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森 英一朗 学位請求論文

審 查 要 旨

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論文審査の要旨及び担当者

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主論文

Lysines 3241 and 3260 of DNA-PKcs are important for genomic stability and radioresistance

DNA-PKcs のリジン 3241 と 3260 はゲノムの安定性と放射線抵抗性に重要である

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論文審査の要旨

電離放射線によって、DNA は様々な損傷を生じる。なかでも、DNA 二本鎖切断は修復されずに残ると、致命的である。DNA-PK (DNA-dependent protein kinase) は、セリン・スレオニンをリン酸化する酵素であり、DNA 二本鎖切断の修復で重要な経路である非相同末端結合において中心的な役割を果たす。DNA-PK は、酵素活性部位 (DNA-PKcs) と DNA 結合部位からなる複合体を形成する。これまでに、DNA-PKcs のリン酸化修飾に関する研究は盛んに行われてきたが、DNA-PKcs におけるその他のタンパク質翻訳後修飾に関しては不明であった。申請者は、DNA-PKcs のアセチル化による DNA-PKcs 依存的な DNA 二本鎖切断修復の調節機構について同酵素の欠損細胞株である V3 細胞を用いて解析を行った。DNA-PKcs は細胞内においてアセチル化されており、DNA-PKcs における二つのリジン残基 (K3241 と K3260) のアセチル化が酵素活性に重要であることを明らかとした。次にこれらのリジン残基をアルギニン残基に置換変異することでリジン残基のアセチル化を阻害した分子を V3 細胞に強制発現させると、野生型の分子を発現させた場合に比べて細胞の放射線感受性が増強し、DNA 二本鎖切断修復能が低下し、染色体異常が増加した。この結果はアセチル化によって DNA-PKcs の機能が調節を受けていることを強く示唆するものである。

本研究は、放射線による DNA 損傷の修復を調節する新たなメカニズムを提示し、悪性腫瘍の新たな放射線治療法開発に繋がる有意義な成果と評価される。参考論文と合わせて博士 (医学) の学位に値すると考える。

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