6 Targeted and Non-Targeted Induction of Chromosomal Rearrangements After Exposure to Ionizing Radiation

WILLIAM F. MORGAN AND MARIANNE B. SOWA

Abstract

Exposure to ionizing radiation can result in chromosomal rearrangements in a cell cycle dependent manner. This is presumably due to the deposition of energy in the nucleus of the irradiated cell causing DNA double-strand cleavage and the failure of the DNA repair machinery to faithfully restore the integrity of the genetic material. There is also increasing evidence that an irradiated cell can signal to a non-irradiated “bystander” cell and elicit cellular responses, including chromosomal rearrangements, in these non-targeted cells. These signals can be communicated between targeted (irradiated) cells and non-targeted (non-irradiated) cells by both cell-to-cell gap junction communication mechanisms as well as soluble factors secreted into the culture medium. In this chapter we review the evidence for targeted and non-targeted induction of chromosomal rearrangements after exposure to ionizing radiation and speculate about potential mechanisms and their significance in radiation risk assessment.

6.1 Introduction

Analysis of chromosomal rearrangements has been used for many years to determine whether an individual has been exposed to ionizing radiation, and to provide a reliable estimate of the exposure dose (reviewed in Cornforth 1998). A rich and well-documented literature indicates that cytogenetic analysis can be used to determine exposures to radiation doses as low as 15–20 cGy, and thus provides the most sensitive and reliable assay for radiation exposure. Implicit in interpreting these types of analysis is that the induced cytogenetic alterations result from the deposition of energy by ionizing radiation and subsequent cellular responses. Specifically, radiation exposure leads to DNA damage, namely, single and double stranded DNA breaks, DNA–DNA and DNA–protein cross-links, and DNA base damages (Ward 1988). The cell then responds to this damage by initiating changes in gene expression, inducing cell cycle checkpoint control strategies and signal transduction pathways, and activating DNA repair processes.
The general consensus in the field has long been that chromosomal rearrangements result from the non-rejoining or misrejoining of radiation-induced DNA double-strand breaks (King et al. 1994). That is, deletion-type aberrations can result from the non-rejoining of an induced break or acentric rings induced by two double-strand breaks. Inversions result in misrejoining of breaks within a chromosome and exchange-type alterations result from the misrejoining of breaks on two or more different chromosomes, leading to insertions, rings, polycentric chromosomes, and/or reciprocal translocations. Given that in most radiation-exposure scenarios cells from irradiated individuals would be in G0/G1 phase, the dominant molecular process giving rise to misrejoining events would likely be non-homologous end joining.

In the present context, chromosomal rearrangements can be equated with the “breakage first hypothesis” (Sax 1938) that predicts breaks must be “open” at the same time and within close enough proximity to interact. While certain fundamental aspects of the formation of chromosomal rearrangements remain contentious, breakage followed by either non-rejoining of the break or misrejoining of induced breaks can satisfactorily describe most of the observed cytogenetic alterations in irradiated cells. In the past decade however, a host of different laboratories have described a number of non-targeted effects associated with exposure to ionizing radiation. In contrast to the traditional paradigm that a cell must be irradiated, or “targeted,” to exhibit those detrimental effects associated with radiation exposure, these non-targeted effects occur in cells that were not subject to energy-deposition events because they were not irradiated. These non-targeted effects include radiation-induced chromosomal instability, bystander effects, the death-inducing effect, clastogenic factors, as well as abscopal effects described in the clinical literature as effects occurring outside the directly irradiated tissue volume (reviewed in Morgan 2003a,b). They occur in cells that were not irradiated but that either were neighbors of irradiated cells or received soluble signals from irradiated cells. A schematic summarizing the concept of targeted and non-targeted effects associated with observed chromosomal rearrangements is presented in Fig. 6.1. In this chapter we will review the evidence for non-targeted radiation-induced chromosomal instability, and discuss how factors produced by irradiated cells may communicate the legacy of radiation exposure to non-targeted cells resulting in DNA double strand break formation and ultimately chromosomal rearrangements.

6.2 Radiation-Induced Chromosomal Instability

First described by Kadhim et al. (1992), radiation-induced chromosomal instability refers to the induction of chromosomal rearrangements in the progeny of an irradiated cell. Instability was observed in cells that had undergone multiple cell division cycles after exposure to ionizing radiation. This