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Review

Chromatin structure and radiation-induced DNA damage: From structural biology to radiobiology

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ABSTRACT

Genomic DNA in eukaryotic cells is basically divided into chromosomes, each consisting of a single huge nucleosomal fiber. It is now clear that chromatin structure and dynamics play a critical role in all processes involved in DNA metabolism, e.g. replication, transcription, repair and recombination. Radiation is a useful tool to study the biological effects of chromatin alterations. Conversely, radiotherapy and radiodiagnosis raise questions about the influence of chromatin integrity on clinical features and secondary effects. This review focuses on the link between DNA damage and chromatin structure at different scales, showing how a comprehensive multiscale vision is required to understand better the effect of radiations on DNA. Clinical aspects related to high- and low-dose of radiation and chromosomal instability will be discussed. At the same time, we will show that the analysis of the radiation-induced DNA damage distribution provides good insight on chromatin structure. Hence, we argue that chromatin "structuralists" and radiobiological "clinicians" would each benefit from more collaboration with the other. We hope that this focused review will help in this regard.

Contents

Abbreviations: AR, adaptive response; BD, base damage; bp, base pair; CT, computed tomography [or] chromosome territory; DDR, DNA damage response; DSB, double strand break; FISH, fluorescence in situ hybridization; HDC, highly damaged cells; HR, homologous recombination; HRS, hyper-radiosensitivity; IR, ionizing radiation; IRR, induced radio-resistance; LET, linear energy transfer; LINE, long repetitious interspersed sequence; LNT, linear no threshold; LORD, low and repeated doses; NCP, nucleosome core particle; NHEJ, non-homologous end joining; NLT, non-linear threshold; PFGE, pulsed-field gel electrophoresis; SF, surviving fraction; SB, strand break; SINE, short repetitious interspersed sequence; SSB, single strand break.

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1. Introduction

Our genome is constantly attacked by cellular metabolic products and environmental agents (e.g. chemical agents or ionizing radiation (IR)), triggering a DNA damage response (DDR) as a series of coordinated events that allow DNA damage detection, signalling, repair and, ultimately, survival, death or transformation. This response occurs in the context of chromatin, a dynamic entity comprising DNA associated with histone octamers and other non-histone components. Far from being a "repetitive unit" of chromatin, nucleosomes show various characteristics (sliding propensity, conformational dynamics) which are conferred by histone variants and their post-translational modifications along with the physical properties of the DNA (Lavelle, 2009). The local structure of chromatin and its dynamical features influence the outcome of environmental aggression. The presence of a ligand (mainly histones) reduces the probability of strand break (SB) production by a local masking of the attack sites. The way nucleosomes can change conformation and interact with neighbouring nucleosomes influences the higher structure and dynamics of chromatin. The distribution of damage along the DNA molecule depends on these features.

Indeed, the pattern of discrete energy deposition along the track of the ionizing radiation combined with local chromatin structure defines the spatial distribution of the lesions induced in DNA (Fig. 1). Clustered damage sites are usually a signature of IR, and are known to produce complex damage–including double-strand breaks (DSB)–which are more difficult to repair than other lesions (Eccles et al., 2011; Schipler & Iliakis, 2013). More precisely, low linear energy transfer (LET) radiation (e.g. X-rays, beta or gamma emissions) induces lower concentrations of ionization events, hence less complex DNA damage – including DSB – than high LET (e.g. alpha emissions and heavy ions) (Nikjoo et al., 1998). Now, IR can be considered as a 'two-edged sword' in that it may lead to the formation of mutations and genetic instability in normal tissue while favouring cell killing in tumour cells after radiotherapy (Eccles et al., 2011). Therefore, a precise knowledge of both track structure and chromatin organization are required not only for the understanding of the mechanisms of radiation effect in cells but also in practical aspects of radiotherapy.

There exist already many good reviews on chromatin and DNA repair protein choreography (Altmeyer & Lukas, 2013; Bao, 2011; Goodarzi & Jeggo, 2013; Gospodinov & Herceg, 2013; Lisby & Rothstein, 2009; Loizou et al., 2006; Lukas & Bartek, 2004; Papamichos-Chronakis & Peterson, 2013; Price & D'Andrea, 2013; Soria et al., 2012) with some specifically focusing on DSB and other radiation-induced damage (Hunt et al., 2013; Lomax et al., 2013). Larry Thompson recently presented a quite comprehensive review addressing the biochemistry of repair pathways after ionizing radiation (Thompson, 2012); we wish here to build on this with a complementary perspective, addressing the relationship between chromatin research and radiobiological research from a physical point of view, mainly focusing on chromatin 3D organization.

An interesting aspect of IR is that it can serve both as a curing or investigating device (Fig. 1). Indeed, experimentally induced DNA damage is a useful tool to study chromatin structure at its various levels of organization (Rydberg, 2001). On the other hand, radiotherapeutic protocols usually based on empirical knowledge on DNA repair would benefit from a more thorough utilization of the knowledge of the spatio-temporal organization of repair processes in the context of higher-order chromatin structure (Jezkova et al., 2013). Both aspects are discussed in this review. Section 2 is dedicated to structural (fundamental) issues, discussing (1) how a good knowledge of DNA organization at various scales can indeed help to understand better the effect of IR on DNA and (2), the other way round, how the data collected from radiobiological studies might feed models of chromatin structure models and yield a better knowledge of DNA organization at all scales. Section 3 is dedicated to clinical issues; a general approach consists in increasing the severity of DNA damage in tumors and facilitating their repair in normal tissues. However, individual factors and other technical parameters such as dosage and the repetition of doses during radiotherapy or radiodiagnosis must be taken into account to better evaluate risk and anti-tumor efficiency.

The linkage between structural and clinical issues is clear in vivo, even if it is somewhat neglected in the scientific and medical literature, where papers dealing with most aspects of radiation/radiotherapy are published mostly in specialized journals -even when they provide valuable information on genome structure and properties, that would interest a broader audience. We argue in this review that the radiobiology and chromatin fields should be intrinsically coupled. As we will see from Sections 2 and 3 below, both domains have different aims but rest upon common ground. Since the outcome of radio-induced damage (including potential chromosome instabilities) is influenced by local chromatin conformation, chromatin "structuralists" and radiotherapists would each benefit from tighter collaborations with the other. We hope that this focused review will help in this regard, and anticipate that within ten years Sections 2 and 3 will truly merge, and that the fuzzy "because of chromatin structure" argument used anytime/anywhere will be replaced with a precise description of what actually happens in the nucleus upon radio-induced DNA damage and repair.

2. Structural aspects of radio-induced DNA damage

2.1. General considerations

2.1.1. Mechanisms of DNA attack and protection

IR induces strand breaks (SB) along with sugar and base modifications in DNA (Fig. 2). SB occur mainly via the reaction of OH radicals produced by water radiolysis with the H atoms of the sugar moiety (Balasubramanian et al., 1998). Interestingly, the SB occurrence is not the same at all nucleotide sites: for example, reduction is obtained in regions where the local structure gives a narrow minor groove, leading to a decrease in the accessibility of these particular attack sites to the radicals (Isabelle et al.,