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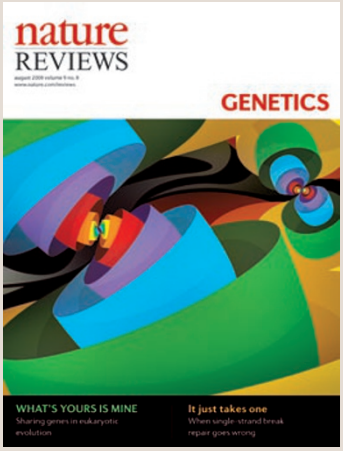

► **COVER:** 'Under wraps' by Patrick Morgan, inspired by the Review on p605.

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Cells face a daily battle for integrity — tens of thousands of single-strand breaks alone are created in each cell from intracellular sources such as free radicals, not to mention insults from external sources. To make matters worse, these impede the passage of other molecules, including DNA polymerases, causing opportunity for further damage to occur.

Given the potentially serious consequences of ignoring genomic damage or repairing it incorrectly — from cancer to inherited disorders — it is understandable that a cell's demand for genomic integrity is not easily met and that a collection of specialized molecules exist to cope with DNA damage. This topic is taken up in two Reviews in this issue. The first, by Keith Caldecott (p619), describes how cells respond to single-strand breaks, the most common form of DNA damage, whereas Larry Loeb and Ray Monnat (p594) focus on the growing number of DNA polymerases in mammalian cells.

Cataloguing these molecules, and understanding how they operate, involves a combination of genetics, cell biology and a good dose of biochemistry. New technologies are hastening the pace of understanding — 40 years ago only one DNA polymerase was known in human cells, a number that has gone up to 14, with most advances in the past decade.

Operational details aside, there is a surprising degree of regulation at the level of complex protein–protein interactions and during the cell cycle and development, through genetic and epigenetic control. For example, some single-strand-break repair genes and replicative polymerases are downregulated in differentiated cells, in which damage would be less crucial.

Existing knowledge can be put to therapeutic ends — nucleoside analogues can inhibit the DNA-replicating ability of infectious agents and so could be used to weaken specific polymerases, for example, in cancer cells.

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Printed in Wales by Cambrian Printers on acid-free paper