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研究課題名(和文) 胚性ゲノムの活性化から着床までのエピジェネティクスと胚の全能性

研究課題名(英文) Epigenetics from zygotic genome activation to implantation controlling the totipotency of the preimplantation embryo

研究代表者

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研究成果の概要(和文)：マウス初期胚発生においては、クロマチンリモデリングを介して新しい発生プログラムが開始する。本研究では、ヒストンH4の20番目のリジン(H4K20)のモノメチル化酵素であるSETD8がマウス初期胚発生に及ぼす影響について検討した。SETD8はH4K20だけでなくp53のような非ヒストンタンパク質をメチル化してその機能を制御するが、SETD8阻害による発生停止はH4K20のモノメチル化によることが明らかになった。また、一過的なSETD8阻害による発生遅延は、DNA損傷修復や細胞周期チェックポイントで必要不可欠な働きをするATR経路の阻害によってレスキューされた。

研究成果の学術的意義や社会的意義

本研究では、ヒストンH4K20のメチル化に関するSETD8の機能を阻害すると、胚の発生停止や発生遅延を引き起こすことを明らかにした。SETD8阻害時に、DNA修復に関わるATR経路を同時に抑制すると、細胞周期が正常に進むことも明らかになり、体外で培養された受精卵が常にDNA修復を必要としていることが示唆された。このことはこれまでに指摘されてこなかったことであり、学術的に大きな意義を持つ。また、ヒトの生殖補助医療においても、できるだけDNA損傷が起こらないような培養環境を作っていくことで、より自然な発生を誘導し、正常な受胎を支持する技術開発にも繋がり、社会的にも大きな意義を持つ。

研究成果の概要(英文)：During mouse preimplantation development, a new developmental program starts through chromatin remodeling. Histone H4 Lysine 20 (H4K20) monomethylation has been reported to control gene expression and DNA damage. However, little is known about the role of methylation by SETD8 in mouse preimplantation development. In the present study, we revealed that SETD8 regulated cell cycle progression during mouse preimplantation development. Although it is known that SETD8 methylates not only H4K20 but also non-histone proteins such as p53 to control its function, we found that developmental arrest of SETD8-inhibited embryos was due to inhibition of H4K20 monomethylation. In addition, development delay caused by transient inhibition of SETD8 was rescued by inhibition of ATR pathway, which play crucial role in DNA damage repairment and cell cycle checkpoint. These results suggest that SETD8-mediated H4K20 monomethylation regulate cell cycle progression in mouse preimplantation development.

研究分野：生殖生物学

キーワード：マウス初期胚 胚性ゲノムの活性化 エピジェネティクス 発生と分化

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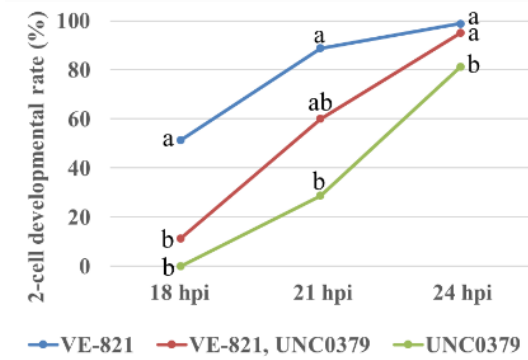
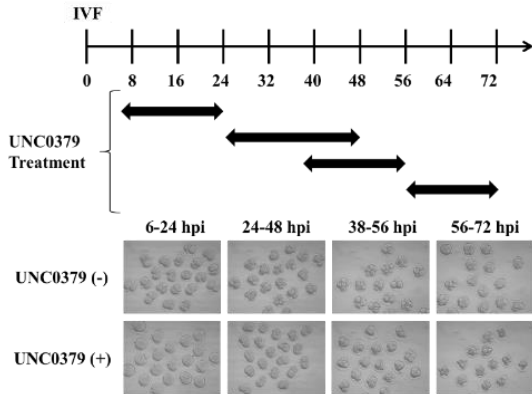
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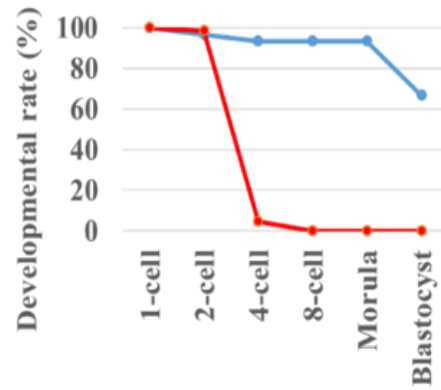
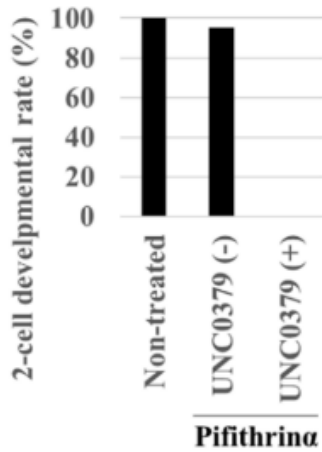
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