正井 久雄 研究室 研究概要

研究テーマ

(1) ゲノム複製メカニズムの普遍性と多様性の解明と複製システムの進化
(2) 核内クロマチン構造・配置の制御と複製の時空間プログラム制御機構
(3) 細胞内グアニン４重鎖構造核酸の形成メカニズムと存在様式の解明とその生物学的意義の解明
(4) 複製障害に対する細胞応答機構と、種々の生体ストレス応答経路とのクロストークの解明
(5) 複製因子、複製チェックポイント因子などを標的とした新規な創薬戦略の開発
(6) 複製因子の個体の分化発生・制御における機能の解明

これに加えて、最近、京都大学医学部　准教授から当研究室に赴任された笹沼博之博士は、乳がんの発生機序の研究を行なっておられます。興味のある方は別途説明しますのでご連絡ください。

研究活動のまとめ

ゲノム DNA 複製は、細胞の増殖・分化において中心的な役割を果たす。ゲノムは細胞の増殖に伴い、正確に、高速に、秩序正しく複製されなければならない。この過程に異常が生じると、がん細胞や老化細胞に見られるゲノムの遺伝的不安定性（変異、染色体の欠損や再編成など）を引き起こすことは容易に想像できる。実際、最近の研究から、内的・外的な原因による複製障害に対する適切な細胞応答の破綻が、初期がん細胞の遺伝的変化の主要な要因になっていることが示されている。

ゲノム複製に関して、３個の重要な事象が知られている。

①　　ゲノム複製は細胞周期に一度のみ起こり、細胞分裂と厳密に連動する。
②　　ゲノム複製は、空間的、時間的な制御の元、すべてのゲノムの複製を完了する。またこの過程はエピゲノム情報の維持や、変化とも連動する。
③　　種々の要因で起こる DNA 複製の停止に細胞が迅速に応答し、ゲノム安定性を維持する。

上記の事象のうち、①と③の破綻は、直ちにゲノム変化、細胞の癌化に直結する。②は、DNA 複製のみならず、ゲノムの修復、変動、機能発現（遺伝子発現）

などとも関連し、生物の可塑性、適応性の基盤となる。私達は、これらに関連する問題を解決するために、主に以下の４個の研究課題を推進している。

1) 染色体 DNA 複製の開始とその時空間的制御の分子機構

真核細胞ゲノム複製では多くの部位から複製は開始する。また複製の時間的タイミングや、核内での複製部位の局在は、細胞型特異的な制御下にあり、染色体の核内配置、高次構造やエピゲノム情報などにも影響される(図 1)。

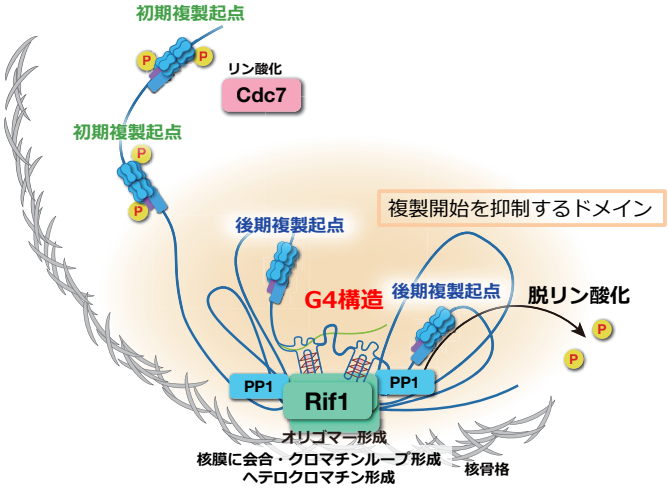

図１ Rif1 による染色体ドメインの形成のモデル:Rif1 は多量体を形成し複数の G4 構造を有する DNA に結合し、核膜近傍に染色体ループ形成を促す。これにより複製や転写の制御ドメインの形成を促進する可能性がある(加納ら、*Nature Structure Molecular Biology*, 2015 より)。

Kanoh, Y. *et al.* (2015) ***Nat. Struct. Mol. Biol.*** 22: 889-897
Toteva, T. *et al.* (2017) ***Proc. Natl. Acad. Sci. USA.*** 114: 1093-1098.

2) 特殊 DNA 構造の生物学的意義の解明

これまでの研究からグアニン４重鎖など非 B 型 DNA 構造が複製開始や染色体の高次構造構築などにおいて重要な役割を果たすことを明らかにしてきた(図 1 および図 2)。特に、グアニン４重鎖は、ゲノム上および転写された RNA 上に非常に頻繁に存在すると想像されており、ゲノム機能の未知の情報を担う可能性がある。

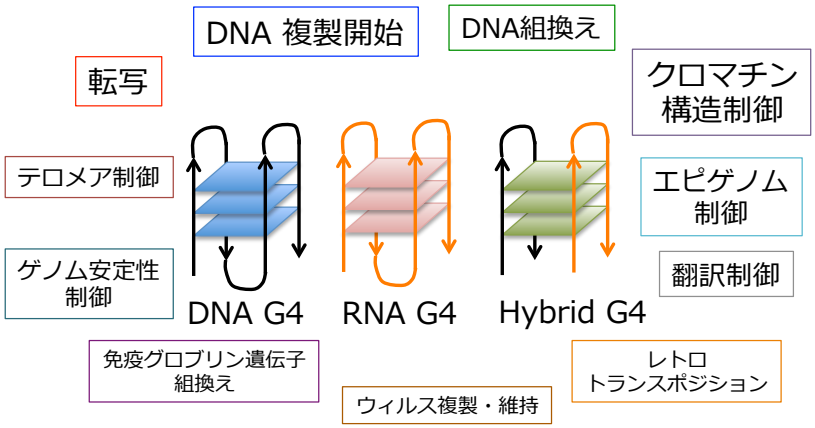

図２ G4（グアニン４重鎖）の多様な機能：G4 は多様な形態で DNA および RNA あるいは DNA-RNA hybrid 上に形成され、核酸が関与する多種多様な反応を制御する。

3) 複製ストレスに対する細胞応答の分子機構の解明とその新規制癌戦略への応用

複製障害は、がん化や老化のもっとも直接的な原因となる。従って、複製ストレスによる、細胞応答機構の解明は、がん化、老化の根本的メカニズム解明に必須である (図3)。さらに私達は最近複製ストレス応答が、浸透圧、酸化、温度、最近感染、低酸素など種々の生体ストレスとクロストークしていることが明らかとなり、これらの生体ストレスがゲノム安定性に及ぼす影響を明らかにする (図 4)。

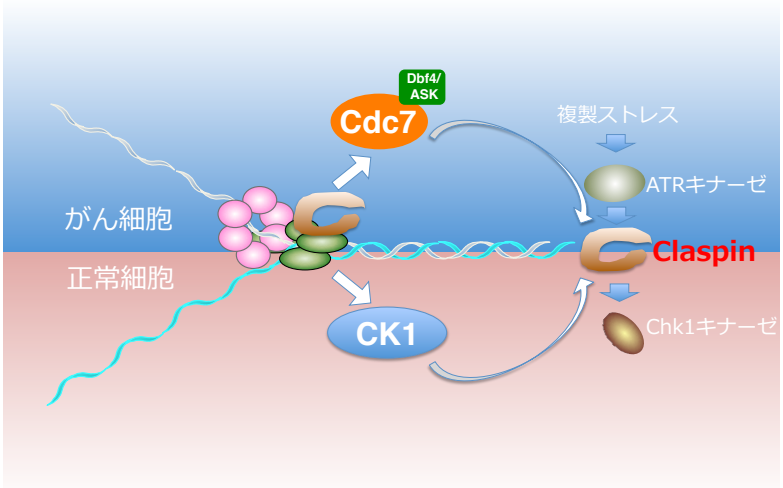

図３　がん細胞と正常細胞の DNA 複製停止に対する細胞応答の違い：複製が予期せずに停止すると細胞は、図の右側に記載される複製チェックポイント反応を誘導する。Claspin はこの反応経路で、複製停止の信号を伝えるために重要な役割を果たす。がん細胞と正常細胞は、異なるタンパク質を用いてこの経路を活性化する。すなわちがん細胞は Cdc7 キナーゼを用いるが、正常細胞では主に CK1 キナーゼに依存する。この違いを用いて、Cdc7 を標的としてがん細胞のみを選択的に除去する治療戦略が可能となる。実際に Cdc7 を制癌剤の標的として現在新規制がん剤の開発を進めている。

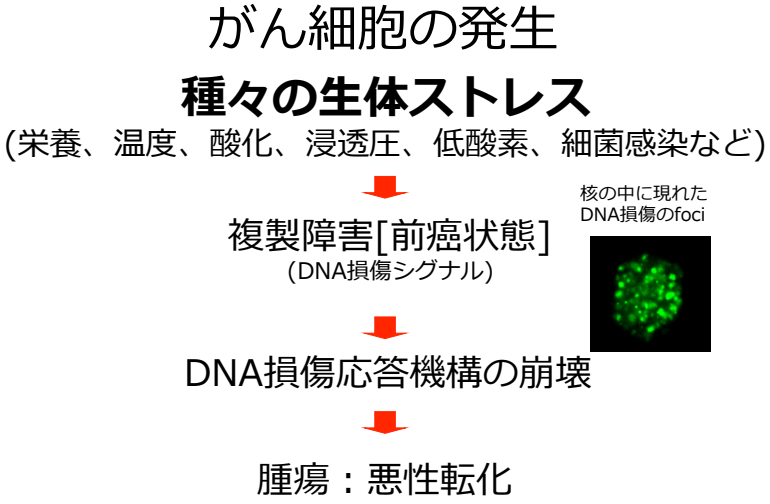

図４　がん細胞の発生：種々の生体ストレスは複製障害を誘導する可能性がある。複製障害は一時的に DNA 損傷をゲノム上に誘導するが、修復される。しかし DNA 損傷応答機構が崩壊すると細胞は腫瘍化する。

4) 複製因子の個体レベルでの機能と疾患への関与

複製因子が、個体の発生、臓器・組織の発生・機能において担う役割を、臓器・組織特異的ノックアウトマウスや、遺伝子改変動物の表現型の解析に基づき明らかにする(図 5)。

多様な生物種と、手法を用いることにより、ゲノム複製のメカニズムの多様性と普遍性を解明し、さらに、核酸の形態が担う、ゲノムに隠された未知の機能シグナルの生物学的意義を解明する。得られた成果を基盤として、がんなどの疾患の予知、予防、診断、治療の新規戦略を開発する。

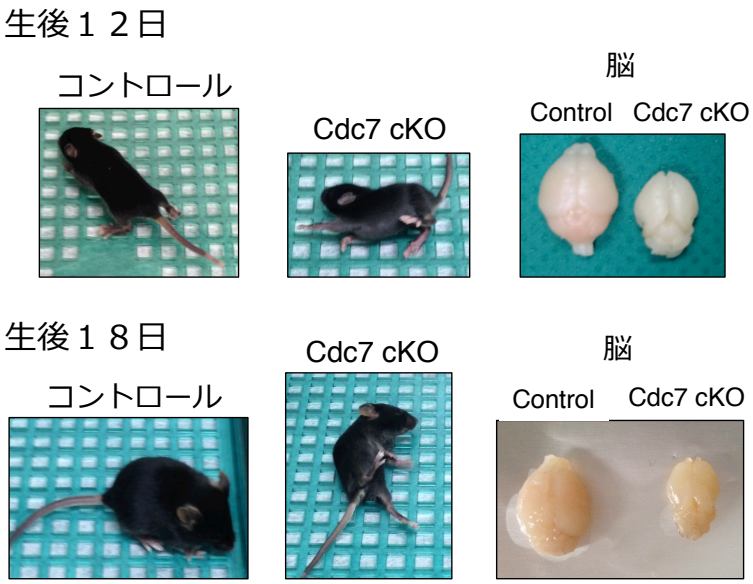

図５ Cdc7 (f/+) *Nestin*^{Cre} マウスは脳の形成異常、成長遅延を示す：神経幹細胞において Cdc7 をノックアウトすると、マウスは誕生するが、生後の脳の形成異常、成長遅延を示し、生後 20 日までで死亡する。Cdc7 の活性化サブユニット ASK の同様なノックアウトにおいても類似の表現型が観察された。

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