Krajowa Konferencja Zastosowań Matematyki w Biologii i Medycynie

Jastrzębia Góra, 16th–20th September 2013

REPAIR OF DNA STRAND BREAKS IN A MINICHROMOSOME IN VIVO: KINETICS, MODELING, AND EFFECTS OF INHIBITORS

Sławomir Kumala[1], Krzysztof Fujarewicz[2,*], Dheekollu Jayaraju[1], Joanna Rzeszowska-Wolny[1] and Ronald Hancock[1]

[1]Laval University Cancer Research Centre, Hotel-Dieu Hospital,
Quebec, Canada
[2]Institute of Automatic Control, Silesian University of Technology,
ul. Akademicka 16, 44-100 Gliwice, Poland
*krzysztof.fujarewicz@polsl.pl

ABSTRACT

To obtain an overall picture of the repair of DNA single and double strand breaks in a defined region of chromatin in vivo, we studied their repair in a 170 kb circular minichromosome whose length and topology are analogous to those of the closed loops in genomic chromatin [1]. The rate of repair of single strand breaks in cells irradiated with γ photons was quantitated by determining the sensitivity of the minichromosome DNA to nuclease S1, and that of double strand breaks by assaying the reformation of supercoiled DNA using pulsed field electrophoresis.

Modeling of the kinetics of repair provided rate constants and showed that repair of single strand breaks in minichromosome DNA proceeded independently of repair of double strand breaks. The simplicity of quantitating strand breaks in this minichromosome provides a useful system for testing the efficiency of new inhibitors of their repair, and since the sequence and structural features of its DNA and its transcription pattern have been studied extensively it offers a good model for examining other aspects of DNA breakage and repair.

Four compartments each containing one form of minichromosome DNA were considered together with the four ordinary differential equations. Fitting to the experimental data depended on estimating parameters and initial conditions in normal conditions or when double strand break repair was inhibited. A number of conclusions which were not directly apparent from the experimental data illustrated the usefulness of modeling. First, when repair of double strand breaks was arrested, the single strand breaks in linear molecules were still repaired and circular molecules containing single strand breaks were converted to supercoiled molecules at close to the normal rate showing that the systems which repair single and double strand breaks operate independently, which has not been demonstrated previously as far as we are aware. Second, the calculated rate constants show that in an average linearised minichromosome the double strand break was repaired three to four times faster than all the single strand breaks, so that the rate limiting step for complete repair of minichromosomes was the repair of single strand breaks.

ACKNOWLEDGEMENTS

This work has been supported partially (K.F.) by Polish National Science Centre under grant DEC–2012/05/B/ST6/03472.

REFERENCES

[1] S. Kumala, K. Fujarewicz, D. Jayaraju, J. Rzeszowska-Wolny, and R. Hancock: *Repair of DNA Strand Breaks in a Minichromosome In Vivo: Kinetics, Modeling, and Effects of Inhibitors*, PLoS ONE **8** (2000), 1–13.