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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

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

complex network of carbohydrates (cellulose is the most abundant) and proteins essential to maintain the osmotic balance between the cytosol and the extracellular environment [16]. The 'organelle landscape' of plant cells is enriched by plastids, closely related membrane-bound organelles, among which are chloroplasts responsible for photosynthesis [17].

In both plants and animals, stem cells generating new cells and tissues are maintained in specialized microenvironments, 'stem cell niches', which prevent differentiation. The plant stem cell niches, localized in the shoot and root apex meristems as well as in vascular tissues, maintain their activity throughout the plant life (in case of trees, up to thousand years), allowing the continuous production of new organs [18]. Conversely, adult animals lack this ability and rely on stem cells only for preserving tissue homeostasis and repairing injuries [18]. Animal and plant stem cell niches are characterized by DNA damage hypersensitivity leading to selective p53-dependent apoptosis and programmed cell death (PCD), respectively [19,20]. Protection of the germline from harmful mutations, ensured by PCD, is essential in the shoot apex meristem. PCD is considered as a faster alternative to remove damaged cells, compared to cell cycle checkpoint activation and DNA repair, in root stem cell niches. Similarly, damaged animal cells undergo apoptosis during gastrulation [21]. In this scenario, the comparison between animal and plant DDR is hereby discussed by dissecting the process at the level of sensors/transducers and effectors.

1.3. Common and divergent features of DDR players in animal and plant kingdoms: an overview

Most of the functionally characterized DDR players are conserved in plants and animals as outlined in Fig. 1. DNA damage can result from both environmental (e.g. IR, UV radiation) and endogenous (e.g. the cellular oxidative phosphorylation that generates reactive oxygen species, ROS) factors. The latter exert their genotoxic activity either directly on the DNA double helix or by inducing structural changes which increase the risk of further injury [22]. The genotoxic impact of physical agents such as UV radiation [23] and IR [24] as well as chemical agents, among which are alkylating agents [25], radiomimetic drugs [26], oxidizing agents [27], and chemicals that induce DNA-DNA/DNA-protein crosslinks [28], has been extensively investigated. DNA strand breaks trigger DDR through the early activation of ATM (ataxia telangiectasia mutated) and ATR (ATM and RAD3-related) protein kinases in both animal and plant cells (Fig. 1). IR-induced DNA double-strand breaks (DSBs) are sensed by the MRN (MRE11-RAD50-NBS1) complex. In both animals and plants, the MRN complex recruits ATM at the DSB site and phosphorylates the kinase, which in turn phosphorylates the histone variant H2AX into γH2AX, perceived as a DNA damage signal for the recruitment of DDR proteins. In animal cells, ATM phosphorylates CHK2 (checkpoint kinase 2) which phosphorylates the p53 transcription factor. The latter mediates the activation of cell cycle checkpoints, allowing up-regulation of DDR genes and thus DNA repair

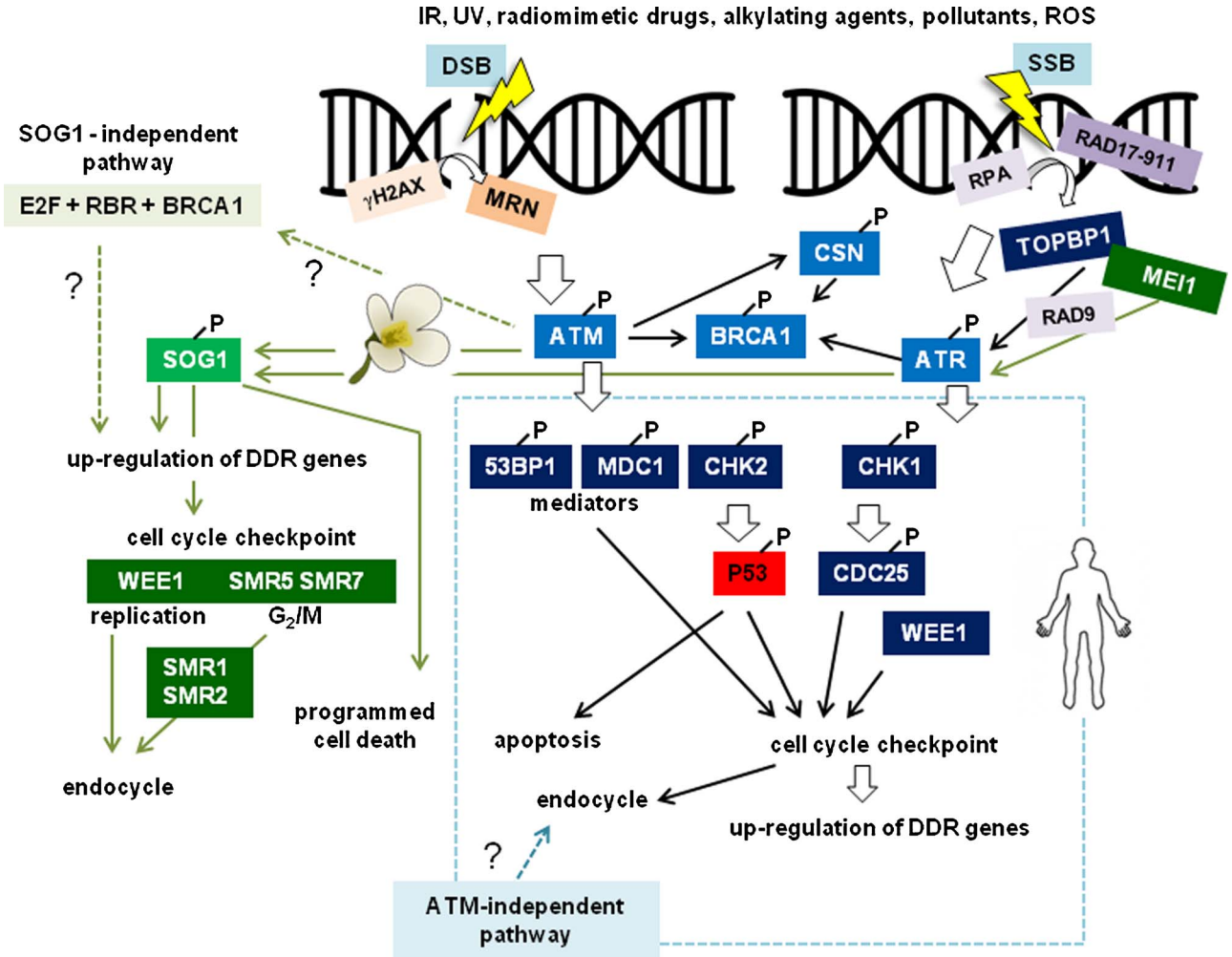

Fig. 1. The DNA damage response (DDR) in human and model plant *Arabidopsis thaliana* with the representation of conserved and divergent DDR pathways and players in animal and plant kingdoms. ATM- and ATR-dependent routes shared by animals and plants are shown. The kingdom-specific master regulators of DDR (SOG1 and p53 transcription factors) and their related pathways are also evidenced.

or, alternatively, it drives cells into apoptosis. Mediator proteins 53BP1 (p53 binding protein 1) and MDC1/NFBD1 (mediator of the DNA damage checkpoint 1/nuclear factor containing a BRCT domain 1), recruited at the DSB site, are required to maintain the cell cycle block [29] (Fig. 1). Single-stranded DNA regions are rapidly coated by RPA (replication protein A) which stimulates the recruitment of the ATR-ATRIP (ATR-interacting protein) kinase complex and its key regulators, the RAD17 (radiation sensitive) and the 9-1-1 complexes [29] (Fig. 1). TOPBP1 (DNA topoisomerase 2-binding protein 1) accumulates on chromatin, interacts with the multipurpose RAD9 protein and finally activates ATR. The latter phosphorylates CHK1, triggering the activation of CDC25 (cell division cycle) phosphatase and leading to delayed cell cycle progression, in collaboration with the G2 checkpoint kinase WEE1 (from the Scottish dialect 'wee' for 'small') [30] (Fig. 1).

As evidenced in Fig. 1, plants show some intriguing differences in DDR, compared to animals. In plants, the mediator proteins 53BP1 and MDC1 are missing while the MEI1 (meiosis defective 1) shares similarity with the human TOPBP1 protein. No homologs of the checkpoint kinases CHK1 and CHK2 have been identified in plants. The animal and plant *BRCA* (breast cancer susceptibility) and *BARD1* (BRCA1-associated ring domain protein 1) genes share a common eukaryotic ancestor, but their products display kingdom-specific structural and functional features. In the DDR context, SOG1 (suppressor of gamma response 1) and p53 transcription factors (Fig. 1) represent a unique example of divergent proteins, lacking significant amino acid sequence similarity, evolved to carry out a similar function (master regulator of DDR and guardian of genome stability) in different kingdoms [31]. A comprehensive list of *Arabidopsis* proteins involved in DDR pathways along with their human orthologs is provided in Table 1. In order to identify the orthologous gene products (proteins) of human and *Arabidopsis thaliana*, symbols and/or descriptions of all the genes/proteins mentioned within this manuscript were used initially to retrieve the corresponding protein sequences from the publicly available database UniProtKB [32]. Then, reciprocal BLASTp [33] was applied to identify the human or the *Arabidopsis* orthologue of each protein. Although most DDR proteins listed in Table 1 are present in both kingdoms, there are DDR components found in plants, but missing in humans, among which some DNA and histone methyltransferases (CMT3, SDG26, SUVH5), the SMR cyclin-dependent protein kinase inhibitors, and several chromatin remodelers (SWC6, BRM, CHR12, CHR23, SYD). Viceversa, plants lack the serine/threonine-protein kinases CHK1 and CHK2, the mediator proteins MDC1 and 53BP1 (Table 1). An in-depth comparison between the most relevant plant and animal DDR players is provided in the following paragraphs.

1.4. Protein kinases ATM and ATR

ATM and ATR are key components of DDR, both in animals and plants, where they phosphorylate hundreds of target proteins within the highly conserved Ser/Thr-Gln (S/TQ) motifs [34,35].

1.4.1. ATM and ATR in animals

ATM regulates the cell response to DSBs. Mutations in the human *ATM* gene cause the rare autosomal recessive disorder named ataxia-telangiectasia while in animal cells such alterations lead to genomic instability and increased IR sensitivity, as in the case of the *Caenorhabditis elegans atm-1* mutant [36]. ATR responds to stalled replication forks and DNA single-strand breaks (SSBs), preventing the accumulation of DNA lesions during replication [37–39]. ATR is thus essential for cell survival in proliferating tissues and its disruption impairs embryonic development, limiting the use of ATR knockout animals [40].

1.4.2. ATM and ATR in plants

Roitinger et al. [41] used a phosphoproteomic approach to investigate the ATM/ATR targets in *Arabidopsis*. They identified LIG4 (ligase 4), MRE11, as well as the chromatin remodelers PIE1 (photoperiod-independent early flowering 1) and SDG26 (SET domain group 26). Additional targets included PCNA1 (proliferation cell nuclear antigen 1), the cohesin-associated proteins WAPL (wings apart like) and PDS5 (precocious dissociation of sisters), and ASK1 (Arabidopsis SKP1-like) involved in meiosis [41]. The *Arabidopsis thaliana atm-1* and *atm-2* mutants are phenotypically identical to the wild type plants, except for the presence of partial sterility, and they show hypersensitivity to IR, but not to UV-B radiation [42]. Conversely, *Arabidopsis atr* mutants are viable, fertile, and sensitive to UV-radiation [42]. In *Arabidopsis*, ATM and ATR delay seed germination during aging while seeds from the *atm* and *atr* mutants germinate showing extensive chromosomal aberrations [43]. The relevance of plant DDR mutants with viable phenotypes *vs*. animal lethal mutants is further discussed in Section 3.1.

1.5. Kingdom-specific master regulators of DDR: the SOG1 and p53 transcription factors

Master regulators of DDR act as 'hubs' where exogenous/endogenous signals converge to help cells to withstand stress.

1.5.1. Master regulators in animals

The p53 transcription factor, the master regulator of DDR in animals, is involved in cell cycle control, DNA repair and apoptosis, and it is phosphorylated by ATM in response to DNA damage [44,45]. According to evolutionary studies, the ancestral p53 protein is specifically committed to DSBs repair in meiotic cells while in somatic cells it is also responsive to other types of DNA lesions, as observed in the nematode *C. elegans* [46]. The expansion of p53 functions in genome surveillance seems to be associated with the evolution of multicellular organisms [46]. Interestingly, long-lived animals possess multiple copies of the *TP53* (tumor protein p53, animal orholog of human p53) gene (e.g. the African elephant genome includes up to 20 copies), with implications in the cellular responses to DNA damage [47].

1.5.2. Master regulators in plants

SOG1, a NAC (NAM, ATAF1/2, and CUC2) transcription factor, was identified based on the phenotype of the *Arabidopsis sog1-1* mutant characterized by a missense mutation resulting in the substitution of a highly conserved amino acid residue in the DNA-binding NAC domain [48,49]. Up-regulation of multiple DNA repair genes was not detected in *Arabidopsis sog1-1* seedlings after exposure to γ-rays, similarly to what was observed in *Arabidopsis atm* mutants [42]. Furthermore, chromatin immunoprecipitation (ChIP)-PCR analysis showed that SOG1 binds directly to the promoter regions of *SMR* 5 (siamese-related 5) and *SMR7* genes (encoding plant-specific cyclin-dependent kinase inhibitors) in response to DNA damage. This finding links the SOG1 master regulator with cell cycle checkpoint control (Fig. 1) [50].

When phosphorylated in an ATM- and ATR-dependent manner, SOG1 triggers transcription of DDR and cell cycle checkpoint genes (Fig. 1). In mammals, the DNA replication checkpoint is predominantly controlled by the CDC25 phosphatase, with the contribution of WEE1. In plant cells, the response to replication stress is mediated by induction of the WEE1 kinase [51] (Fig. 1). However, WEE1-deficient plants can withstand other types of DNA damage, suggesting the involvement of WEE1-independent pathways in cell cycle control. Indeed, SMR5 and SMR7, mainly regulated through ATM- and SOG1-dependent pathways, complement WEE1 in the inhibition of cell cycle progression [50] (Fig. 1).

The function and regulatory mechanisms of SOG1 are similar to those mediated by the animal p53 protein. Although plants apparently lack a p53 orthologue, the discovery of SOG1 revealed that this protein is likely the plant functional homolog of animal p53 (Table 1). Since SOG1 and p53 amino acid sequences are highly divergent, it is possible that a NAC protein evolved in plants to acquire a functional role in DDR [52,53].

Table 1
List of *Arabidopsis thaliana* proteins (protein symbol, description, and accession code according to UniProtKB) involved in DNA damage response pathways along with their Human orthologs. The protein symbol aliases are shown within parentheses. n.d. not detected.

Arabidopsis thaliana			*Homo sapiens*		
Symbol	Description	Accession code	Symbol	Description	Accession code
ARP6	Actin-related protein 6	Q8LGE3	ACTR6	Actin-related protein 6	Q9GZN1
SKP1A (ASK1)	SKP1-like protein 1A	Q39255	SKP1	S-phase kinase-associated protein 1	P63208
ATM	Serine/threonine-protein kinase ATM	Q9M3G7	ATM	Ataxia-Telangiectasia-mutated protein kinase	Q13315
ATR	Serine/threonine-protein kinase ATR	Q9FKS4	ATR	ATM- and Rad3-related protein kinase	Q13535
ATR1	NADPH-cytochrome P450 reductase 1	Q9SB48	POR	NADPH-cytochrome P450 reductase	P16435
BARD1	BRCA1-associated RING domain protein 1	F4I443	BARD1	BRCA1-associated RING domain protein 1	Q99728
BRCA1	Protein BREAST CANCER SUSCEPTIBILITY 1 homolog	Q8RXD4	BRCA1	Breast cancer type 1 susceptibility protein	P38398
BRCA2A	Protein BREAST CANCER SUSCEPTIBILITY 2 homolog A	Q7Y1C5	BRCA2	Breast cancer type 2 susceptibility protein	P51587
BRCA2B	Protein BREAST CANCER SUSCEPTIBILITY 2 homolog B	Q7Y1C4			
CDC25	Dual specificity phosphatase Cdc25	Q8GY31	CDC25C	M-phase inducer phosphatase 3	P30307
FAS1 (CAF1/ FASCIATA)	Chromatin assembly factor 1 subunit FAS1	Q9SXY0	CHAF1A	Chromatin assembly factor 1 subunit A	Q13111
			CHAF1B	Chromatin assembly factor 1 subunit B	Q13112
n.d.			CHEK1 (CHK1)	Serine/threonine-protein kinase Chk1	O14757
n.d.			CHEK2 (CHK2)	Serine/threonine-protein kinase Chk2	O96017
CMT3	DNA (cytosine-5)-methyltransferase CMT3	Q94F88	n.d.		
CSN3	COP9 signalosome complex subunit 3	Q8W575	CSN3	COP9 signalosome complex subunit 3	Q9UNS2
CSN7	COP9 signalosome complex subunit 7	Q94JU3	CSN7A	COP9 signalosome complex subunit 7a	Q9UBW8
			CSN7B	COP9 signalosome complex subunit 7b	Q9H9Q2
CUL4	Cullin-4	Q8LGH4	CUL4A	Cullin-4A	Q13619
			CUL4B	Cullin-4B	Q13620
DDB1A	DNA damage-binding protein 1a	Q9M0V3	DDB1	DNA damage-binding protein 1	Q16531
DDB1B	DNA damage-binding protein 1b	O49552			
DDB2	Protein DAMAGED DNA-BINDING 2	Q6NQ88	DDB2	DNA damage-binding protein 2	Q92466
DMT1 (MET1)	DNA (cytosine-5)-methyltransferase 1	P34881	DNMT1	DNA (cytosine-5)-methyltransferase 1	P26358
E2FA	Transcription factor E2FA	Q9FNY0	n.d.		
ERCC1	DNA excision repair protein ERCC-1	Q9MA98	ERCC1	DNA excision repair protein ERCC-1	P07992
INO80	DNA helicase INO80-like protein	A0A1I9LT22	INO80	DNA helicase INO80	Q9ULG1
KU80	ATP-dependent DNA helicase 2 subunit KU80	Q9FQ09	XRCC5	X-ray repair cross-complementing protein 5	P13010
LTP1	Non-specific lipid-transfer protein 1	Q42589	n.d.		
LTP2	Non-specific lipid-transfer protein 2	Q9S7I3	n.d.		
LTP3	Non-specific lipid-transfer protein 3	Q9LLR7	n.d.		
LTP4	Non-specific lipid-transfer protein 4	Q9LLR6	n.d.		
LTP5	Non-specific lipid-transfer protein 5	Q9XFS7	n.d.		
LTP6	Non-specific lipid-transfer protein 6	F4IXC6	n.d.		
LTP7	Non-specific lipid-transfer protein 7	Q9ZUK6	n.d.		
LTP8	Non-specific lipid-transfer protein 8	Q9ZPW9	n.d.		
LTP9	Non-specific lipid-transfer protein 9	Q6AWW0	n.d.		
LTP10	Non-specific lipid-transfer protein 10	Q9LZV9	n.d.		
LTP11	Non-specific lipid-transfer protein 11	Q2V3C1	n.d.		
LTP12	Non-specific lipid-transfer protein 12	Q9SCZ0	n.d.		
LTP13	Non-specific lipid-transfer protein 13	A8MQA2	n.d.		
LTP14	Non-specific lipid-transfer protein 14	Q9FIT2	n.d.		
LTP15	Non-specific lipid-transfer protein 15	Q9M0T1	n.d.		
LTPG1	Non-specific lipid transfer protein GPI-anchored 1	Q9C7F7	n.d.		
LTPG2	Non-specific lipid transfer protein GPI-anchored 2	Q9LZH5	n.d.		
n.d.			MDC1 (NFBD1)	Mediator of DNA damage checkpoint protein 1	Q14676
MRE11	Double-strand break repair protein MRE11	Q9XGM2	MRE11	Double-strand break repair protein MRE11	P49959
T3F12.3 (MuDR)	Putative MuDR-like transposon protein	O22273	n.d.		
NBS1	Nijmegen breakage syndrome 1 protein	Q0H8D7	NBN	Nibrin	O60934
NPR1	Non-expressor of PR1	Q8L9W4	n.d.		
PCNA1	Proliferating cellular nuclear antigen 1	Q9M7Q7	PCNA	Proliferating cell nuclear antigen	P12004
RAD9	Cell cycle checkpoint control protein family	F4J7B7	RAD9A	Cell cycle checkpoint control protein RAD9A (Homo sapiens)	Q99638
			RAD9B	Cell cycle checkpoint control protein RAD9 B (Homo sapiens)	Q6WBX8
RAD17	Cell cycle checkpoint protein RAD17	Q9MBA3	RAD17	Cell cycle checkpoint protein RAD17	O75943
RAD50	DNA repair protein RAD50	Q9SL02	RAD50	DNA repair protein RAD50	Q92878
RAD51	DNA repair protein RAD51 homolog 1	P94102	RAD51	DNA repair protein RAD51 homolog 1	Q06609
RAD51L1 (RAD51B)	DNA repair protein RAD51 homolog 2	Q9SK02	RAD51B	DNA repair protein RAD51 homolog 2	O15315
RAD51L2 (RAD51C)	DNA repair protein RAD51 homolog 3	Q8GXF0	RAD51C	DNA repair protein RAD51 homolog 3	O43502
RAD51L2/ RAD51D	DNA repair protein RAD51 homolog 4	Q9LQQ2	RAD51D	DNA repair protein RAD51 homolog 4	O75771

(*continued on next page*)

Table 1 (*continued*)

Arabidopsis thaliana			*Homo sapiens*		
Symbol	Description	Accession code	Symbol	Description	Accession code
RBR1	Retinoblastoma-related protein 1	Q9LKZ3	RB1	Retinoblastoma-associated protein	P06400
n.d.			P53	Cellular tumor antigen p53	P04637
n.d.			TP53BP1	TP53-binding protein 1	Q12888
PARP1	Poly [ADP-ribose] polymerase 1	Q9ZP54	PARP1	Poly [ADP-ribose] polymerase 1	P09874
PIE1 (SWR1)	Protein PHOTOPERIOD-INDEPENDENT EARLY FLOWERING 1	Q7X9V2	SRCAP	Helicase SRCAP	Q6ZRS2
ASHH1 (SDG26)	Histone-lysine N-methyltransferase ASHH1	Q84WW6	n.d.		
SMR1	Cyclin-dependent protein kinase inhibitor SMR1	Q9LPP4	n.d.		
SMR2	Cyclin-dependent protein kinase inhibitor SMR2	Q9SGE2	n.d.		
SMR5	Cyclin-dependent protein kinase inhibitor SMR5	Q9LNX4	n.d.		
SMR7	Cyclin-dependent protein kinase inhibitor SMR7	Q9LVX6	n.d.		
SNI1	Negative regulator of systemic acquired resistance SNI1	Q9SWA6	n.d.		
SOG1	Suppressor of gamma response 1	Q6NQK2	n.d.		
SUVH5	Histone-lysine N-methyltransferase, H3 lysine-9 specific SUVH5	O82175	n.d.		
SWC6	SWR1 complex subunit 6	Q9FHW2	n.d.		
BRM	ATP-dependent helicase BRM	Q6EVK6	n.d.		
CHR12	Probable ATP-dependent DNA helicase CHR12	F4J9M5	n.d.		
CHR23	Probable ATP-dependent DNA helicase CHR23	F4K128	n.d.		
SYD	Chromatin structure-remodeling complex protein SYD	F4IHS2	n.d.		
LIG4	DNA ligase 4	Q9LL84	LIG4	DNA ligase 4	P49917
MEI1 (TOPBP1)	Transcription coactivator	F4I701	TOPBP1	DNA topoisomerase 2-binding protein 1	Q92547
At5g47690 (PDS5)	Binding protein	B3H5K3	PDS5A	Sister chromatid cohesion protein PDS5 homolog A	Q29RF7
			PDS5A	Sister chromatid cohesion protein PDS5 homolog B	Q9NTI5
AtWAPL1	WAPL (Wings apart-like protein regulation of heterochromatin) protein	F4I7C7	WAPL	Wings apart-like protein homolog	Q7Z5K2
WEE1	Wee1-like protein kinase	Q8L4H0	WEE1	Wee1-like protein kinase	P30291
XPD (UV6)	DNA repair helicase XPD	Q8W4M7	ERCC2	TFIIH basal transcription factor complex helicase XPD subunit	P18074
UVH1 (XPF)	DNA repair endonuclease UVH1	Q9LKI5	ERCC4	DNA repair endonuclease XPF	Q92889
XRCC1	DNA-repair protein XRCC1	Q24JK4	XRCC1	DNA repair protein XRCC1	P18887
XRCC2	DNA-repair protein XRCC2 homolog	Q682D3	XRCC2	DNA repair protein XRCC2	O43543
XRCC3	DNA-repair protein XRCC3 homolog	Q9FKM5	XRCC3	DNA repair protein XRCC3	O43542

SNI1 (suppressor of NPR1-1 inducible 1) is a negative regulator of homologous recombination (HR) in plants, not found in mammals (Table 1), involved in signaling pathways that modulate the action of the NPR1 (nonexpressor of PR genes 1) master regulator of plant immunity [54]. SNI1 controls the expression of several HR genes, among which are *RAD51D*, *SWI2/SNF2*, *MuDR*, *BRCA2*, *RAD51*, *RAD17*, *ATR1*. Overexpression of human *p53* gene in *Arabidopsis* revealed the ability of p53 to interact with SNI1 in the context of HR. Indeed, ectopic expression of *p53* gene *in planta* caused early senescence and enhanced HR frequency mediated by the SNI1-RAD51D signaling pathway [54].

SOG1 orthologs have been detected in most land plants, including gymnosperms. The presence of SOG1 in mosses is still debated since this protein shows the conserved NAC domain but the region responsible for protein–protein interaction is structurally different [46,52]. Recent work in *Arabidopsis* has highlighted the role of the RBR (retinoblastoma-related) transcription factor in safeguarding genome integrity through the interaction with BRCA1 [55]. The observed recruitment of RBR-E2FA complex at DNA damaged sites might trigger the signaling pathway that modulate DDR genes. AtBRCA1, independently recruited to DNA damage foci, interacts with RBR, thereby contributing to a novel regulatory pathway which acts in parallel with the SOG1-mediated transcriptional control of DDR genes (Fig. 1).

1.6. Ubiquitination in DDR

Ubiquitination is a versatile and reversible post-translational modification, particularly suited for the modulation of dynamic and complex cellular processes as DDR. The molecular players involved in ubiquitin-mediated signaling during DDR are still not fully understood. A range of ubiquitin and ubiquitin-like modifiers, among which SUMO (small ubiquitin-like modifier), coordinate the multiple cellular events underlying DSB repair [56]. Ubiquitylation requires the ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2) and a ubiquitin ligase (E3), which coordinately transfer the ubiquitin moiety to a lysine residue within the target protein.

1.6.1. Ubiquitin-dependent signaling in animals

The overall human proteome includes more than 1.000 components of the ubiquitin system and more than 10.000 ubiquitylation sites [57]. Ubiquitin and SUMO signals are deciphered by effectors containing the so-called ubiquitin-binding domains (UBDs), some of them frequently found in DDR proteins [58]. Protein recruitment at DSB sites is mediated by the RNF (Ring Finger Protein)8-RNF168 pathway. Ubiquitylation of histones and other chromatin-associated proteins at the K63 lysine residue is carried by the E2 enzyme UBC13 and the E3 ligases RNF8 and RNF168. In this way, binding sites for DDR proteins that contain UBDs are generated in the regions flanking the DSB lesion [59]. RNF168 catalyzes the monoubiquitination of histone H2A whereas RNF8 extends monoubiquitination on H2A to form K63-linked ubiquitin chains, crucial for the recruitment of DDR effectors, such as the BRCA1-A complex. RNF168-catalyzes H2A monoubiquitination affects repair pathway choice through recruitment of 53BP1 (p53 binding

protein) to DSB lesions. 53BP1acts then as a scaffold to assemble other proteins that control DNA end resection. The current model integrating ubiquitylation and DDR in animals is based on the concept that specific ubiquitination of histones at different sites directs the choice of the appropriate repair pathway [60].

1.6.2. Ubiquitin-dependent signaling in plants

The interaction between ubiquitylation and DDR is less explored in plants, however reports on the highly conserved features of ubiquitin-dependent signaling in DDR are available [61–63]. No plant homologs of the ubiquitin ligases RNF168 and RNF8 have been so far identified whereas *Arabidopsis* mutants of the ubiquitin ligase RAD5 show increased sensitivity to DNA damaging agents [62].

1.7. BRCA1 and BARD1

The *BRCA1* and BARD1 genes are part of a molecular network which controls the radiation-induced bystander response, particularly the activation of intra-S-phase checkpoint and HR-mediated DNA repair [64].

1.7.1. BRCA1 and BARD1 in animals

The human BRCA1 protein contains an N-terminal RING domain and two C-terminal BRCT (BRCA1 C-terminal domains). The N-terminal RING domain displays E3 ubiquitin ligase activity and interacts with BARD1 (BRCA1-associated RING domain protein 1), thus forming a heterodimer with enhanced E3 ubiquitin ligase activity and ability to bind DNA repair intermediates. The C-terminal BRCT domain interacts with proteins containing a phosphorylated serine residue in the Ser-X-X-Phe motif. The latter is present in several DNA repair and cell cycle players [65,66]. Following ATM/ATR-mediated phosphorylation (Fig. 1), BRCA1 controls 5′–3′ DNA end resection at break sites, a critical step for the selection of the DSB-repair pathways HR or NHEJ. The recent work by Isono et al. [67] showed that BRCA1 promotes DSBs repair *via* HR during G2 and S phases by triggering dephosphorylation of 53BP1, a key regulator of NHEJ. Following ATM-mediated phosphorylation, 53BP1 is recruited at the damaged site where it prevents DNA resection in cooperation with RIF1 (RAP1-interacting factor 1) and PTIP (PAX transactivation domain-interacting protein), facilitating NHEJ in G1 phase [68].

1.7.2. BRCA1 and BARD1 in plants

Orthologues identified in *Arabidopsis* contain the conserved RING and BRCT domains [69,70]. Under physiological conditions, *AtBRCA1* and *AtBARD1* genes exhibited similar expression profiles *in planta*. However, only *AtBRCA1* was strongly induced by γ-irradiation, suggesting the occurrence of different regulatory mechanisms in plants, compared to humans [71]. A distinct role for the *AtBRCA1* and *AtBARD1* genes in DDR activated by cross-linking agents was suggested, based on the increased sensitivity of *Arabidopsis brca1* and *bard1* mutants to mitomycin C and comet assay analysis [71,72]. The same authors investigated the involvement of *AtBARD1* gene in HR-mediated DSBs repair. In *Arabidopsis*, DNA repair after exposure to acute X-rays doses (5 or 15 Gy) includes 'slow' (80–120 min) and 'rapid' (< 30 min) phases. The slow phase, an early period of HR-based DSBs repair, involves up-regulation of *AtBRCA1* and *AtRAD51* genes [71]. The most conserved part of the plant BRCA1 and BARD1 proteins, the PHD (plant homeodomain) region, is missing in their animal counterparts. This finding raises intriguing questions about the evolution of breast cancer genes and the time when the PHD domain was acquired in plants. The function of PHD domain is still unknown, however it has been suggested that it might be responsible for the recruitment of *At*BRCA1 at the DSB site [73,74].

1.8. CSN and UV-mediated stress

The CSN complex, consisting of eight different subunits, was first identified as a negative regulator of light-mediated plant development. CSN controls protein degradation using deneddylation and deubiquitination [75,76].

1.8.1. CSN in animals

CSN interacts with CRL4 (cullin ring ubiquitin ligase) complexes involved in DNA repair, cell cycle checkpoint control and chromatin remodeling [77–79]. The CSN8 subunit interacts with ATM while the CSN3 subunit is phosphorylated following DNA damage [78] (Fig. 1). By interacting with CRL4 complexes, CSN participates to Nucleotide Excision Repair (NER) pathway required for the early recognition and subsequent repair of UV-induced photoproducts [80–82]. The interaction of the damage sensor protein DDB2 (DNA damage binding) with CRL4 is stabilized under physiological conditions by CSN-mediated deneddylation. Upon exposure to UV, DDB2 recognizes and binds UV-induced lesions, leading to DNA unwinding. Once the DDB2-CRL4 complex associates with chromatin, CSN is released, thereby facilitating histone ubiquitination and recruitment of NER proteins to damaged sites [83].

1.8.2. CSN in plants

Arabidopsis csn mutants undergo enhanced DSBs accumulation leading to delayed cell cycle progression at G2 phase [84]. The ATR-dependent role of CRL4 in the maintenance of genome integrity (global genome repair-GGR) upon UV-stress has been demonstrated [85]. The *Arabidopsis csn7*-null mutants which lack the functional CSN7 subunit showed increased ribonucleotide reductase (RNR2) activity, resulting in the up-regulation of DNA repair genes, including *BRCA*, *RAD51*, and *PARP1* (poly(ADP-ribose) polymerase 1) [86].

1.9. Chromatin remodelers as DDR players

Besides DDR master regulators, the role of chromatin remodelers should be also considered when searching for novel predictive DNA damage biomarkers. Chromatin remodeling is essential to provide accessibility of enzymes to damaged sites and a docking platform for the DNA repair machinery [87–95]. Therefore, chromatin remodeling factors could be regarded as putative predictive biomarkers of DNA damage. Highly-conserved histones, basic proteins associated with DNA to form chromatin, undergo post-translational modifications crucial for the modulation of replication, transcription and DNA repair. Exchange of core histones with histone variants, methylation, acetylation, and phosphorylation of specific Arg, His, Lys, Ser, and Thr residues occurring on the histone tail contribute to the regulation of chromatin dynamics during DDR [88,91–93]. Incorporation of the histone H2A variant H2AX and its subsequent phosphorylation on Ser139 (γH2AX) is an early event in DDR, conserved throughout evolution. ATM, ATR and DNA-PK (DNA-dependent protein kinase) regulate the spreading of γH2AX along the site, controlling in this way DNA damage signaling and the subsequent recruitment of the DNA repair machinery [93].

1.9.1. Chromatin remodelers and DDR players in animals

In human cells, incorporation of the H2AZ histone variant at the damaged site promotes the transition into transcriptionally active chromatin structures, facilitating access of the DNA repair machinery to DSBs [88]. The INO80 (inositol requiring) and SWR1 (SWI2/SNF2-related) chromatin remodeling complexes, which drive nucleosome eviction and incorporation of H2AZ into nucleosomes, modulate DNA mobility during DDR and control the recruitment and spreading of DNA repair factors [89,90]. Chromatin structure also influences the timing of DNA repair. Indeed, euchromatic regions, more prone to DNA damage due to an 'open' chromatin state, are repaired more efficiently compared to heterochromatin [94]. A recent work [95] revealed that CRL4

ligase is required for histone biogenesis, ensuring proper histone levels not only during DNA replication but also for genome maintenance.

1.9.2. Chromatin remodelers and DDR players in plants

Although many orthologues of animal chromatin remodelers have been identified in plants, their role in DDR remains largely unknown [96]. Histone variants and post-translational modifications are conserved in plants, but their effects on the modulation of DNA exposure and gene expression are still poorly investigated [97]. In *Arabidopsis*, the SWR1 complex which deposits histone H2AZ, is implicated in DNA repair. Mutations in genes coding for the SWR1 complex subunits named PIE1 (photoperiod-independent early flowering 1), ARP6 (actin-related protein 6), and SWC6 (SWR1 complex 6) result in DNA damage accumulation in the absence of genotoxic stress as well as in hypersensitivity to genotoxins [98].

1.10. Safeguarding genome integrity in embryos

SMC (structural maintenance of chromosome) proteins are highly conserved ATPases that control chromosome replication and segregation, playing a crucial role in genome stability.

1.10.1. SMC in animals

Six SMC proteins (SMC1-6) are assembled to form the SMC heterodimer complexes cohesin, condensin, and SMC5/6, all of them contributing to DNA repair [99,100]. All SMCx/x heterodimers are associated with non-SMC elements, e.g. SMC1/3 heterodimer forms a ring-like structure by association with RAD21, which is a kleisin (the Greek word for 'closure') [101,102]. The SMC5/6 complex contains, besides SMC5 and SMC6 proteins, the non-SMC elements NSE1, NSE2/MMS21, NSE3/MAGE-G1, NSE4, NSE5, and NSE6 [100]. Actually, *NSE1*, *NSE3*, and *NSE4* (a kleisin complex) as well as *SMC5*, and *SMC6* are essential genes and null mutants are lethal. In mammals, mutations in *NSE1* and *NSE3* genes are associated with cancer [103]. A common feature of SMCs is the formation SMC/kleisin complexes. Kleisin proteins are responsible for bridging and circularization of SMC complex. In case of SMC5/6, a kleisin complex is NSE1, NSE3, and NSE4 (plants), NSE1, MAGE, and NSE4 (humans). Kleisin of Cohesin SMC1/3 is Scc1 and Scc3, RAD21.1 and RAD21.3 in plants [101,102].

In mammals, two major steps of DNA methylation reprogramming are observed during early development. Active DNA demethylation is found during early germ cell development and in the zygote soon after fertilization. Methylated cytosine is removed through different repair mechanisms, thus DDR is crucial in animals at fertilization and during the onset of embryonic development. Surveillance mechanisms remove DNA damage, avoiding deleterious effects on zygotic reprogramming [104,105]. Replacement of methylated cytosines requires the BER glycosylases and generates DSBs. The involvement of HR for DSBs repair and the CHK1-mediated checkpoint activation during zygotic reprogramming have been hypothesized. According to Ladstatter and Tachibana-Konwalski [106], the cohesin complex accumulating in oocytes plays an essential role in repairing endogenous DNA lesions whereas repair failure results in embryo loss. In zygotes, the DDR kinases ATM, ATR, and DNA-PK activate the cell cycle CHK1-dependent checkpoint in response to endogenous DNA lesions [106].

1.10.2. SMC in plants

SMC proteins mediate DDR in the crucial phases of early embryo development both in animals and plants, another conserved *trans*-kingdom feature. In Angiosperms, double fertilization produces the embryo and the endosperm, the major constituents of seeds. The embryo undergoes sequential cell divisions during which new tissues are formed whereas the endosperm enters a series of mitoses, developing into the syncytial endosperm which is degraded in late embryogenesis. In *Arabidopsis*, the *AtNSE1* and *AtNSE3* genes encoding components of the SMC5/6 complex are essential for early embryogenesis and post-embryonic development since mutations cause disordered cell division in early embryos and enhanced sensitivity to DSBs, with the consequent seed abortion [107]. The same authors showed that *AtNSE1* and *AtNSE3* gene expression was significantly up-regulated in *Arabidopsis* transgenic lines overexpressing *AtSOG1*, suggesting for the ATM- and SOG1-mediated transcriptional control of *AtNSE1* and *AtNSE3* genes.

1.11. Endoreduplication: the 'third option'

Endopolyploidy takes place when the canonical cell cycle consisting of four phases (G1, S, G2, and M) is converted into the endoreduplication cycle (endocycle) in which DNA replication takes place without cell division. Cells use this strategy to overcome adverse conditions that would prevent growth and tissue regeneration [108]. Genotoxic stress promotes endoreduplication in certain tumor cells, possibly contributing to radioresistance [109]. The plant endocycle is part of a complex regulatory system that coordinates cell proliferation and post-mitotic cell expansion during development. The so-called 'compensation phenomenon' [110] is observed in seedlings irradiated with γ-rays which develop leaves with fewer but larger cells, compared to non-irradiated seedlings. The highly-conserved CAF-1 (chromatin assembly factor 1), a histone chaperon involved in the recruitment of histones H3 and H4 onto newly synthesized DNA, is required for survival in animal cells [111] while the *Arabidopsis fas* (fasciata) mutants with defective CAF1 are viable and display compensation phenotypes [112]. Adachi et al. [113] showed that both the ATM-SOG1 and ATR-SOG1 pathways are involved in DSBs-induced endoreduplication occurring in the *Arabidopsis fas* mutants. ATR, which senses DNA replication stress, might be required to cope with stress arising during the repeated progression of endocycles. Following genotoxic injury, the endocycle is considered as the 'third option' of plant cells, besides PCD and DNA repair. Plant cells, as opposed to animal cells, do not migrate within tissues to replace the missing populations, thus endoreduplication has evolved as a strategy to preserve tissue integrity during the plant life cycle, preventing the proliferation of damaged cells [113]. The *Arabidopsis fas* mutants are characterized by hypersensitivity to genotoxic agents and compensate for genome instability with enhanced HR activity and endoreduplication [112,114,115]. The plant-specific SMR family of cyclin-dependent kinase inhibitors controls the transition from the mitotic cell cycle to endocycle (Fig. 1), with a predominant involvement of SMR2 during the early transition from proliferation to endoreduplication and a late role for SMR1 in blocking cell proliferation and maintaining the endocycle [115].

2. Gene expression profiling as a source of 'radiation exposure monitoring' biomarkers

The identification of novel radiation-responsive genes participating in DDR in plants and comparison to their animal counterparts, in terms of expression profiles, could provide novel candidates to be tested as DNA damage biomarkers in basic and applied research, covering both biomedical and environmental issues. While transcriptional changes at the level of a single gene might be difficult to decipher, due to the possible convergence of different transduction pathways as well as the effects of cell-specific factors, an impressive amount of data can be produced with high-throughput technologies, providing a pool suitable for biomarker selection.

Conventional biomarkers are monitored by means of cytogenetic assays, e.g. micronucleus assay in mitogen-stimulated peripheral blood lymphocytes [116] and chromosome aberration analysis in circulating lymphocytes performed by *in situ* hybridization [117]. Chromosome aberrations are observed under light microscope after staining, whereas another classic toxicology method, the SCE (sister chromatid exchange) assay, detects recombination between old and newly synthesized DNA strand by monitoring bromodeoxyuridine (BUdR) incorporation [118]. However, these assays are time consuming and they can be applied only

to proliferating cell populations. Unstable chromosomal aberrations, such as dicentrics, are highly reliable standards in biodosimetry, since they are specifically associated with radiation exposure whereas micronuclei can be easily scored as by-products resulting from damaged chromosomes. Advantages and limitations of standard cytogenetic methods are currently discussed in view of the need for novel REM biomarkers allowing rapid dose assessment, a better prediction of health consequences, and addressing issues of individual radio-sensitivity [119]. Comet assay has gained attention as a sensitive and rapid technique, able to reveal DNA damage and repair in both proliferating and non-proliferating cells [120]. Induction of apoptosis has been also regarded as a possible indicator of radiation-induced damage [121].

REM biomarkers are essential tools used to evaluate cyto- and genotoxicity at the tissue level in radiation oncology [122,123], or for biodosimetry purposes in the case of nuclear catastrophe/accidental radiation exposure [124]. However, studies at the level of whole-genome transcriptome provide a global picture of the stress response within specific cell types [122]. Rapid diagnostic protocols work with a limited number of genes (from 10 to 100) whose expression profiles can be utilized as reliable REM biomarkers [122]. It is also recommended that only those genes significantly up-regulated upon radiation exposure should be selected as biomarkers [125]. When DDR genes are used as biomarkers, their expression ratio profiles can be exploited to develop prediction models and to establish reliable radiation dosimetry protocols or sensitive tests for the screening of genotoxic chemicals [126]. In both animals and plants, DDR genes are generally included in those gene arrays which are significantly affected by radiation exposure. An update of the recent studies on radiation-responsive transcriptomes in animals and plants and their usefulness as a source of potential biomarkers is provided and the most representative reports are listed in Table 2.

2.1. Complexity of IR-responsive transcriptomes in humans and plants

2.1.1. Landscape in humans

Although the molecular mechanisms underlying the activation of DDR in IR-treated cells have been extensively investigated in humans [11,127–129], there are several issues that still remain unclear. Different transcriptional responses have been described, depending on the cell type [130–133], as well as radiation qualitative/quantitative features such as total dose, dose rate [134–137], linear energy transfer-LET [138,139]. Another relevant issue deals with differences between *in vitro* and *in vivo* conditions [140], although several studies have demonstrated that the transcriptional response observed *in vitro* adequately reflects the *in vivo* picture [141,142]. Reports have been published, regarding the use of gene expression profiles to predict radiation responses in humans [126,143–148]. The potential of the peripheral blood mononuclear cells (PBMCs) transcriptome as a source of radiation biomarkers has been investigated [145–148]. Microarray techniques revealed that p53-dependent DDR genes were responsive to IR high doses [126,146] while IR low doses preferentially affected genes involved in the immune response [145,147–150]. In subsequent studies, the complexity of the radiation-responsive molecular networks was evidenced, and the use of alternative transcripts and splicing products as REM biomarkers was investigated. Macaeva et al. [144] suggested the use of alternative transcription and splicing profiles as REM biomarkers with increased sensitivity. Indeed, by combining molecular data and predictive statistical models, these authors demonstrated that gene and exon signatures can represent reliable radiation biomarkers.

2.1.2. Landscape in plants

Most reports currently available describe the γ-ray-responsive transcriptome in the model system *Arabidopsis thaliana* and highlight variability in the results, possibly due to changes in experimental parameters, *e.g.* plant tissue and developmental stage, radiation dose and post-irradiation time. Plant exposure to acute or chronic radiation resulted into different transcriptional responses, as reported by Kovalchuk et al. [151] who investigated the effects of acute and chronic IR exposure on *Arabidopsis* plants irradiated with γ-rays and cultivated on soil artificially polluted with ^{137}Cs, respectively. The 'acute' IR transcriptome showed the cell response to a severe stress. Most of the differentially expressed genes were also found in the heavy-metal responsive and UVC responsive transcriptomes, respectively [151]. Chronic IR treatments can influence plant morphology more than exposure to acute radiation, thus patterns of gene expression under chronic radiation might help understanding signaling pathways and molecular networks that are activated by IR perception and play a critical role in the plant adaptive response. The *Arabidopsis* 'chronic' transcriptome highlighted gene expression profiles typically found in the so-called 'common stress transcriptome' observed when plants are challenged with a range of abiotic stresses (*e.g.* salt, drought, cold) [151]. Following acute IR exposure, DSBs were repaired within 6 h while higher DSBs levels were detected in the chronically treated plants throughout the growth period. Enhanced HR frequency was also observed in response to chronic exposure [151]. Additional information was provided by Kim et al. [152] who compared the γ-ray responsive transcriptomes of *Arabidopsis* seedlings at different time points (6, 12, 24, 48 h) during 200 Gy-exposure. DDR genes, among which *RAD51-like* and *BRCA1* were strongly induced at 8 h and transcript levels were maintained until 48 h of exposure. The *Arabidopsis* transcriptome was analyzed by Kim et al. [153] in vegetative tissues (rosette leaves) exposed to γ-ray (100 and 800 Gy) for 24 h, revealing down-regulation of *LTP* (lipid transfer protein) genes involved in stress-mediated signaling. Sidler et al. [154] showed that exposure of *Arabidopsis* to low (10 Gy) and high (100 Gy) IR doses triggers expression of mismatch repair genes, as well as genes encoding the epigenetic regulators MET1 (methyltransferase 1), CMT3 (chromomethylase 3), and SUVH5 (SU(VAR) homolog) in 20-day old plants undergoing transition from vegetative to reproductive phase. Such findings underline the need for genome maintenance in response to IR during this critical growth stage. ATM-dependent up-regulation of DDR genes involved in HR- and NHEJ-mediated DSBs repair was observed in *Arabidopsis* plants irradiated with X-rays [155]. The global early transcriptional response to IR in *Arabidopsis* wild-type and *atm* mutant seedlings exposed to X-rays featured ATM-dependent up-regulation of DDR genes responsive to X-rays and modulation of transposable elements [156].

An interesting example of *trans*-kingdom conserved features in the response to specific types of IR has been reported [7,157]. The effects of γ-rays and HZE (high atomic number Z and energy) radiation, consisting of Fe nuclei with high LET, on the transcriptome of *Arabidopsis* seedlings were investigated. HZE treatment resulted in enhanced levels of clustered DNA lesions, and both treatments triggered the expression of genes involved in DSBs repair at 1.5 h. Interestingly, induction of DSBs repair genes was strongly ATM-dependent in HZE treated cells. Other DDR genes involved in NHEJ, NER, and BER were significantly induced only in HZE-treated plants [7]. The late response of *Arabidopsis* to γ-rays and HZE radiation, monitored at 24 h, was characterized by the induction of genes typically triggered by conventional abiotic stresses (*e.g.* salt, drought, UVB) and genes involved in the plant defence response. The work by Ding et al. [157] has described similar picture in human bronchial epithelial cells (HBECs) irradiated with γ-rays and HZE particles. The BRCA1-dependent DDR pathway was activated in response to both treatments, whereas genes involved in the pro-inflammatory acute phase response signaling pathway were specifically induced by HZE irradiation [154].

2.2. UV-responsive transcriptome analysis reveals similarities in the human and plant defence strategies

2.2.1. Landscape in humans

The most abundant (> 90%) UVA radiation (400–315 nm) has limited genotoxic effects since it is not absorbed by DNA, but instead, it

Table 2
Summary of studies describing the IR- and UV-responsive transcriptomes in *Arabidopsis thaliana* and *Homo sapiens*.

IR-responsive gene expression profiles (transcriptomes, microarrays, *q*RT-PCR)							
Arabidopsis thaliana				*Homo sapiens*			
Cell/tissue	Dose (D) Dose rate (DR)	Methodology	Ref.	Cell/tissue	Radiation Dose (D) Dose rate (DR)	Methodology	Ref.
Whole plant	-'Acute' γ-rays 1 Gy; 0.025 Gy/s - 'Chronic' ^{137}CsCl 199.2 μGy	qRT-PCR	[127]	Foreskin fibroblasts	X-rays 2 Gy ~2 Gy/min	- Bromouridine (Bru) incorporation - Bru-Seq/BruChase-Seq/BruUV-Seq	[125]
Rosette leaves	γ-rays 200 Gy 50 Gy/h	Microarrays	[128]	Keratinocytes	X-rays 0.01 Gy	- XTT and colony-forming assays - Microarrays	[126]
Rosette leaves	γ −rays 100, 200, 300, 400, 800, 1200, 1600, 2000 Gy	Microarrays	[129]	Fetal lung fibroblasts	γ-rays 1 Gy 1 Gy/min	- Cells treated with NO/ROS scavengers following irradiation - Microarrays	[130]
Whole plant	γ-rays 10, 100 Gy	*q*RT-PCR	[131]	Embryonic stem cells Induced pluripotent stem cells Primary dermal fibroblasts	γ-rays 0.25, 0.5, 1 Gy 2, 5, 10, 15 Gy	- Flow cytometry (γH2AX) - *q*RT-PCR	[11]
Whole plant	X-rays 10, 40 Gy 1.7 Gy/min	Whole transcriptome	[132]	Lymphoid cells	X-rays 4 Gy	Microarrays	[133]
Seedlings	X-rays 80 Gy	RNA-Seq	[134]	Embryonic stem cells	γ-rays 0.05, 1 Gy	Microarrays	[135]
				Peripheral blood mononuclear cells	γ-rays 0.1–2.0 Gy 1 Gy/min	Comet assay Western blot *q*RT-PCR	[136]
				Breast epithelial cells	High-LET α particles 0.6 Gy	Microarrays	[137]
				Fibroblasts	- γ-rays 1 Gy 1 Gy/min (HDR) 0.0007 Gy/min (LDR) - High LET-like ^{125}I	Microarrays	[138]
				Peripheral blood cells	X-rays 0.1–1.0 Gy 0.1 Gy/min	*q*RT-PCR	[139]
				Peripheral blood cells	High-energy photons 0.15–0.2 Gy	Microarrays	[140]
				Peripheral blood cells	High-energy photons 1.25 Gy 0.1 Gy/min	Microarrays	[141]
				Peripheral blood mononuclear cells	High-energy photons 0.2 Gy 0.02 Gy/min	Microarrays	[142]
				Peripheral blood cells	X-rays 0.1–1.0 Gy 0.26 Gy/min	Microarrays	[143]
				Peripheral blood mononuclear cells	α particles (^{124}Am) 0.5, 1, 1.5 Gy 0.98 Gy/min	Flow cytometry (γH2AX) Whole transcriptome microRNA expression profile	[144]
				Peripheral blood mononuclear cells	γ-rays 0.9–60 Gy	Microarrays microRNA expression profile	[145]
				Peripheral blood cells	X-rays 0.05, 1 Gy 0.003 Gy/min	Microarrays	[146]
				Peripheral blood cells	γ-rays 5–500 mGy 50 mGy/min	Microarrays	[147]
				Peripheral blood mononuclear cells	α particles (^{124}Am) 0.5, 1, 1.5 Gy 0.98 Gy/min	Flow cytometry (γH2AX) Whole genome transcriptome microRNA expression profile	[126]

(*continued on next page*)

Table 2 (*continued*)

IR-responsive gene expression profiles (transcriptomes, microarrays, *q*RT-PCR)

Arabidopsis thaliana				*Homo sapiens*			
Cell/tissue	Dose (D) Dose rate (DR)	Methodology	Ref.	Cell/tissue	Radiation Dose (D) Dose rate (DR)	Methodology	Ref.
				Brochial epithelial cells	γ-rays 1, 3 Gy High LET ^{56}Fe 0.5,1 Gy ^{28}Si 0.5, 1 Gy	Clonogenic assay Whole transcriptome	[148]

UV-responsive gene expression profiles (transcriptomes, microarrays, *q*RT-PCR)

Arabidopsis thaliana				*Homo sapiens*			
Cell/tissue	Dose (D) Dose rate (DR)	Methodology	Ref.	Cell/tissue	Dose (D) Dose rate (DR)	Methodology	Ref.
Seedlings	UVB fluence rate 2.5 μmol $m^{-2}s^{-1}$	- E.L.I.S.A. based photodimer detection - *q*RT-PCR	[149]	Adrenal cortex carcinoma cells	UV 10 Jm^{-2}	Microarrays	[150]
Plants	UVC fluence rate 0.6,1.2 J m^{-2} 0.01 J $m^{-2}s^{-1}$	Reporter-based dectecion of HR events ROPS (random oligonucleotide-primed synthesis) *q*RT-PCR	[151]	Primary keratynocites	UV 10, 20,30 mJ/cm^{-2}	RNA-Seq	[152]
Plants	UVB, UVA 2, 0.65 W m^{-2}	monoclonal antibody- based photodimer detection ChIP assay *q*RT-PCR	[153]				

represents a powerful source of oxidative stress [158]. Singlet oxygen ($^1O_2^-$) acts as a signaling component in UVA-mediated transduction pathways in human keratinocytes [159]. In humans, defects in the NER pathway impair the efficient removal of pyrimidine dimers and result in severe sensitivity to UVC radiation and pathological disorders [160]. Genome expression studies revealed the role of the mammalian SWI/SNF chromatin remodeling complex in the modulation of UV-responsive genes [161,162]. Furthermore, 'omics'-based analysis on UV-irradiated HEK293 (human embryonic kidney) cell lines confirmed the involvement of TC (transcription coupled)-NER genes in UV-mediated DDR [162]. A panel of biomarkers including UV-responsive genes with potential clinical applications has been identified, based on RNA-Seq analysis of human keratinocytes exposed to UV [163]. Genome-wide transcriptome analyses performed in different plant species revealed the requirement for BER, NER, and photoreactivation pathways in UV-triggered DDR [164–167]. Mutation analysis of the overall genome revealed strong mutagenesis leading almost exclusively to GC:AT transitions. This finding suggests the occurrence of effective error-prone bypass replication allowing genome to withstand photodimers. [168,169]

2.2.2. Landscape in plants

Plants and animals share common photo-protective mechanisms [170]. In plants, multiple photoreceptors are activated in response to UVA triggering accumulation of UV-absorbing molecules and antioxidant mechanisms [171] as well as DDR [172]. ATR, the mitogen-activated protein kinase (MAPK) signaling pathway, and SOG1 mediate the response to UVB radiation in *Arabidopsis* [173]. The characterization of the *Arabidopsis AtXPD* (UVH6, UV-hypersensitive) gene, homologous to the human *XPD* gene (Table 1), has provided an intriguing background for the *trans*-kingdom comparison of UVC-induced DDR pathways [174]. The *Arabidopsis uvh6*-1 mutant, with a mutation in the helicase domain of the AtXPD (UVH6) protein exhibits increased UVC sensitivity and reduced ability to repair the 6,4-photoproducts (or 6,4 pyrimidine-pyrimidones). In addition, the *Arabidopsis uvh6*-1 mutant shows enhanced frequency of spontaneous mutations and higher expression levels of DNA repair enzymes [174].

3. Use of plants as sources of novel DNA damage biomarkers: advantages and limitations

Highly conserved features have been identified in animal and plant DDR pathways, further supporting the usefulness of plant genomes as sources of novel REM biomarkers. However, the pronounced differences between plant and animal cells need to be carefully considered to avoid any misleading interpretations.

3.1. Knockout mutations of DDR genes: lethal effects in animals vs. viable phenotype in plants

Plants, characterized by enhanced capacity to withstand DNA damage compared to animals [175,176], represent an ideal system for the functional analysis of knockout mutations in DDR genes which compromise cell survival in animals. Knockout mutations of HR and NHEJ genes are in most cases lethal to mammals, whereas they are compatible with viability in plants, as reported for *Arabidopsis rad50* [177,178], *mre11* [179], and *ercc1* mutants [180]. Contrary to what is observed in mammals, the *Arabidopsis* homozygous *brca1*or *brca2* mutants develop into mature plants, thereby providing the opportunity to study the function of these proteins throughout the life cycle of a multicellular eukaryotic organism [71]. Similarly, the *Arabidopsis atr* mutant is viable [42] while defects in the animal *ATR* gene are lethal [42].

The observation that plant mutants defective in key genes for DSBs repair can nevertheless achieve rapid DSBs repair [181–183] suggests that these organisms (from mosses to seed plants) have evolved mechanisms for the rapid resumption of the overall genome integrity. Kozak et al. [184] reported for the first time the occurrence of an efficient two-phase DSB repair pathway in *Arabidopsis*, where the rapid phase is dependent on *MIM* (*AtSMC6b*), *LIG1*, *RAD21.1* and *BRU1* genes. Moreover, kinetic of DSBs removal was almost 2 times quicker in

atku80 and *atlig4* mutants than in wild-type *Arabidopsis*, and half-life of DSBs removal resulted in 5 *vs*. 8 min, respectively.

Charbonnel et al. [185] showed that DSBs repair in γ-irradiated *Arabidopsis* cells at G2/M accounts for at least three distinct repair processes, driven by the KU80, XRCC1, and XPF proteins. The high-fidelity canonical (C)-NHEJ pathway is activated first at the DSB sites where KU heterodimers localize. In the absence of C-NHEJ, KU-independent mechanisms are activated: the error-prone alternative DNA-end joining pathway (A-NHEJ, or microhomology-mediated end joining, MMEJ), and backup-NHEJ (B-NHEJ). These partially overlapping pathways exploit microhomology-mediated end joining at the damaged site and rely on the XPF/ERCC1 function. Based on radiosensitivity and DSBs repair profiles described in *Arabidopsis* mutants, C-, A-, and B-NHEJ pathways are activated a few minutes following irradiation [185]. Interestingly, the *Arabidopsis* quadruple *ku80 xrcc1 xrcc2 xpf* mutant plants lacking the KU-dependent and XRCC1-dependent NHEJ pathways are still able to repair DSBs within 10–90 min from irradiation. However, according to Charbonnel et al. [185], this novel DSBs repair pathway results in high levels of chromosomal aberrations and genome instability.

Viable plants carrying defective DNA repair genes provide a unique opportunity to investigate the role(s) of these genes in meiosis, chromatin remodeling, and telomere homeostasis. Moreover, these systems are useful to assess the involvement of DDR genes in the radiation response. Such an approach can be used only with individual DDR genes having structural and functional features, as well as interactions, greatly conserved among eukaryotes. In this case, plant mutants that are viable and even fertile, contrary to their mammalian counterparts, can be really useful tools to decipher the mechanism of action of specific DDR genes. On the other hand, there are DDR genes extremely divergent in the animal and plant kingdoms but playing conserved functions, *e.g.* the DDR master regulators p53 and SOG1. For such genes, it would be extremely difficult to draw a direct comparison.

3.2. Plant natural radiotolerance: limitations and possible advantages in biodosimetry applications

Living organisms are continuously exposed to cosmic radiation and natural radiation, emitted from rocks and soils, while anthropogenic activities contribute, in some cases, to radiation enhancement [186]. Radiation sensitivity is often associated with reduced ability to activate DDR and/or DSBs repair [187]. The IR-resistant fungus *Ustilago maydis* shows enhanced HR-dependent DNA repair activity mostly supported by the *UmBRH2* gene, homolog of the human *BRCA2* gene [188]. In the radioresistant basidiomycetous fungus *Cryptococcus neoformans*, the novel transcription factor BDR1 (bZIP transcription factor for DNA damage response) modulates the expression of DNA repair genes [189]. Like eubacteria and fungi, plants also exhibit natural inherent radioresistance, a feature often considered as a limiting factor for their application as biodosimeters [190].

Animals and plants display different levels of radiosensitivity, with a radiotolerance range of 0.01–1 Gy and 1–100 Gy, respectively [187]. Tardigrades, small aquatic animals able to withstand extremely high IR doses (up to 1000 Gy dose for γ-rays and 4000 Gy dose for heavy ions, respectively) in the dehydrated state, represent an exception [191]. The genome of the most stress-tolerant species *Ramazzottius varieornatus* contains a tardigrade-unique protein able to suppress X-ray-induced DNA damage, thus increasing radiotolerance [192]. The *R. varieornatus* *Rv*DSUP (damage suppressor) protein expressed in human cells was shown to associate with nuclear DNA, preventing SSBs and DSBs accumulation under irradiation [192]. It has been hypothesized that *Rv*DSUP might represent a DNA-targeted protectant similar to several known biomolecules, *e.g.* trehalose, which protects the cell macromolecules against severe injury. At the moment, a specific role for *Rv*DSUP as one of the DNA repair effectors, cannot be ruled out, while *R. varieornatus* genome sequencing data suggest for the occurrence of additional factors involved in extreme radiotolerance [192].

Plants have been exposed to IR, which is part of the natural background radiation, throughout evolution, with the consequent enhancement of DNA repair mechanisms required to cope with genotoxic stress. Radioresistance positively correlates with genome size since polyploidy facilitates protection against DNA damage. Sparrow et al. [193] demonstrated a clear relationship between the average nuclear volume of apical meristem cells and tolerance to chronic γ-irradiation. In the polyploid *Chrysanthemum* spp. and *Sedum* spp. genera, radioresistance increased parallel with the degree of polyploidy. Authors provided a model in which changes in radiosensitivity might depend on the dose required to produce a critical number of DNA breaks in nuclei of different size. Thus, for a defined dose, the occurrence of polyploidy results in reduced chromosome damage. Friesner et al. [194] reported that the number of IR-induced γ-H2AX foci in *Arabidopsis*, revealed by immunoblotting and immunofluorescence analyses, was significantly lower compared to mammalian cells. Taking in account that approximately one single DSB is associated with one γ-H2AX focus, pulsed-field gel electrophoresis (PFGE) showed an estimated DSB induction of 2.0 and 6.6 DSBs/Gy/Gbp (1 Gbp = 1×10^9 bp) in tobacco (*Nicotiana tabacum* L.) and chinese hamster ovary (CHO) cells, respectively [195]. Approximately, 1.5 Gy radiation dose applied to the diploid genome of human fibroblasts induces up to ~54 DSBs and results into 50% cell lethality (LD_{50}), whereas in *Arabidopsis* a significantly higher dose (400 Gy dose, corresponding to 125–200 DSBs) is required to impair plant growth [194,195]. However, the use of PFGE to monitor γ-H2AX as a marker of DSBs has been critically discussed since divergences between the kinetics of DSBs accumulation/repair and γ-H2AX occurrence/decay have been highlighted, suggesting some limitations in this approach [196].

Long-lived trees, such as the radiosensitive conifers, represent suitable bioindicators for IR exposure monitoring. In particular, forty-year-old Scotch pine populations (*Pinus sylvestris* L.) located in the contaminated area following Chernobyl accident have been extensively investigated in the effort to develop a plant-based model for the assessment of the biological effects of chronic LD exposure. According to Geras'kin et al. [197], the consequences of IR exposure can be predicted in natural Scotch pine populations based on the frequency of null mutations and aberrant cells, in the root meristem of seedlings. Isozyme analysis, carried out for highly conserved enzymes (*e.g.* glutamate dehydrogenase, malate dehydrogenase), suggested that this approach could be undertaken as a predictive parameter of the IR impact on animals and humans [197]. Limited changes in gene expression were observed in both *Pinus sylvestris* L. and *Pinus taeda* L. at the Chernobyl site [198]. The YD_{50} parameter (exposures required to reduce yield by 50%) has been used to quantify the impact of fallout radiation on crops [199]. According to this evaluation, cereals show high radiosensitivity (YD_{50} values in the 10–40 Gy range), legumes include both sensitive and resistant species (YD_{50} ranging from 10 to 120 Gy), and root crops display a wider sensitivity spectrum (YD_{50} in the 10–160 Gy range). In the case of pasture and forage crops, the YD_{50} varies from 20 to 200 Gy [199].

Based on these premises, radioresistant plant systems might be useful for the investigation of the effects caused by LD and LDR irradiation, currently difficult to analyze in animals due to technical constrains [200].

3.3. LD/LDR responses in radioresistant plants and the search for novel REM biomarkers

According to UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation), a low total dose (LD) is currently defined as a value below 100 mGy whereas a low dose rate (LDR) is any value below 6 mGy/h [201]. At the moment, knowledge concerning the effects of chronic exposures under LDR is extremely scanty. Only a few studies have been performed in animals exposed to LDR < 6 mGy/h

[202], due to the lack of facilities for long-term *in vivo* LDR exposure. The linear no-threshold (LNT) theoretical model has been adopted since 1970s to estimate the risk associated with LD exposure by extrapolation from the risk measured with high doses. However, according to epidemiological and experimental studies, the LNT model overestimates the LD risk [203]. For long term exposures at LD < 100 mGy, increased cancer risks are difficult to detect in populations and one of the most controversial issues is that the LNT model does not consider the role of mechanisms, such as DNA repair, that could significantly change the risk of cancer under LD conditions. To overcome these constraints, researchers have started looking at radiotolerant non-human species as potential sources of information on the mechanisms involved in LD/LDR responses [204–207]. At the moment it appears extremely difficult to figure out whether studies on plants will result in information that could directly impact the current way LD/LDR risk is assessed in humans. However, we cannot rule out the possibility that investigations carried in this field might help in future a better understanding of the highly conserved molecular mechanisms involved in the LD/LDR response.

The shape of the dose-response curve was investigated by Zaichkina et al. [207] in CHO fibroblasts irradiated with γ-rays (acute exposure: 0.05–2 Gy with dose rate of 28.2 Gy/h; chronic exposure: 0.84 Gy with dose rate of 0.0061 Gy/h) and *Vicia faba* roots irradiated with γ-rays (acute exposure: 0.1–2.5 Gy with dose rate of 28.2 Gy/h). In addition, *V. faba* seeds irradiated with 2–40 Gy (dose rate of 1.4 Gy/h) were analyzed. Based on the micronucleus test, the dose-response curves of animal and plant samples shared a common profile consisting of *1)* a low-dose linear segment, *2)* a plateau at intermediate doses, and *3)* a high-dose linear segment. This reflects the hypersensitivity of both animal and plant cells to LD radiation. Using DNA repair inhibitors and radioprotectors, the same authors provided evidence for lack of DDR under LD radiation exposure [207]. A study was performed on barley (*Hordeum vulgaris* L.) seeds exposed to γ-rays (0.1–300 Gy) [208]. Considering the high radioresistance of dormant dry seeds, the estimated LD range for barley was defined up to 5–10 Gy doses. Dose-dependent effects were not observed in the 1–25 Gy range (plateau phase), based on the analysis of chromosome aberrations, while damage showed a linear, dose-dependent increase for doses > 25 Gy. A similar non-linear relationship between dose and cytogenetic injury was reported for barley meristematic cells [208]. As for the effects of dose rate, it has been reported that mutations and chromosomal anomalies per unit dose increase at LDR compared to higher dose rates (HDR), due to lack of DDR activation [209,210]. This was also detected in barley root meristem cells exposed to dose rates of 0.1, 0.3, and 0.9 Gy/h [208]. Another relevant aspect is related to the species-dependent changes in the critical dose at which slope modifications of the dose-response curve are detected. As demonstrated by Geras'kin, et al. [208], the herbaceous plant *Tradescantia* showed a curve in which the plateau was reached with doses in the 0.02–0.2 Gy range, while in barley the plateau occurred in the 0.08–0.5 Gy range, indicating that *Tradescantia* is much more radiosensitive than barley.

Based on the current literature, dose-response curves in radioresistant plant systems might contribute to expand the current knowledge on the way living organisms cope with LD/LDR [200]. However, it should be also considered that major differences exist not only between the two Kingdoms but also between species. Under chronic exposure, woody species, *e.g.* conifers and deciduous trees, are the most radiosensitive whereas *Cryptogams* (plants that reproduce by spore) display high radioresistance. Crop cereals can vary in their radiosensitivity and legumes show radiation-sensitive growth stages. Effects of chronic

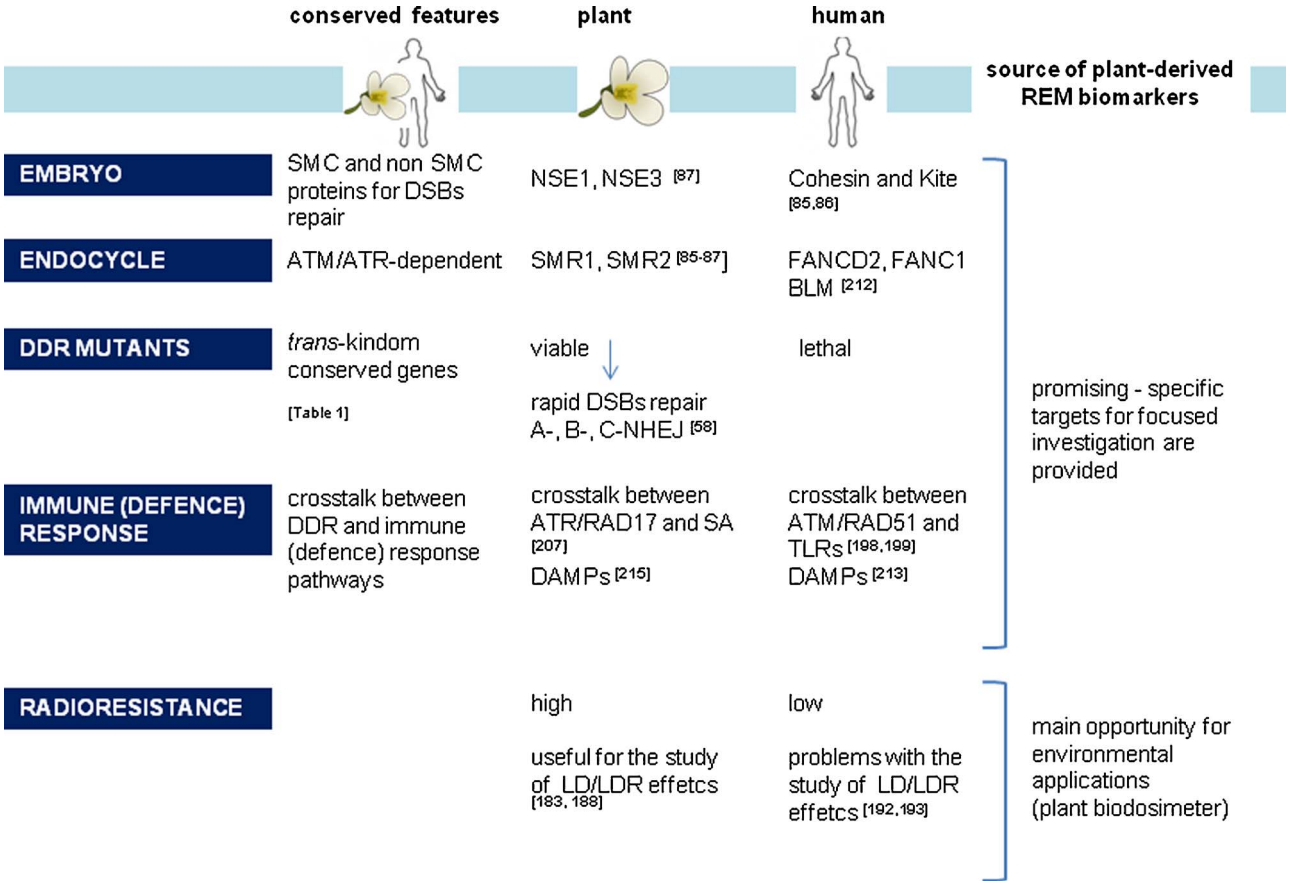

Fig. 2. Schematic representation of conserved and divergent aspects of the multi-faceted DDR in human and model plant *Arabidopsis thaliana*. For each DDR context (embryo, endocycle, mutants, crosstalk with immune or defence response, radioresistance), the most representative conserved and kingdom-specific gene signatures are indicated as well as the potential (promises and/or limitations) as a source of novel plant-derived REM biomarkers.

radiation exposure have been so far investigated in non-mammals (fish, rodents, pigs, donkeys, cows, bulls, sheep, goats, dogs, rabbits and monkeys) resulting into a heterogeneous profile of radiation sensitivity [211].

The current dosimetric approaches for assessing environmental risks in non-human biota rely on softwares that calculate the adsorbed energy within a defined geometry corresponding to the body of the target organism. The need for dynamic models able to integrate the temporal parameter into dose calculations has been underlined [212]. A dosimetry model for assessing dose rate and absorbed dose during *Arabidopsis* seedling development has been described and used to compare the dose/dose rate calculations for $^{(241)}$Am (α-radiation), $^{(90)}$Sr (β-radiation) and $^{(133)}$Ba (γ-radiation) radionuclides under laboratory conditions [213]. With this approach, the rapid changes in the plant organ (shoots and roots) geometry occurring during growth as well as changes in radionuclide up-take were estimated and then used to calculate dose rates and absorbed doses for each type of radiation. Results from this investigation showed that shoot dosimetry depends on the exposure time and type of radiation while root dosimetry was not so variable, thereby providing a robust dynamic dosimetry system for more realistic predictions of radiation effects in environments [213]. In this context, the concept of 'phytosensor' has emerged in recent years, based on the use of transgenic *Arabidopsis* plants with defective DNA repair able to express the green fluorescent protein as a function of genome instability triggered by IR exposure (the so-called 'Fukusensors') [214].

In a recent study, Nikitaki et al. [72] demonstrated the feasibility of an integrated approach for the search of novel REM biomarkers, using information available from plant and human databases to design a 'plant radiation biodosimeter'. The latter is defined as a platform including a collection of plant DDR genes, mostly derived from *Arabidopsis*, that show expression profiles useful as REM biomarkers for assessing environmental radiation exposure. Interestingly, the list contains a significant number of genes, both in human and *Arabidopsis*, not yet charaterized as DDR players, that will deserve future investigation.

4. Current expectations from the plant kingdom

Based on the picture hereby described, shall we forecast a future, concrete contribution of the plant kingdom to novel REM biomarkers? Caution should be taken when comparing animal and plant DDR, however the current knowledge is expanding and informations from different sources can be effectively integrated. Similarities between animals and plants at the level of DDR seem to be strong enough to support the discovery of novel REM biomarkers. From an evolutionary point of view, these similarities are even strengthened since studies on the phylogenetic relationships between archeal and eukaryal DDR proteins suggest the existance of a minimal pool of DDR genes in the last universal common ancestor (LUCA) [215]. The intricated network of DDR proteins subsequently evolved from this ancestral pool, displays similar pathways for the control of undesired genotoxic effects in bacteria, lower and higher eukaryotes, and plants.

Another crucial point is the need for comparing the largest number of systems, ranging from model organisms to 'real situation' studies. The latter should include experimental approaches designed on the real-time radiation exposure measurements in patients, as well as the screening for congenital malformations whereas for plants it would be advisable to expand field studies on the local communities or with species collected from contaminated sites.

At the moment, there are some aspects of the DDR process that might represent promising sources of plant-derived REM biomarkers (Fig. 2). Such DDR components offer novel sets of targets suitable for more in-depth investigations by means of 'omics' approaches. Considering the recent advances in the study of DNA repair mechanisms associated with early development, it should be noticed that embryogenesis and post-embryonic development in plants as well as germ cell development and zygotic reprogramming in animals represent an interesting example of comparable and informative systems, sharing some conserved players as SMC proteins [99,100,107]. Novel mechanisms have been recently disclosed in animal cells, providing insights into non-canonical DDR pathways. *Drosophila melanogaster* papillar cells have been used as model system to investigate the role of DNA repair in endocycle [216]. Despite the lack of conventional DDR pathways, these cells showed tolerance to enhanced DSBs accumulation responsible for consistent chromosomal damage. A non-canonical, ATM-independent DDR pathways was observed in *Drosophila* endocycling cells, involving the Fanconi anemia protein FANCD2, its partner FANCI and the Bloom (Blm) helicase (Fig. 1). FANCD2 promoted alignment and segregation of damaged chromosome fragments [216]. Thus, distinct DDR players act under emergency to overcome genotoxic injury. *Drosophila* cells represent a successful example of a working model useful to disclose unknown functions in DNA repair. The crosstalk beween DDR and immune response (animals) and defence response (plants) (Fig. 2) is a fascinating topic which is providing a consistent body of experimental evidences such as the involvement of conserved ATM/ATR-dependent pathways useful for retrieving additional REM biomarkers.

Another starting point for the search of plant-derived REM biomarkers would be definitely the production and characterisation of plant DDR mutants that are lethal in animals. These plant mutants could be powerful sources of information that otherwise would be lost in animals. Some of these mutants have brought to light the occurrence of the so-called 'rapid' DSBs repair rising in a DDR defective genetic background [71]. To date, only a few animal DDR genes have been expressed in plant cells [54] but what about the overexpression of those DDR genes unique to plants (Table 1) in animal cells? Do we expect that the plant genes will perturbate the animal endogenous DDR pathways in such a way that unknown potential functions will be manifested? It is difficult to answer but discussion on these issues should be encouraged.

Definitely, plant-based biomarkers should be extremely useful as exposure probes for monitoring radiation-mediated genotoxic damage. Would it be possible to expand the use of such biomarkers for the large-scale testing of pharmaceuticals? The potential application of plant cells as a reliable and low-cost alternative to animal models in pharmacological research, at least in preliminary large-scale cytotoxicity tests, is currently discussed, however this challenging idea still needs to be corroborated by deeper studies [217,218].

5. Concluding remarks

Interdisciplinary research provides powerful means to answer open-ended questions related to the urgent need for novel and reliable DNA damage biomarkers, or 'molecular signatures', that could significantly improve the current REM protocols. In this context, the fundamental mechanisms underlying the maintenance of genome integrity that are shared by animals and plants can be utilized efficiently. Knowledge is rapidly expanding, as evidenced in the present review, offering unique opportunities for identifying novel DNA damage biomarkers shared by the animal and plant kingdoms. Using meta-analysis and bioinformatics tools, comparative studies of plant and animal DDR genes can be performed to select the best candidate genes able to reveal, based on their expression profiles, the occurrence of radiation-induced genotoxic damage both in the biomedical and environmental context. Following experimental validation, this approach should hopefully lead to the systematic development of accurate biomarkers for clinical use and environmental applications.

Conflict of interest statement

None.

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