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Review

Integrating plant and animal biology for the search of novel DNA damage biomarkers

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ABSTRACT

Eukaryotic genome surveillance is dependent on the multiple, highly coordinated network functions of the DNA damage response (DDR). Highlighted conserved features of DDR in plants and animals represent a challenging opportunity to develop novel interdisciplinary investigations aimed at expanding the sets of DNA damage biomarkers currently available for radiation exposure monitoring (REM) in environmental and biomedical applications. In this review, common and divergent features of the most relevant DDR players in animals and plants are described, including the intriguing example of the plant and animal kingdom-specific master regulators SOG1 (suppressor of gamma response) and p53. The potential of chromatin remodelers as novel predictive biomarkers of DNA damage is considered since these highly evolutionarily conserved proteins provide a docking platform for the DNA repair machinery. The constraints of conventional REM biomarkers can be overcome using biomarkers identified with the help of the pool provided by high-throughput techniques. The complexity of radiation-responsive animal and plant transcriptomes and their usefulness as sources of novel REM biomarkers are discussed, focusing on ionizing (IR) and UV-radiation. The possible advantages resulting from the exploitation of plants as sources of novel DNA damage biomarkers for monitoring the response to radiation-mediated genotoxic stress are listed. Plants could represent an ideal system for the functional characterization of knockout mutations in DDR genes which compromise cell survival in animals. However, the pronounced differences between plant and animal cells need to be carefully considered in order to avoid any misleading interpretations. Radioresistant plant-based systems might be useful to explore the molecular bases of LD (low

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Abbreviations: ARP, actin related protein; ASK, Arabidopsis SPK1-like; At, *Arabidopsis thaliana*; ATAF, arabidopsis transcription activation factor; ATM, ataxia telangiectasia mutated; ATR, ATM and Rad3-related; ATRIP, ATR-interacting protein; BARD, BRCA1-associated RING domain protein; BDR, bZIP TF for DNA damage response; BER, base excision repair; BP, binding protein; 53BP1, p53 binding protein; BRH, BRCA homolog; BRCA, breast cancer susceptibility; BRM, Brahma; CAF, chromatin assembly factor; CDC, cell division cycle; CHA, Chinese hamster ovary; CHK, checkpoint kinase; CHR, chromatin remodeling; CMT, chromomethyltransferase; COP, constitutive photomorphogenesis; CRL, cullin RING ubiquitin ligase; CSN, COP9 signalosome; CUC, cup-shaped cotyledon; DDB, DNA damage binding; DDR, DNA damage response; DDT, DNA damage tolerance; DNA-PK, DNA-dependent protein kinase; DSB, double-strand breaks; ERCC, excision repair cross complementation; FAS, fasciata; FHA, forkhead-associated domain; GGR, global genome repair; Gy, gray; HBEC, human bronchial epithelial cells; HD, high dose; HDR, high dose rate; HEK, human embryonic kidney; HR, homologous recombination; HZE, high atomic number (Z) and energy; INO, inositol requiring; IR, ionizing radiation; LD, low dose; LDR, low dose rate; LET, linear energy transfer; LIG, ligase; LNT, linear no-threshold; LTP, lipid transfer protein; MDC, mediator of the DNA damage checkpoint; MEI, meiosis defective; MET, methyltransferase; MPK, mitogen-activated protein kinase; MRE, meiotic recombination; MuDR, mutator transposon; NAC, NAM ATAF1/2 and CUC2; NAM, no apical meristem; NBS, Nijmegen breakage syndrom; NER, nucleotide excision repair; NFBD, nuclear factor with BRCT domain; NHEJ, non-homologous end joining; NPR, nonexpressor of PR genes; Os, *Oryza sativa*; PARP, poly(ADP-ribose)polymerase; PBMC, peripheral blood mononuclear cell; PCNA, proliferating cell nuclear antigen; PDS, precocious dissociation of sisters; PHD, plant homeodomain; PIE, photoperiod-independent early; PR, pathogenesis related; RAD, radiation sensitive; RBR, retinoblastoma related; REM, radiation exposure monitoring; RNR, ribonucleotide reductase; RNF, ring finger protein; ROS, reactive oxygen species; RPA, replication protein A; Rv, Rammazzottius varieornatus; SA, salycilic acid; SDG, SET domain-containing group; SMC, structural maintenance of chromosome; SMR, siamese-related; SNI, suppressor of NPR1-1 inducible; SOG, suppressor of gamma response; SPK, spike; SSB, single-strand breaks; STING, stimulator of IFN genes; SUMO, small ubiquitin-like modifier; SUVH, SU(VAR)3-9 homologue; SWC, SWR1-associated complex; SWR1, Swi2/Snf2-related; SYD, splayed; TC-NER, transcription coupled nucleotide excision repair; TLR, Toll-like receptor; TOPBP, topoisomerase binding protein; UBC, ubiquitin conjugating enzyme; UBD, ubiquitin-binding domain; UV, ultraviolet; UVH, UV hypersensitive; WAPL, wings-apart like; XP, xeroderma pigmentosum

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dose)/LDR (low dose rate) responses since nowadays it is extremely difficult to perform an accurate assessment of LD/LDR risk to human health. To overcome these constraints, researchers have started exploring radiotolerant non-human species as potential sources of information on the mechanisms involved in LD/LDR and general radiation responses.

1. Introduction

The entangled DNA damage response (DDR) network is an impressive array of DNA damage sensing and signal transduction pathways leading to DNA repair and cell survival or, alternatively, triggering cell death. Interactions between DDR sensors, transducers, and effectors contribute to the maintenance of genome integrity, providing a unique example of 'DNA self-awareness' or 'chemical intelligence' [1]. The current knowledge of DDR in plants is rapidly expanding, providing insights into the way a sessile organism can cope with genotoxic stress induced by adverse environments and chemical/physical agents [2–4]. Nevertheless, the strategies plants use to integrate genotoxic stress detection with signaling and repair responses still need to be fully elucidated, although innovative technologies (e.g. 'omics') have significantly contributed to the field [5–9]. The conserved features of DDR highlighted in plants and animals represent a challenging opportunity to develop novel interdisciplinary investigations aimed at expanding the sets of DNA damage biomarkers currently available for radiation exposure monitoring (REM) in environmental and biomedical applications. In an effort to verify the feasibility of this innovative approach, the current review highlights some conserved and divergent features of DDR components in animals and plants, providing an update on the available radiation-responsive transcriptomes, with a focus on ionizing radiation (IR) and UV light. Pros and cons of the use of plants as sources of novel DNA damage biomarkers, consisting of transcriptomics profiles, for monitoring the response to radiation-mediated genotoxic stress are presented and discussed in view of the current literature.

1.1. Radiation biomarkers

Irradiation triggers cellular and molecular events leading to effects identified as specific endpoints of clinical, cytogenetic, molecular processes ('exposure biomarkers') as well as 'response biomarkers' which endpoints are expected to reveal kinetic changes in relation to treatments, providing useful hints for optimizing radiotherapy protocols. Four different classes of radiation biomarkers have been defined: *i) predictive* (detectable before irradiation takes place) and *ii) prognostic* (detectable after exposure), both indicative of increased risk for health, *iii) diagnostic* (concomitant with the clinical symptom, indicative of radiation effect) and *iv) dosimetric* (indicative of the dose delivered to the organism) [10]. Identification of radiation biomarkers is challenging and the search for markers enough sensitive and specific for clinical and environmental purposes has prompted to dissect the DDR networks in animal cells. Researchers investigate the impact of radiation on DDR gene expression and correlate the resulting molecular profiles with radiation sensitivity. High-level resolution of multiple DNA repair pathways and cell cycle-/cell death-related processes at the transcriptional level is a promising route for prediction of the radiation response. At the same time, novel molecular endpoints measured with transcriptomics are emerging, expanding the range of conventional of endpoints (e.g. chromosome aberrations) [11].

The review provides an updated knowledge of DDR in plants and animals and asks a question whether the current knowledge is sufficiently detailed to support use of plants as a possible source of radiation biomarkers for risk assessment in humans. This raises a challenging question: how should the plant-derived radiation biomarkers work? Moreover, considering the distinctive features of plant and animal cells, would it be feasible to integrate plant and animal endpoints for risk assessment in humans? On the other hand, plant DDR provides researchers with unique features together with underscored potential in terms of molecular mechanisms underlying radiotolerance. To date, the most realistic scenario may be the use of plant biomarkers/endpoints to monitor environmental risks as well as entry screen for the introduction of new chemicals and medical drugs that might help a more accurate prediction of human health.

Indication of plant-based biomarkers in other organisms should fulfill two functions: *i)* monitor external genotoxic threat within biota as environmental stress due to natural or anthropic contamination and test the risk associated with new chemicals or drugs, *ii)* help describe intracellular processes that, due to biological constrains, are unaccessible in animals and particularly in mammals. In this context, the selection of plant/animal models used to assess the resulting gain in knowledge, and then the efficacy and compatibility of biomarkers, is a relevant issue. Proper models should help identifying in details biological pathways in which clinical biomarkers are involved and whether they are appropriate biomarkers of drug efficacy or safety monitoring studies. Plants and plant-based biomarkers could be used to assist selection, approval, validation, and association with statistical variables used in research and clinical endpoints as well as for the design of diagnostic kits for research, clinical or monitoring purposes. The relevance of using plants as informative models for radiation response relative to the human organism is proven by the continuous research in the field. Currently, there are worldwide laboratories using a variety of plant systems, besides *Arabidopsis thaliana*, to study the ionizing radiation response and DNA repair mechanisms. Einset and Collins [12] investigated DNA damage, measured as total strand break frequency, in isolated nuclei of six different plant species (genome size from 2.6 to 19.2 Gbp) exposed to X-rays, using alkaline comet assay. High radiation sensitivity was detected in plants with large genome size. Differential repair capacity was also observed, similarly to mammalian organisms. Earlier and very recent studies on the mutagenic effect of high-LET (linear energy transfer) carbon ion in *Arabidopsis thaliana* revealed very useful information on the ability of high-LET radiations to induce genome instability [13,14].

1.2. The intrinsic plasticity of plants

Due to their sessile lifestyle, plants are equipped with a prodigious genomic plasticity. Aside from their extensive tropism driven by resource availability, plants definitely lack mobility as it is observed in animals. Plants capture solar energy and store it in the form of chemical products. They use highly sensitive mechanisms to perceive spatiotemporal changes in the environment, in terms of light, water, and nutrient sources. The concept of 'plant perceptron' has been recently introduced by Scheres and van der Putten [15], based on the analogy with mathematical models applied to neurons as input-processing units. The resulting information-processing system has been defined 'perceptron'. According to these authors, plant genes and proteins can be considered as processing units with biochemical connections that result into an information-processing system able to select the most suitable options for coping with a changing environment [15]. The presence of a cell wall and highly specialized plastids in plants are the most striking differences compared to animals. Animal cells are embedded in an extracellular matrix made of polysaccharides and proteins, thereby providing structural support to tissues and regulating the fundamental cellular interactions within a multicellular organism. The most abundant protein in the matrix of animal tissues is collagen. Differently, the plant cell is surrounded by a rigid envelope, the cell wall, which is a