II. EARLY RESPONSES AND REPAIR PROCESSES

Immediate reaction: repair or die

The cell reacts immediately to any damage to its DNA in the minutes, hours and days following an injury. It is well used to repairing naturally-occurring defects. Actually, the human body, which renews some 250 thousand million cells every day, is not beyond making some mistakes in the synthesis of new DNA molecules. But to these spontaneous errors must be added those due to physical, chemical or thermal stress, including radiation, both natural and man-made. Accordingly, molecular systems of ranging complexity exist in the cells to maintain the integrity of its genetic heritage. The occurrence of human pathologies linked to the dysfunction of one or another of these systems has enabled us to characterize them and evaluate their importance.

When the cell is not dividing, if a lesion affects only one DNA strand, a succession of specialized repair enzymes cuts out the damaged sequence and then uses the complementary sequence present on the other strand as an exact template for rapid accurate resynthesis of the excised segment. However, if both strands are broken at the same place repair is slow and made difficult by the absence of a template. Several enzymatic pathways are then used. p53 protein in particular interacts with these specialized enzymes to facilitate DNA repair. In humans, many genes involved in the different repair pathways are identifiable by their similarity with those that exist in bacteria and yeasts, and even in the plant kingdom.

When the cell is rapidly dividing, the cell division cycle is slowed down or even blocked. This interruption enables various repair systems to come into play and restore, to a greater or lesser degree of perfection, the integrity of the genetic material before the crucial step when the DNA stock is duplicated. A monitoring mechanism induces a stay in the cycle at checkpoints situated at the transition between one of the «preparation» phases and either of the two «motor» steps in the cycle, namely the duplication of the DNA and the division of the cell. Here again, p53 protein intervenes to «steer» the genes involved in the cycle control.

If complete repair is unfeasible, either because the DNA is too damaged or because the cell division cycle is not halted, then the cell commits suicide. This programmed death eliminates from the body those cells that may bear genetic errors. This natural process is also responsible for morphological and physiological changes during embryogenesis and later growth. p53 protein is involved here too. The death of irradiated cells thus shields the organism against the proliferation of potentially cancer-forming abnormal cells.

The quantitative evaluation of chromosomal anomalies and visible effects linked in particular to DNA degradation during cell suicide offers, at the molecular level, a biological indicator of induced damage, thereby extending the physical methods of dosimetry. This allows the effects to be assessed more accurately, and so helps improve our understanding of the causes that underlie them.

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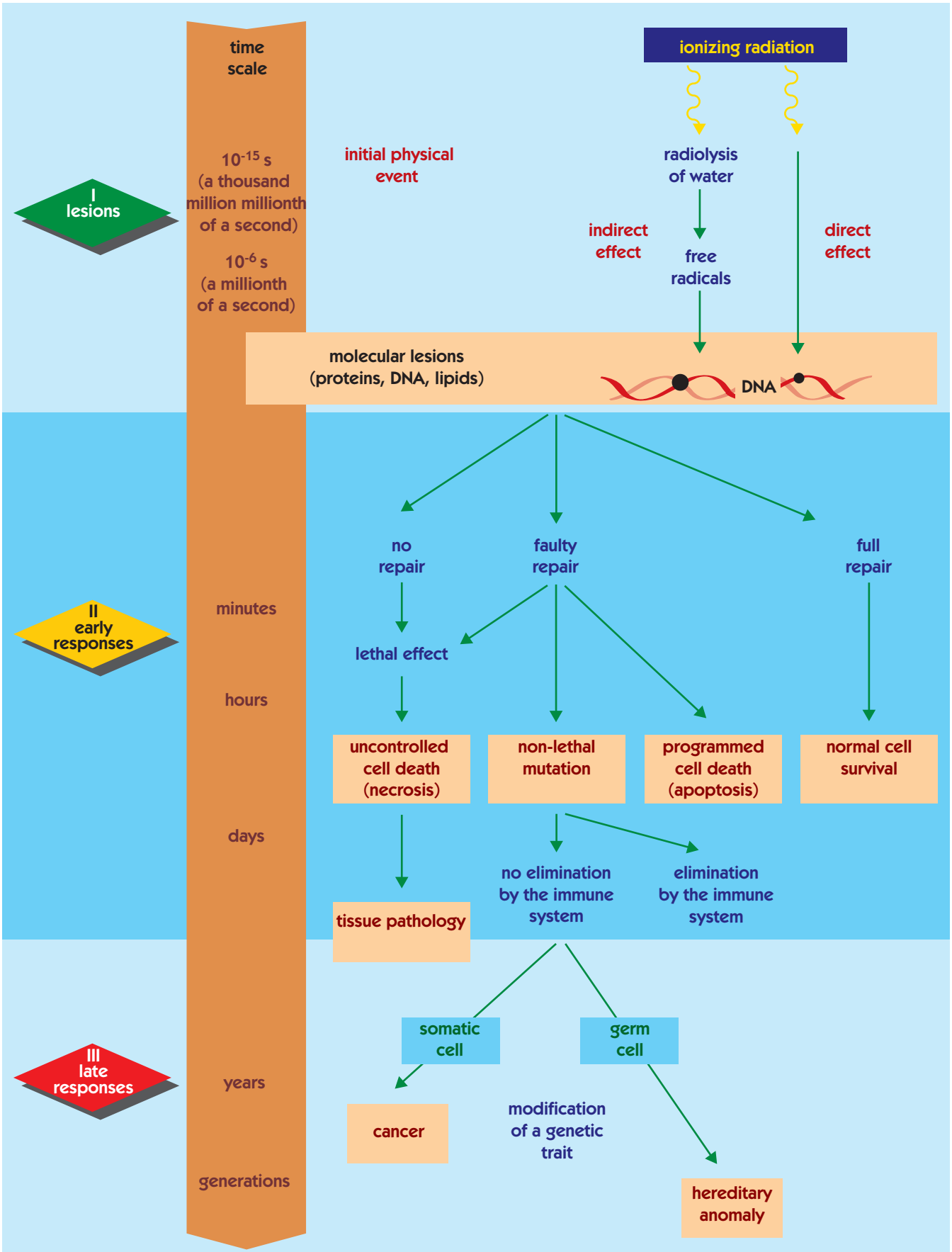

Biological effects of ionizing radiation. Time course of possible outcomes at the cell level.

N.B. *Not all the events indicated have the same probability of occurring. Normal cell survival, for example, is the most frequent outcome after DNA repair.*