

성체줄기세포 표지 분석기술 개발

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연구내용

성체줄기세포의 비대칭적 자기복제(asymmetric self-renewal) 현상을 단백질 생체표지분자(바이오마커)와 면역세포화학염색법을 이용한 바이오이미징 기법으로 분석하는 기술 개발에 성공함.

성체줄기세포는 비대칭적 자기 복제라는 독특한 세포 분열방식을 통해 2개의 딸세포 중, 향후 줄기세포가 될 1개의 딸세포에게만 줄기세포 고유의 '불멸 유전 정보 (immortal DNA)'를 전달하고, 다른 딸세포는 유전 정보를 전달 받지 못한 상태에서 분화 후 세포사멸에 이르게 됨.

이번 연구는 이들 2개의 딸세포 중, 어느 쪽이 줄기세포 고유의 불멸 유전정보를 전달받아 성체줄기세포로 분화되는 지를 밝혀내는 분석법을 개발한 것으로, 이번 에 새롭게 발굴된 성체줄기세포 바이오마커 후보 분자인 '5- 수산화메틸시토신(5-hydroxymethyl - cytosine)'과 기존에 알려진 immortal DNA 표지분자인 BrdU에 대한 이중면역형광염색을 실시한 후 바이오이미징 분석이 이루어짐.

본 연구결과, 향후 성체줄기세포가 될 딸세포의 DNA에 '5-수산화메틸시토신'이 세포사멸될 운명인 다른 딸세포에 비해 상대적으로 훨씬 많이 분포함을 밝혀냄에 따라, '5-수산화메틸시토신'이 성체줄기세포를 특이적, 효율적으로 표시할 수 있는 바이오마커임을 확인하였음.

기대효과

인체 내에 극소수로 존재하는 성체줄기세포를 손쉽게 표시할 수 있는 분석기술 관련 정보를 제공하는 것이 가능할 전망이며, 향후 성체줄기세포 표지 바이오마커의 지속적인 추가 발굴 연구 및 성체줄기세포 표지, 분리, 대량배양 등의 관련 연구 뿐 아니라, '성체줄기세포를 이용한 세포노화방지전 연구'나 손쉽고 효과 적인 '암 초기진단 분석법 개발' 등의 후속 연구에도 크게 기여할 것으로 기대

Higher 5-hydroxymethylcytosine identifies immortal DNA strand chromosomes in asymmetrically self-renewing distributed stem cells

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Immortal strands are the targeted chromosomal strand of asymmetric cell division, a molecular mechanism that allows stem cells to self-renew. Immortal strands are proposed to reduce the rate of accrual of chromosomal errors by being protected from asymmetrically segregating differentiating progeny cells, which retain unreplicated and unreplicated replication errors as a safeguard of genomic integrity (1, 2). Nonrandom segregation of immortal DNA strands may limit DNA mutagenesis, preserve DNA fidelity, and contribute to DNA repair. The mechanisms responsible for identification and maintenance of immortal DNA strands are unknown. To discover them, we have used a novel method to identify the 5-methylcytosine and 5-hydroxymethylcytosine (5hmC) content in chromosomes in mouse fetal thymic DNA during asymmetric segregation. Although 5-methylcytosine content did not differ significantly, the relative content of 5hmC was significantly higher in chromosomes containing immortal DNA strands than in opposite sister chromatids containing younger mother DNA strands.

The difference in relative 5hmC content was caused by the loss of 5hmC from mother chromosomes. These findings imply that 5hmC is a specific molecular determinant of immortal DNA strand chromosomes. Because 5hmC is an intermediate during DNA demethylation, we propose a new mechanism for asymmetric segregation: a mechanism by which 5hmC "marks" the germline age of immortal DNA strands. The mechanism is supported by molecular expression data and accounts for the selection of newly replicated DNA strands when nonrandom segregation is initiated. These molecular findings also provide a possible basis for another characteristic property of immortal DNA strands, their genomic chromosomal dependency.

Keywords: 5-hydroxymethylcytosine; asymmetric segregation; DNA; stem cells

Although distributed stem cells (DSCs) are naturally essential for natural tissue function, health, and longevity (1–3), understanding of the cellular mechanisms responsible for their unique tissue functions is quite limited. In particular, the mechanisms responsible for the defining properties of DSCs—asymmetric self-renewal (ASR) and nonrandom chromosomal segregation—are unknown.

ASR is a special subclass of asymmetric cell division by which DSCs continuously divide asymmetrically to produce daughter cells (4–6). During ASR, DSCs divide asymmetrically with retention of their own stem cell phenotype while continuously producing new daughter cells that are preprogrammed for short-lived tissue-specific differentiating cell fates. This long-lived role of DSCs for the cell lineage architecture of every tissue is the basis for the reproductive stem cell gene maintenance (7, 8).

Nonrandom chromosomal segregation is tightly associated with ASR (1, 2). During mitosis, nonrandomly segregating DSCs (aDSCs) continuously segregate to themselves the set of sister chromatids that contain the bulk of the parental template DNA strands. By retaining the same set of template

Significance

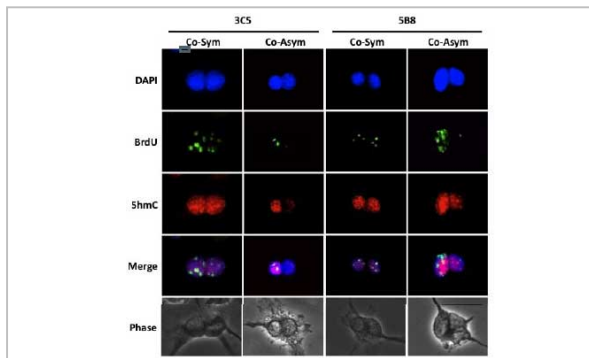
Distributed stem cells (DSCs), which continuously divide asymmetrically to regenerate mature tissue cells, adopt a special form of mitotic chromosome segregation. Chromosome segregation is nonrandom instead of random. DSCs segregate the set of sister chromatids with the bulk of the parental template DNA strands used for nonrandom DNA replication during the preceding division. Because the asymmetric molecular mechanisms that govern the asymmetric segregation of DSCs are unknown, there was a need to develop a method to identify the molecular mechanisms that govern the asymmetric segregation of DSCs. We propose that asymmetric chromosomal segregation is a key feature of a stem cell lineage. We identify 5-hydroxymethylcytosine (5hmC) as a molecular marker for the DSC, identifying the DSC template strands from progenitor cells.

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[그림 2] 논문

[그림 1] 생쥐 피부의 성체줄기세포 분열 시, 딸세포 중 불멸 유전정보(immortal DNA, 이미지 상에서 BrdU로 표시됨)를 지닌 성체줄기세포에 5-hydroxymethylcytosine 분자가 비대칭적으로 다량 분포함을 보이는 이미지