# A mathematical model of the proliferating cell nuclear antigen *(PCNA)*

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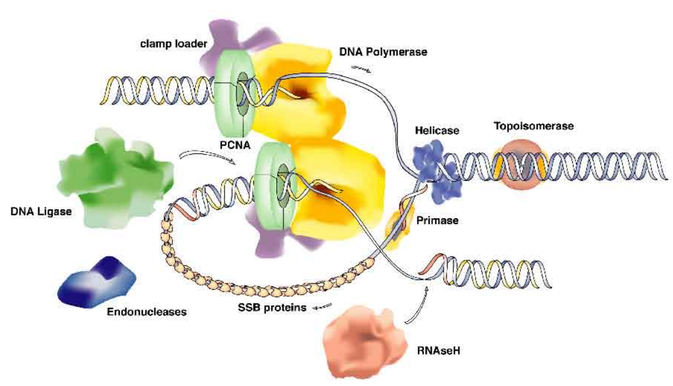
## Short informations about DNA replication and PCNA

**DNA replication:**

- Process of copying a double-stranded DNA molecule to form two double-stranded molecules
- A fundamental process used by all living organisms as it is the basis for biological inheritance
- Problem: A fast duplication of the genetic information without errors
- Possible solution: proofreading and error-checking mechanisms exist to ensure near perfect fidelity

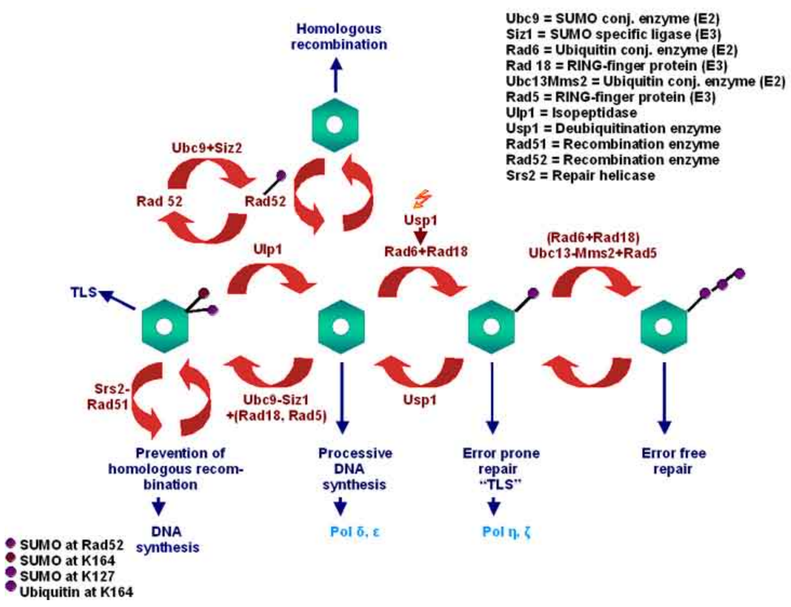



**PCNA (proliferating cell nuclear antigen):**

- A central element for DNA replication and repair
- It works as a "sliding clamp" and encircles double-stranded DNA and ensures the processivity of the DNA polymerases δ and ε
- The modification of PCNA by ubiquitin and SUMO contributes the close coordination of DNA replication, repair and damage tolerance

## A mathematical model of PCNA

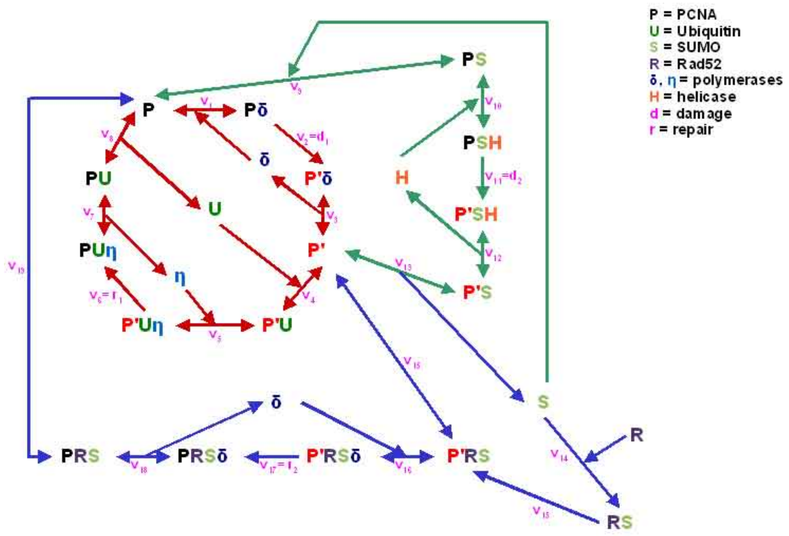
**Effect of PCNA during DNA replication:**




- The monoubiquitination promotes the translesion synthesis (TLS), which ignores failures during DNA synthesis and requires the polymerases η and ζ. This procedure prevents a stoppage of the DNA replicati on machinery
- The continuation of ubiquitination causes an error free bypass replication that is believed to use the genetic information of the undamaged sister chromatid

- During S phase SUMO binds to PCNA at the conserved lysine residues K164 and K127
- The SUMO-modified PCNA cooperates with the helicase Srs2 and inhibits the recombinational repair by disrupting the attendant Rad51 nucleoprotein filaments
- This reaction prevents unrequested recombination events and an unregulated sequence substitution

**Schematic expiration:**

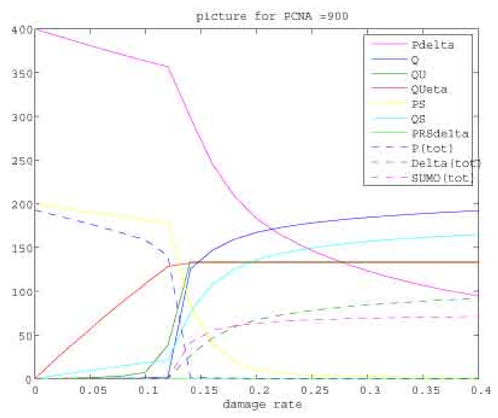


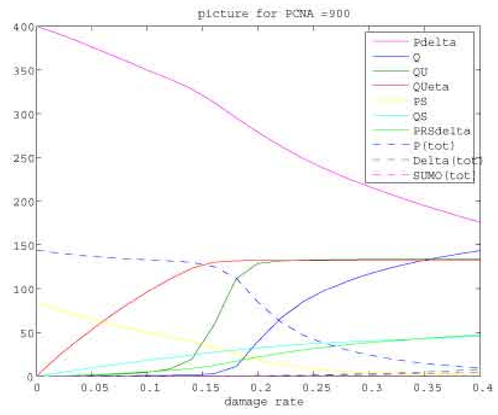

We develop a mathematical model simulating the interaction between these different modes of DNA replication and repair

## First Results

- The model is based on sets of ordinary diff erential equations in which the variables describe the states of the central participating proteins.
- The goal of our model is to reproduce the diff erent UV sensitivities of various mutant strains and to assess how damage tolerance depends on key parameters such as total protein concentrations, binding affi nities, repair rates and amount of damaged DNA.

**The different modules have an influence on the DNA replication rate:**




**Pictures on the left hand side:**

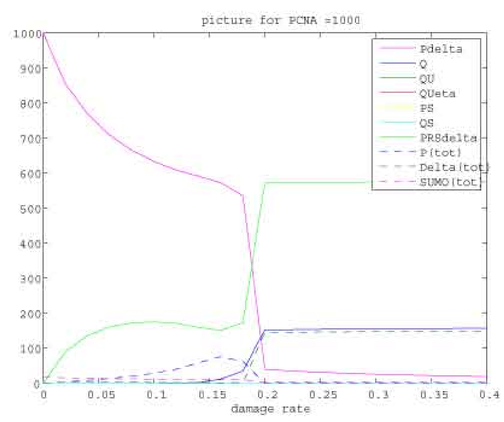
- The knock-out of homologous recombination (blue pathway) leads to an increased liability to disadvantages during DNA replication
- The replication rate *(Pdelta)* sinks faster in spite of a lower damage rate and results in a high level of fl awed DNA *(Q)*
- As a result of this inhibition, there exists no free polymerase Delta and no free PCNA, which benefi ts DNA replication

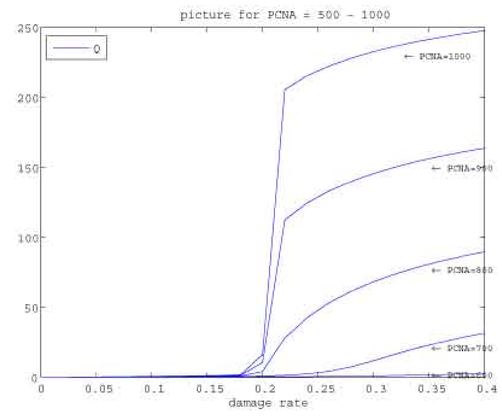
**Pictures on the right hand side:**

- The inhibition of translesion synthesis (TLS) causes in a breakdown of replication *(Pdelta)*, but the homologous recombination *(PRSdelta)* shows the ability to fi ll this gap
- The calculation demonstrates that replication by homologous recombination has a lower level until a damage rate of 20%. After this point, the rate rises suddenly, because of replication by processive DNA synthesis which is impractically

- The frequency of damaged DNA during replication relates to elevated concentrations of PCNA

➡ **These first calculations show that a mathematical characterisation of DNA replication and PCNA provides biological information**

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