The Mother of All Stem Cells?

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The stem cells that sustain metazoan tissues face a difficult challenge. Each time a stem cell divides—it can divide indefinitely—it risks damage from errors in the duplication and segregation of genetic and cellular material that could stunt its vitality or propel it toward a cancerous state. Normally, each division must be asymmetric to ensure that only one daughter cell differentiates, while the other becomes a stem cell, thus renewing the stem cell population. Yet stem cells safely grow and divide many more times than other cell types, including their own daughters. On page 518 of this issue, Yamashita et al. (1) examine the role of one of the most fundamental cellular components in supporting stem cell function—the centrosome. Centrosomes organize the microtubule-rich mitotic spindle that directs how chromosomes and other materials are distributed between daughter cells at cell division (mitosis). The authors show that male germline stem cells in the fruit fly Drosophila melanogaster differentially position their mother and daughter centrosomes during mitosis. As part of this strategy, which ensures asymmetric division, the stem cell permanently retains the mother centrosome across many cell divisions, raising the possibility that differential centrosomal inheritance is essential to stem cell biology.

Unlike other known animal cell organelles, the two centrosomes inherited by daughter cells at division are not identical. All normal cells initially have one centrosome, comprising a mother and daughter centriole as well as pericentriolar material. The mother centriole contains structures and proteins that are absent from the daughter centriole, and it nucleates more microtubules than the latter. During each cell division cycle, the centrosome replicates. The mother centrosome retains the original mother centriole. In contrast, the daughter centrosome undergoes maturation during mitosis and during the G1 phase of the next cell division cycle, converting its inherited daughter centriole into a new mother centriole (2). Whether this intrinsic asymmetry facilitates asymmetric stem cell division has remained a mystery.

Yamashita et al. took advantage of centrosomal asymmetry to follow the fates of mother and daughter centrosomes during germline stem cell division in the testis of Drosophila. These germline stem cells, which give rise to sperm, have already divided 12 or more times when they become established in their niche, adjacent to stromal cells known as the hub (see the figure). Germline stem cells complete as many as 30 additional cell cycles over the life of the animal, each time sustaining themselves while producing one non-stem cell daughter, the gonialblast. Each gonialblast divides just six times before differentiating.

The authors genetically engineered flies to produce a centrosomal protein, known as PACT, tagged with green fluorescent protein. By inducing the expression of this fluorescent protein at different times, they could selectively label either mother or daughter centrosomes. Mother centrosomes were almost always located near the hub, which ensured that after mitosis they would be inherited by the daughter that remains in the niche and remains a stem cell. Daughter centrosomes, on the other hand, always migrated to the opposite end of the stem cell and were inherited by the daughter cell destined to become a gonialblast. Thus, germline stem cells retain their mother centrosome from the time they first enter their niche.

What advantage might such a strategy confer on the stem cell? The most likely answer is to help control the orientation of cell divisions. Germline stem cells in the Drosophila testis position their mitotic spindles at right angles to cell division as well as the stem cell–specific inheritance of the mother centrosome.

Studies of other asymmetrically dividing cells suggest possible additional roles for programmed centrosome inheritance in stem cells. Aside from their participation in spindle assembly, centrosomes associate with membrane-bound organelles such as the Golgi and recycling endosomes. Centrosomes also regulate cytokinesis by delivering membranes asymmetrically to the cleavage furrow (4, 5). Thus, differential centrosome inheritance might contribute to stem cell maintenance and daughter cell programming by partitioning membrane-bound organelles and signaling molecules asymmetrically between the germline stem cell and gonialblast. Indeed,
asymmetric segregation of cell fate determinants through recycling endosomes has been implicated in specifying cell fate in the developing Droso phila nervous system (5). The mother centrosome might also act as a basal body that nucleates a primary cilium, at least in mammalian stem cells (6). Primary cilia can serve as signaling organelles (7) and might provide a means for stem cells to communicate with their niche and to receive a maintenance signal.

Could retention of the mother centrosome contribute to stem cell longevity as well as to developmental programming? The most relevant information comes from studies of asymmetric cell division in the budding yeast Saccharomyces cerevisiae. Mother cells have a lower replicative potential than buds they produce, and selectively retain damaged molecules (8, 9). Interestingly, the fungal counterpart of the mother centrosome, the mother spindle pole body, is selectively inherited by the bud (10). By inheriting centrosomes, stem cells may likewise use the robust microtubule array to repel molecules that promote replicative senescence. However, in yeast, other types of damage, such as chromosome breaks that cause loss of heterozygosity, accumulate preferentially in the bud (11), so the importance of maternal centrosome inheritance in promoting longevity remains unclear.

Is differential centrosome inheritance the long-sought secret of stem cell function? It should now be possible to determine whether maternal centrosomes are retained by several other well-characterized Droso phila stem cells. In male germline stem cells, such behavior seems likely to contribute to the stable asymmetric programming of stem cell and daughter. And it is satisfying to contemplate the possibility that this strategy might also promote stem cells’ remarkable stability and longevity.

References

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CHEMISTRY

Single-Molecule Catalysis
Ian Smith

To some, the word catalysis conjures up images of large-scale industrial processes. For example, the Haber process, discovered about 100 years ago, makes use of supported iron catalysts to speed up the conversion of nitrogen and hydrogen to ammonia at moderate temperatures. Worldwide, this process is responsible for the annual manufacture of more than 100 million metric tons of ammonia (1). In contrast, the paper by Vöhringer-Martinez et al. on page 497 of this issue (2) addresses a fundamental question: Can single molecules serve as catalysts? That is, can individual molecules accelerate chemical reactions?

This question is best answered by experiments in the gas phase, where the overall reaction comprises a series of elementary reactions, each involving a small number of molecules. One well-known example is the catalytic destruction of ozone in the upper atmosphere by species such as halogen atoms, nitric oxide, and hydroxyl radicals (3). These species (X) participate in chain reactions (X + O₃ → XO + O₂, and XO + O → X + O₂), whose net effect is to speed up the conversion of “odd oxygen” (O atoms and O₂ molecules) to dioxygen O₂, thereby lowering the amount of ozone present in the stratosphere.

This destruction of ozone can be thought of as an example of homogeneous catalysis (the catalyst is in the same phase as the reactants), familiar in reactions in solution. By contrast, Vöhringer-Martinez et al. provide an example of gas-phase catalysis more akin to heterogeneous catalysis. They report that the reaction between hydroxyl radicals and acetaldehyde, OH + CH₃CHO → H₂O + CH₂O, is accelerated by the participation of single molecules of water. They argue convincingly that this is because hydrogen-bonded complexes of CH₃CHO and H₂O form and that these complexes react faster with OH radicals than do individual molecules of CH₃CHO. The binding to water is thus analogous to binding to a surface in

A single water molecule can act as a catalyst in a gas-phase reaction by forming a complex with a reactant that reacts faster than the “bare” reactant.

Catalysis by single water molecules. Energy profiles for (A) reactions between hydroxyl radicals and “bare” acetaldehyde molecules (the “higher road” traced in blue) and (B) reactions between hydroxyl radicals and acetaldehyde molecules that are associated with single molecules of water (the “lower road” traced in green). The horizontal lines show maxima and minima along the reaction path of minimum energy, with energy differences given in kJ mol⁻¹. The arrows are used to indicate that on pathway B all the reactive flux that reaches the minimum associated with the prereaction complex passes through the inner transition state and becomes products, whereas on pathway A some of this flux is reflected at the inner transition state, reducing the reaction rate. The cartoons show the structures at the maxima and minima, in most cases of hydrogen-bonded complexes. More details are given in (2).

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