Abstract

DNA repair is a vital process of a living organism. Inherited or acquired defects in DNA repair systems and cellular surveillance mechanisms are expected to be important, if not crucial factors in the development of human cancers. DNA repair is a multigene and multifactorial process which is most comprehensively characterized by the phenotypic evaluation of DNA repair capacity (DRC). DRC represents a complex marker with high informative value, as it comprises all genetic, epigenetic and non-genetic factors, by which it is modulated. Accordingly, DRC reflects the actual capability of the cell, tissue or organism to protect its DNA integrity.

The present PhD study was focused on investigating DRC, which specifically involves base and nucleotide excision repair pathways, in human populations with different characteristics. The main aim was to answer substantial questions on the possible use of DRC as biomarkers in epidemiological studies. The study was in fact designed to understand the extent of physiological variability of DRC in a population, its modulation by genetic and non-genetic factors, tentative adaptability to high genotoxic stress and, finally, its involvement in cancer aetiology. In order to explore these issues, DRC, in respect to genetic and environmental variability, was investigated in healthy subjects as well as in individuals with higher requirement for DNA stability maintenance, i.e. workers occupationally exposed to carcinogens, and in newly diagnosed cancer patients. Additionally, from a methodological aspect, the study was also aimed to ameliorate the comet-based repair assays for their wider applicability in human epidemiological studies.

The major outcomes of the PhD study, which are fully reported in the five publications included in the present Thesis, are: 1) The demonstration of feasibility to study phenotypically DRC in large-scale epidemiological studies on different types and quality of biological material, 2) Evidence that the marker of DRC provides fundamental information that cannot be obtained by single gene or single transcript analysis, 3) The observation of substantial biological variability in the DNA repair processes among healthy individuals which is modulated by the genetic variability in DNA repair genes and by the inter-sexual differences and lifestyle factors, 4) Lack of alteration of DRC by means of potential adaptive response to chronic exposure to high doses of carcinogens, 5) Proof of suboptimal activity of DNA repair and high level of DNA damage in cancer patients, showing the significance of DRC in the

individual susceptibility to cancer, 6) An upgrade of comet repair assay by its optimization for DRC measurement in human solid tissues with 6-times higher yield number of samples per analysis, which was finally followed by 7) The achievement of a first study on DRC in cancer-target tissues and tumors.