Scientists reveal the secret of polyamines function in DNA repair

How metabolites and cellular small chemicals contribute to genome integrity has been poorly explored. A research team led by Prof. Peter Chi from National Taiwan University found that natural occurring small cations called polyamines (Fig. 1a for schematic) play an essential role in DNA repair process. By combining animal study, cell-based analysis, and biochemical assays, their study reveals that polyamines specifically facilitate homologous recombination-mediated DNA double-strand break repair. It is worth noting that many cancers harbor elevated levels of polyamines to sustain their survival. Thus, their findings provide a fundamental base for further studies directed at devising the strategies for cancer treatment. This work is now published in ***Nature Communications***, a well-known international scientific journal.

Homologous recombination is a predominantly error-free repair pathway in cells to fix DNA double-strand breaks (DSBs). Furthermore, it is a prerequisite for maintenance of genome integrity and prevention of tumorigenesis. Initiation of homologous recombination is catalyzed by RAD51 recombinase. RAD51 assembles onto single-strand DNA (ssDNA) forming a nucleoprotein filament within damage sites. The RAD51-ssDNA filament then engages duplex DNA, searches for homology in the duplex, and upon homology location, catalyzes the invasion of the duplex DNA for subsequent DNA exchange and synthesis to repair DSBs. However, the underlying mechanism of homology search process remains unclear. Importantly, what cellular factors might be involved in homology search is a crucial issue to be addressed.

In this study, the research team provides the evidence for the first time that polyamines specifically promote homologous recombination (HR), but not other DSB repair pathways such as non-homologous DNA end-joining (NHEJ) and single-strand DNA annealing (SSA; Fig. 1b). Mechanistically, polyamines significantly stimulate the DNA strand exchange activity of RAD51 by the enhancement of duplex DNA capture in the DNA homology search process (Fig. 1c).

The first author, Dr. Chih-Ying Lee, proposes three possible mechanistic actions to explain how polyamines stimulate RAD51-mediated DNA exchange activity (Fig. 1d). First, polyamines could act as a linker to facilitate the collision between RAD51 filament and duplex DNA (Fig. 1d, inserted box i). Second, polyamines could stabilize the pairing between invading single-strand DNA with complementary ssDNA of the duplex template (Fig. 1d, inserted box ii). Finally, polyamines could condense duplex DNA to allow RAD51 filament searching for homology in multiple

regions simultaneously (Fig. 1d, inserted box iii). Dr. Lee points out that their study reveals how polyamines expedite RAD51 filament to search for homology through the vast genome efficiently.

Their fundamental work has important clinical implications. As cancer cells possess elevated level of polyamines, their DNA repair activity is expected to be upregulated. Consistent with this premise, the research team found that the small molecule drug, 2-difluoromethylornithine (DFMO), significantly reduces level of polyamines and leads to impaired DNA repair activity. Most excitingly, their team also shows that both combination treatment of DFMO with radiation; and DMFO with FDA-approved drug, olaparib, suppress cancer cell survival. It is worth noting that DFMO drug is being tested in the phase II clinical trial for neuroblastoma and showing a significant therapeutic benefit. “Our work thus provides a mechanistic link directed at devising the strategies for cancer treatment such as the combination of DNA damaging agents with DFMO,” said Prof. Peter Chi.

The study “Promotion of homology-directed DNA repair by polyamines” is now published in *Nature Communications* and is carried out by Chih-Ying Lee, Guan-Chin Su, Wen-Yen Huang, Min-Yu Ko, Hsin-Yi Yeh, Geen-Dong Chang, Sung-Jan Lin, and Peter Chi. This work was supported by National Taiwan University, Academia Sinica, and Taiwan Ministry of Science and Technology.

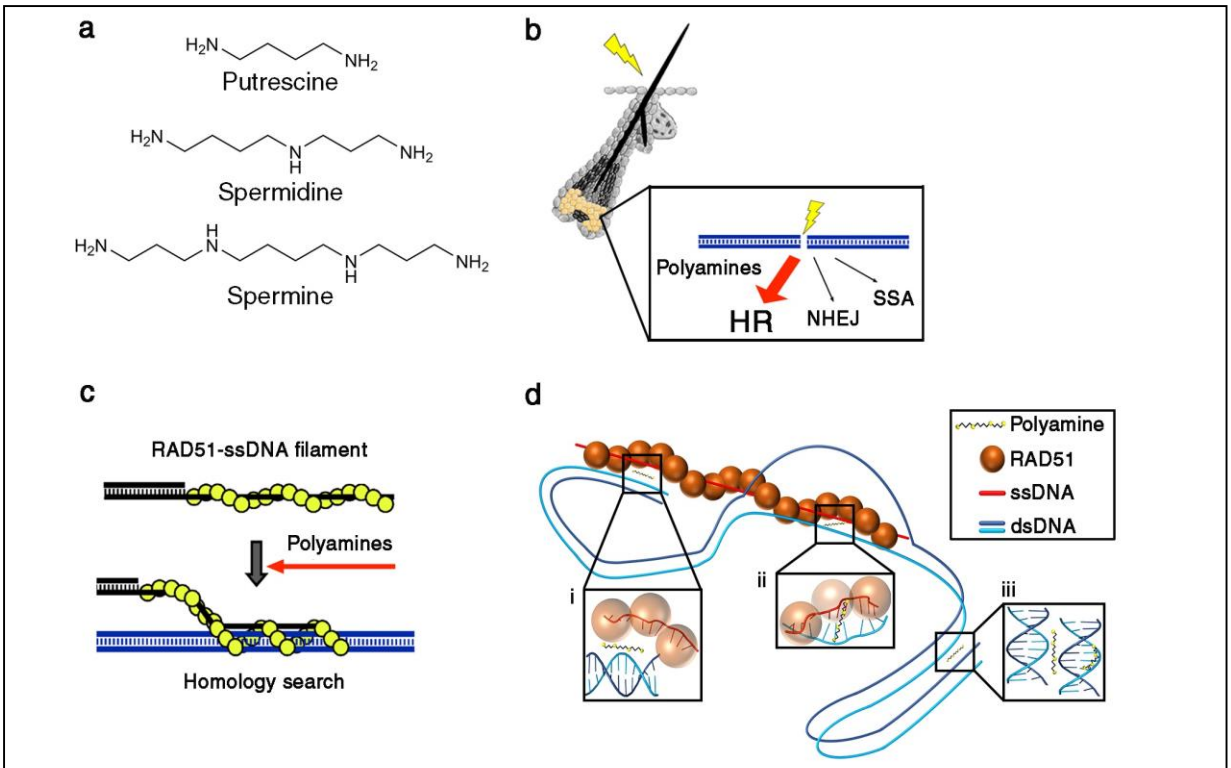

Figure 1. Polyamines Enhance DNA Break Repair

(**a**) Structures of polyamines. (**b**) The morphology of hair follicle. Polyamines promote homologous recombination (HR), but not non-homologous DNA end-joining (NHEJ) and single-strand DNA annealing (SSA), repair. (**c**) Polyamines facilitate duplex capture of RAD51 nucleoprotein filament. (**d**) Model depicting the mechanistic action of polyamines in promoting RAD51-mediated recombination.