発現が顕著に減少していることを明らかにした。これらの結果から、無秩序なNF- B経路の亢進がCHC-Bの癌化を誘導するのではないかと考えている。

リンパ球に増殖形質やアポトーシス抵抗性を賦与してリンパ性増殖を誘発するのに重要な因子は、(IL-2), IL-10 と HCV コア蛋白質である事が明らかとなった。HCV を持続的に発現するとBリンパ腫が一定の頻度で発生する事があきらかとなった。HCVの直接作用でBリンパ腫発症を誘導できる事が強く示唆された。B リンパ腫の発症に関連する宿主因子の１つとしてsIL-2R が明らかとなった。CN2-IRF1-/-マウス、RzCD19Creマウスの解析を通じ、HCVによるリンパ性増殖、B リンパ腫発症機序を解明できると共に、HCV 病原性発現に関する新たな知見が得られる可能性も期待できる。

HCV レプリコン細胞、HCV J6/JFH1 感染細胞の解析から、HCV 感染により GLUT2 の肝細胞表面への発現が抑制され、糖の取り込みが抑制される。これは HCV 感染細胞においてHNF-1αのmRNAおよび蛋白量が減少することによって生じることが明らかとなった。また、HCV感染により、HNF-1αの蛋白質がライソソームプロテアーゼ (特に酸性プロテアーゼの関与) により分解が促進されてGLUT2転写抑制が引き起こされると考えられた。HCV NS5A蛋白質がライソソーム依存性分解を誘導すると考えられた。

HCV は感染に伴い、肝細胞内での脂質の蓄積と培養上清中の VLDL の割合の増加という、HCV 増殖に好都合な環境を作り出しているものと考えられた。メタボローム解析の結果、感染細胞のエネルギー代謝および蛋白核酸合成は低下し、糖代謝は解糖系の亢進が認められた。これは、ミトコンドリア障害によるエネルギー産生の低下とウイルスゲノム複製によるエネルギー消費の亢進によるものと考えられ、感染細胞は解糖系を亢進させてエネルギー産生を行っている可能性が示唆された。

肝臓の慢性炎症の場におけるＨＢＶ遺伝子産物と宿主のがん抑制遺伝子（p53 および pRb)、酸化ストレス径路（NFkB)、転写因子（STAT3）との相互作用が、がん化に促進的に作用することが示された。

当初目的としていたＣ型肝炎ウイルス研究に寄与するベクターの作製及び精製ロットでの供給、肝細胞癌に対する治療用ベクターの新規開発及び播種モデルマウスシステムの確立において一定の進展をみた。

Ｃ型肝炎の脂肪化は　ＢＭＩと血清中性脂肪レベルに大きく反映されている。また、脂肪化はＰＥＧ－Ｒｉｂａ療法の効果に影響を及ぼす可能性がある。適正な減量を行うことがＣ型肝炎の長期予後を改善させる可能性がある。

E. 自己評価

1) 達成度について：当初設定した目標について、ほぼ各項目について、３年間の目標通りに研究が遂行されたと考える。

2) 研究成果の学術・国際・社会的意義について：C 型肝炎を全身疾患として捉えるという概念のもつ社会的な意義は大きいと考えられる。特に、代謝異常の惹起とそれによるＣ型肝炎病態の修飾・予後変化が明らかにされたことの意義は大きい。C 型肝炎患者における代謝異常をコントロールすることによって、予後、QOL の

改善が期待される。

3) 今後の展望について：HCV 感染症と代謝系の相互作用について、肝発癌における役割については未解決である。この点を更に明らかにして肝癌対策を練ることが必要である。

F. 結論

HCV 感染症は肝臓、代謝、循環器等を巻き込む全身疾患である。この様な認識をもって感染者の管理・治療に当ることにより、患者の予後、QOL を大幅に改善することが期待される。

G. 健康危険情報

なし

H. 研究発表

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