SAGE1's Sage Wisdom Stabilizes Genomes

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In a recent publication in *Vita*, Li *et al.*[1] reveal that SAGE1, a simian-specific X-linked protein, promotes error-free homologous recombination and suppresses error-prone non-homologous end joining to safeguard the germline; its tandem repeat domain explains primates' low mutation rates and offers new insights into infertility and SAGE1-positive cancers.

The faithful transmission of genetic information depends on germline genome integrity. DNA double-strand breaks (DSBs) are especially dangerous, as they can cause mutations or cell death. Germ cells counter this using two repair pathways: error-free homolo-gous recombination (HR), which uses a sister chromatid template, and error-prone non-homologous end joining (NHEJ). Pathway choice is tightly regulated, because unrepaired or misrepaired DSBs become heritable mutations, which cause various diseases[2].

For decades, comparative genetics has revealed a puzzle: simian primates (including humans) have significantly lower per-generation germline mutation rates than non-simian mammals like rodents, despite longer generation times and larger genomes[3,4]. This suggests primate germlines have evolved enhanced genome surveillance, yet the molecular basis remains unknown. Most DNA damage response (DDR) factors are ancient and conserved, leaving a gap in understanding how lineage-specific adaptations fine-tune DSB repair in the primate germline. No simian-specific regulator had been identified that actively promotes HR while suppressing NHEJ in spermatogonia or oogonia — the cells that propagate the species' blueprint.

Li *et al.*[1] now fill this gap by uncovering *SAGE1*, a simian-specific X-linked gene highly expressed in spermatogonia, as a novel DDR regulator that orchestrates a germline genome stability "upgrade" via HR. Their work integrates evolutionary genomics, primate biology, and mechanistic biochemistry to show how a lineage-specific tandem repeat domain enables SAGE1 to tilt DSB repair toward HR and away from NHEJ.

At the core of this study are the simian-unique tandem SAGE1-specific exon repeats (SERs), a structural feature that confers SAGE1's specialized DDR function. Unlike most DDR genes that arose early in eukaryotes, *SAGE1* emerged specifically in simians, with SERs absent in prosimians, rodents, and other placental mammals. The authors demonstrate that SERs are both necessary and sufficient for SAGE1's rapid recruitment to DSB sites, mediating direct interactions with three core repair machineries: CtIP, the SOSS complex, and the NuA4 complex. This repeat-driven binding illustrates how evolution co-opted a tandem repeat expansion to add a regulatory layer onto conserved HR, a "tinkering" model where novel traits arise from modifying existing machinery.

Mechanistically, SAGE1 acts as a spatiotemporal coordinator of DSB repair pathway choice (Fig. 1). Upon DNA damage, its recruitment downstream of the MRN complex is mediated by SER–CtIP interaction, promoting DNA end resection which is a committing step for HR. Concurrently, SAGE1 stabilizes the SOSS complex at DSBs through its C-terminal domain, boosting resection efficiency and reinforcing RPA/RAD51 loading. In parallel, SAGE1 recruits the NuA4 complex via SERs, triggering TIP60-mediated H4K16 acetylation, which blocks 53BP1 recruitment and suppresses NHEJ[1,5]. This dual action occurs specifically in S/G2 phases, matching HR's cell-cycle restriction. Super-resolution imaging shows that SAGE1 segregates from 53BP1 and colocalizes with BRCA1 at the damage foci. This multi-step cascade is unusual for a lineage-specific DDR factor.

Evolutionarily, SAGE1 may explain differences in primate germline mutation rates. Its simian-specific expression in mitotic spermatogonia (and fetal oogonia) appears to optimize DDR in germline cells. Cross-species assays (knockdown in macaque, humanized mouse models, and *Drosophila* ectopic expression) suggest SAGE1 is portable and sufficient to enhance genome stability in heterologous systems lacking SERs. This implies the simian DDR upgrade is a modular, gain-of-function trait, potentially selected to reduce heritable mutations in long-lived primates. SAGE1 thus joins a small set of evolutionarily novel DDR factors, *e.g.*, Shieldin[6,7], that shape lineage-specific genome maintenance.

Beyond evolution, the study has implications for reproductive medicine and oncology. In fertility, *SAGE1*'s role in spermatogonial stability positions it as a candidate gene for idiopathic male infertility and premature ovarian insufficiency[8]. Its expression in fetal oogonia warrants study in ovarian aging. In cancer, SAGE1's aberrant reactivation in multiple tumor types bolsters HR-mediated repair and therapy resistance, creating a therapeutic vulnerability. Targeting SAGE1's SER-mediated interactions could sensitize SAGE1-positive cancers to DNA-damaging agents while sparing normal somatic tissues (which lack SAGE1 expression). This approach parallels PARP inhibitors but may apply to HR-proficient tumors[9]. More broadly, evolutionarily novel lineage-specific genes are not curiosities but drivers of disease susceptibility and treatment responses.

Conceptually, this work highlights DDR network plasticity. For decades, DDR was viewed as largely conserved across vertebrates, but *SAGE1* demonstrates that even late in mammalian evolution, lineage-specific genes can fine-tune core repair pathways. The study also underscores the value of primate-specific biology: rodent models lack regulators like SAGE1, limiting their utility for some aspects of human ger-

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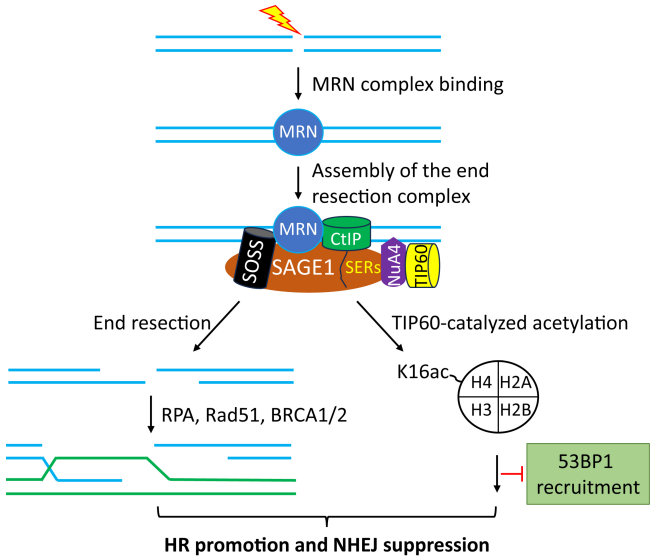

Fig. 1 Schematic depicting the role of SAGE1 in promoting HR while suppressing NHEJ following a DSB. The MRN complex detects the break and recruits SAGE1. SAGE1 acts as a signaling hub: its unique tandem repeats bind CtIP and NuA4, while its C-terminal domain binds the SOSS complex. This leads to two divergent branches. CtIP and SOSS cooperate to promote DNA end resection, committing repair to the high-fidelity HR pathway. Concurrently, the NuA4–TIP60 complex triggers acetylation of H4K16 (K16ac), which blocks 53BP1 recruitment, thereby suppressing the error-prone NHEJ pathway. The combined effects of HR promotion and NHEJ suppression result in a genome stability upgrade within the germline.

mline biology. The multi-model approaches, human/macaque spermatogonia, *in vivo* primate/mouse/*Drosophila* models, and *in vitro* biochemistry, provide a robust framework for studying lineage-specific genes.

In summary, this study integrates evolutionary genetics, molecular DDR, and reproductive biology. SAGE1 emerges as a simian-specific DDR regulator that uses tandem repeat-mediated multi-complex interactions to promote HR and safeguard germline genome integrity. Its discovery offers insights into germline mutation rate control and suggests potential avenues for infertility treatment and cancer therapy. Overall, this work exemplifies how studying lineage-specific genetic innovations can reveal important aspects of human biology and disease.

COMPETING INTERESTS

The author declares no competing interests.

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ADDITIONAL INFORMATION

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