、Affymetrix社GeneChip HGU133A & B（44,000 probe sets = 33,000遺伝子）を用いた解析を行い、上記99例における全ヒト遺伝子の発現プロファイルデータベースを構築した。これら膨大な遺伝子発現データおよび、各症例の臨床情報フォローアップデータより、初回寛解導入療法の成績にリンクする遺伝子、治療開始後365日の時点で寛解を維持できているか否かにリンクする遺伝子、など様々な臨床データに発現量が連関する遺伝子セットを抽出することに成功した。さらにこれら遺伝子の発現量を基にAMLの新たなサブグループを定義可能なこと、またこれらサブグループが患者長

期予後に連関することなども明らかにした。
4）これまで急性白血病の予後予測は主に白血病細胞の核型を基に行われてきた。同分類法によって「予後不良群」に分類された患者の予後はきわめて不良であることが知られているが、「予後良好群」と「予後中間群」はいずれも予後良好患者と不良患者の両者を含んでおり、実際の予後判定に有効ではなかった。そこで我々の遺伝子発現データから「予後良好群」＋「予後中間群」の中で長期完全寛解患者に特異的な発現を示す遺伝子セットを選出し、これら遺伝子の発現量から長期予後良好患者を予測するコンピューターアルゴリズムを開発した。本アルゴリズムの有効性をテストセットサンプルにおいて検証したところ長期予後を有効に予測する事が出来た。
5）急性期ATL患者特異的に高発現している成長因子受容体および、そのリガンド濃度が患者末梢血中で高値であることが実際のATL細胞の増殖に関与していることを検証する目的で、ATL由来細胞株KK1に対してその成長因子を培養上清に添加したところ、成長因子濃度依存性にKK1細胞の増殖が誘導されることが明らかになった。以上より本成長因子-受容体シグナルがATL細胞の増殖を直接的に制御可能なことが明らかになった。
6）U937, HL-60, TCC-SのGOに対するIC_{80}は各々10.2、5.5、103 ng/mlであった。これらの細胞による併用実験では、GOはいづれの細胞をもちいても、mitoxantrone と相乗作用、cytarabine、doxorubicin、idarubicin、etoposide、6-mercaputopurineと相加作用、methotrexateおよびvincristineと拮抗作用を示した。

D&E. 考察及び結論

本研究事業において各種白血病類縁疾患の大規模な純化細胞 DNA チップ解析を行い、膨大な遺伝子発現データを得た。これらを元に「発現量から統計的有意に診断」を可能にする遺伝子群の抽出に成功し、カスタム DNA チップによる診断法の可能性を示した。

GO は本邦で昨年、発売された新しいユニークな抗がん剤である。私達は、GO と他剤との併用効果を 3 種の CD33(+)白血病株化細胞を用いて検討した。GO に対する感受性は細胞によりかなり異なったが、他の抗がん剤との併用効果について調べてみると、殆ど差を認めなかった。すなわち、いずれの細胞を用いても GO は mitoxantrone と相乗作用、cytarabine、doxorubicin、idarubicin、etoposide および 6-mercaputopurine と相加作用、methotrexate および vincristine と拮抗作用を示した。このことから臨床において GO は methotrexate、vincristine を除くすべての薬剤との併用において優れた抗腫瘍効果が期待される

F. 健康危険情報

無し

G. 研究発表

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H. 知的財産権の出願・登録状況

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出願番号：特願２００５－１６８３３６。出願日：平成１７年6月8日。発明名称：成人T細胞白血病予防治療剤

米国国際出願番号：10/514235。発明名称：Method of identifying pancreatic ductal carcinoma-specific genes using pancreatic ductal cells

カナダ国際出願番号：2486028。発明名称：Method of identifying pancreatic ductal carcinoma-specific genes using pancreatic ductal cells

研究成果の刊行に関する一覧表

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発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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研究成果の刊行に関する一覧表

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