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# 自己評価報告書

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## １．研究計画の概要

変形性関節症（ＯＡ）の予防・治療法の確立に対する社会的ニーズの高まりは疑いの余地がない。我々は最近、OA の分子メカニズム解明から画期的な予防・治療法の開発を目指した戦略的 OA 統合研究計画として、ROAD プロジェクトを樹立した。本研究課題では、1）軟骨変性制御分子のクローニングと分子ネットワークの解明、2）重症度評価システムの開発、3）遺伝・環境因子の網羅的・系統的探索、の 3 テーマについての研究を行う。

## ２．研究の進捗状況

1）軟骨変性制御分子のクローニングと分子ネットワークの解明

我々が確立したマウスの膝関節 OA モデルの関節軟骨の経時的な観察から、軟骨破壊の初期に X 型コラーゲン（COL10）発現で示される軟骨細胞の肥大化が OA の引き金となることを示した。軟骨肥大化分子の網羅的スクリーニングによって、HIF2A、C/EBPβ、cGKII、KLF5 が強力に軟骨細胞の肥大分化を促進することを見出した。中でも HIF2A の転写活性は強力で、複数の分子を転写誘導することによって肥大分化以降の軟骨内骨化過程を広く制御し、NF-κB の下流シグナルとして OA の発症・進行に関与する主要分子であることをマウスのみならずヒトにおいても解明した（***Nat Med***, in press）。また、オステオプロテジェリン（OPG）、Akt1 などの軟骨細胞のアポトーシスや石灰化関連分子も OA の発症・進行に関与していた。これらは軟骨内骨化の過程で見られる現象であり、永久軟骨であるはずの関節軟骨においても、過度のメカニカルストレスの蓄積に抗しきなくなって軟骨内骨化が誘導されることによって OA が発症・進行するものと考えられた。HIF2A / NF-κB シグナルに代表される軟骨内骨化関連分子が OA の治療標的となることが解明された。

2）重症度評価システムの開発

立位膝関節単純 X 線画像において OA の 6 項目の重症度指標（内・外側の関節裂隙の最小距離および面積、骨棘面積、大腿脛骨角）を全自動で計測し、定量値を出力する PC ソフトウエア KOACAD の開発に成功し、特許出願を行った。また、KOACAD の臨床利用を目的に、国内外の大規模観察研究である ROAD と米国 NIH 主導の大規模 OA 疫学プロジェクト OAI データベースにおいて撮影した膝 X 線画像の OA 重症度指標の定量値を解析したところ、膝関節痛の有病と最も強い相関を示したのは関節裂隙最小距離の減少であり、1 ㎜減少することにより男女ともに約 25-40%膝関節痛のリスクが高まることが明らかになった。

3）遺伝・環境因子の網羅的・系統的探索

日本の 4 地域のコホート参加者 3,500 名から得た末梢血より DNA を抽出し、上記の KOACAD による各種計測値を含む臨床情報をデータベース登録した。まずゲノムワイド関連解析(GWAS)による 1 次スクリーニングを実施した。東京地域のコホートより、膝 OA 患者 200 名と正常対照者 200 名を抽出し、Affymetrix 社製 GeneChip Human Mapping 500k Array による 50 万 SNP タイピングを実施した。

その結果得られた P-value<0.001 の 379 SNP について、東京地域で GWAS の対象とならなかった集団から抽出した膝 OA 患者 200 名、正常対照者 200 名と、日本の他の 3 地域コホートよりそれぞれ膝 OA 患者 200 名、正常対照者 200 名を抽出した計 4 つの集団を用いて replication study を行ったが、全てで再現性が確認できた SNP は存在しなかった。次に、関連解析で P-value<0.01 であった SNP は 3,328 SNP あり、この中に真の膝 OA 感受性 SNP が存在する可能性があるため、更なる検索を予定している。

一方、OA ゲノム研究の国際コンソーシアムである TREAT-OA に我々も共同研究者として参加しているが、2009 年、TREAT-OA に参加している欧米 4 地域コホートの GWAS データのメタアナリシスにより、20 個の膝 OA 感受性候補 SNP が抽出された。それをもとに、他の欧米地域とアジア地域で replication study が行われ、我々のグループも参加した。その結果、全世界の膝 OA 患者 7,892 名と正常対照者 45,684 名における検討により、第 7 染色体上の 7q22 の領域に存在する rs4730250 が膝 OA 感受性 SNP であることが同定された。rs4730250 が存在する 7q22 の 500kb の連鎖不平衡領域内には、WNT シグナルに関与する HBP1 などを含む 6 個の遺伝子が存在しており、現在その機能解析が進行中である。

## ３．現在までの達成度

1）軟骨変性制御分子のクローニングと分子ネットワークの解明：80%

2）重症度評価システムの開発：80%

3）遺伝・環境因子の網羅的・系統的探索：60%

## ４．今後の研究の推進方策

OA の治療標的としてマウス・ヒトで特定した HIF2A / NF-κB シグナルに関して根本的治療法への臨床応用を目指す。また、発現クローニングとマウスの in vitro および in vivo の系で同定した複数の候補分子について、ヒト手術摘出標本およびヒトゲノム解析を行ない、可能性が確認された分子については関連する分子ネットワークの解析を進める。

また、医用工学的手法を用いて、膝・股関節・脊椎の単純 X 線画像の実測値を連続量として自動的に出力できるシステムを確立し、観察研究で得られた疫学指標と組み合わせて客観的な診断基準を設けることで、OA の診断および予防についての臨床エビデンスを確立することを目指す。

ゲノムに関しては、Affymetrix 社製 GeneChip Human Mapping 900k Array による GWAS による１次スクリーニングの結果に基づいて、膝 OA 感受性候補 SNP の選定を行う。更に、これらの知見をもうひとつのサブテーマより得られた分子ネットワークのデータと随時照合し、OA の分子背景の解明・創薬ターゲットの同定、そして画期的な予防・治療法の開発を目指す。

## ５． 代表的な研究成果

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〔産業財産権〕
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