2015

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Redox Biology 6 (2015) 396–400

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Research paper

Role of nitric oxide in the radiation-induced bystander effect

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ARTICLE INFO

Article history:
Received 2 July 2015
Received in revised form
27 August 2015
Accepted 31 August 2015
Available online 1 September 2015

Keywords:
BRCA1
DNA double-strand break
Gap junction intercellular communication
Genomic instability
Homologous recombination repair
Non-homologous end-joining
Nitric oxide
Radiation-induced bystander effect
Reactive nitrogen species

ABSTRACT

Cells that are not irradiated but are affected by "stress signal factors" released from irradiated cells are called bystander cells. These cells, as well as directly irradiated ones, express DNA damage-related proteins and display excess DNA damage, chromosome aberrations, mutations, and malignant transformation. This phenomenon has been studied widely in the past 20 years, since its first description by Nagasawa and Little in 1992, and is known as the radiation-induced bystander effect (RIBE). Several factors have been identified as playing a role in the bystander response. This review will focus on one of them, nitric oxide (NO), and its role in the stimulation and propagation of RIBE. The hydrophobic properties of NO, which permit its diffusion through the cytoplasm and plasma membranes, allow this signaling molecule to easily spread from irradiated cells to bystander cells without the involvement of gap junction intercellular communication. NO produced in irradiated tissues mediates cellular regulation through posttranslational modification of a number of regulatory proteins. The best studied of these modifications are S-nitrosylation (reversible oxidation of cysteine) and tyrosine nitration. These modifications can up- or down-regulate the functions of many proteins modulating different NO-dependent effects. These NO-dependent effects include the stimulation of genomic instability (GI) and the accumulation of DNA errors in bystander cells without direct DNA damage.

1. Introduction

The radiation-induced bystander effect (RIBE) has been studied widely over the past 20 years, since the description of this phenomenon by Nagasawa and Little in 1992 [1]. It has been shown that irradiated cells release "stress signal factors" (SSFs) that affect adjacent cells or cells that have received the medium from irradiated cells. The role of a soluble transmissible factor(s) generated by irradiated cells that in turn induces toxic effects in non-irradiated cells has been demonstrated in many medium-transfer experiments (reviewed by [2]). Cells that are not irradiated but are affected by SSFs are called bystander cells. SSFs stimulate expression of DNA damage-related proteins, excess DNA damage, chromosome aberrations [3–5], mutations [6–9], and malignant transformation in bystander cells [10,11]. To identify SSFs, investigations of RIBE have measured either the ability of factors to be transferred from irradiated to non-irradiated cells by medium transfer or the response of cultures to low fluence of α-particles, wherein only a small percentage of cells were exposed. Using these approaches, several factors have been identified as playing a role in the bystander response. This review will focus on nitric oxide (NO), an important signaling molecule, and its role in the stimulation and propagation of RIBE.

2. RIBE and gap junctions

One controversy in studies on RIBE is whether RIBE is mediated directly by gap junction intercellular communication (GJIC) and/or diffusible cellular factors excreted from irradiated cells [12–16]. Gap junctions were favored candidates for explaining bystander effects because they form clusters of intercellular membrane channels connecting the cytoplasm of two neighboring cells. The phenomenon of the bystander effect mediated by GJIC derives originally from an observation in ganciclovir cancer gene therapy that gap junctions mediate the transfer of gene products from transfected to non-transfected cells, resulting in neighboring cell death [17]. Although gap junction communication has been shown to play an important role in the induction of bystander effects in

Abbreviations: BRCA1, breast cancer type 1 susceptibility protein; Cav-1, caveolin 1 protein; cGy, centigray; cNOS, constitutive nitric oxide synthase; c-PTIO, 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide; DSB, double-strand break; E2F4, transcription factor E2F4; eNOS, endothelial nitric oxide synthase; GJIC, gap junction intercellular communication; GI, genomic instability; HRR, homologous recombination repair; iNOS, inducible nitric oxide synthase; L-NAME, L-NG-nitroarginine methyl ester; MN, micronuclei; NHEJ, non-homologous end-joining; NO, nitric oxide; NOS, nitric oxide synthase; PP2A, protein phosphatase 2A; RBL2, retinoblastoma-like protein 2; RIBE, radiation-induced bystander effect; RNS, reactive nitrogen species; SSF, stress signal factor

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http://dx.doi.org/10.1016/j.redox.2015.08.018
2213-2317/

some cell systems [12], there is a growing number of reports of gap junction independent RIBE. It was shown that a bystander effect stimulated in human lung carcinoma cell lines or in a rat tumor cell line was not altered by gap junction inhibitors or enhancers [18]. Yang et al. (2005) demonstrated a bystander effect in X-ray irradiated human fibroblasts that was independent from gap junctional communications [19]. In his model, the irradiated and non-irradiated normal human skin fibroblast cells shared the medium, but never touched each other. Banaz-Yasar et al. (2008), in studies with co-cultured malignant trophoblasts, showed that RIBE was independent of direct cell-to-cell communication via gap junction channels and independent of connexin isoforms [20]. Moreover, Gerashchenko and Howell (2003) demonstrated that only cell proximity was a prerequisite for the bystander response of γ-irradiated cells and not gap junctional communication or soluble extracellular factors [21].

3. Ionizing radiation, NO, and the bystander effect

NO, generated from arginine by the activity of different isoforms of nitric oxide synthase (NOS), is a major signaling molecule in the immune, cardiovascular, and nervous systems (reviewed by [22]). The uniqueness of NO as a redox signaling molecule resides in part in its relative stability and hydrophobic properties that permit its diffusion through the cytoplasm and plasma membranes over several cell diameter distances [23]. NO does not need GJIC to reach bystander cells. Hence, stimulation of NO generation can affect different pathways within the cell in which it is produced and diffuse through cell membranes to modulate signaling pathways in bystander cells [24].

A number of studies have demonstrated activation of NOS and stimulation of NO production by low-dose irradiation. Matsumoto et al. have shown that X-ray irradiation activates inducible NOS (iNOS) expression as early as 3 h post-irradiation and iNOS activity continues to increase over a period of 24 h post-irradiation [25].

Just as iNOS activation has been reported to be important for the induction of late events of RIBE (such as the formation of micronuclei [MN]), activation of another type of nitric oxide synthase, constitutive NOS (cNOS), has been shown to stimulate the early signaling effects of low-dose irradiation. Leach et al. revealed that after 2 Gy of X-ray irradiation, the activity of cNOS is transiently enhanced at 5 min post-irradiation and by 30 min the activity has returned to basal levels [26]. In both phases NO can diffuse into and affect adjacent cells and stimulate RIBE.

DNA double-strand breaks (DSBs) are considered to be the most relevant lesion for the deleterious effects of ionizing radiation [27–29] and have been detected by several groups in bystander cells using γH2AX as a marker [5,19]. Han et al. demonstrated NO-dependent stimulation of DNA DSBs in bystander cells within 30 min of a low-dose radiation exposure [30]. The authors assumed that this early bystander effect was cNOS-dependent. Shao et al. [31,32] demonstrated a significant increase in the incidence of MN in non-irradiated bystander cells that were in the vicinity of cells irradiated through either the nucleus or the cytoplasm with a microbeam of α-particles. Pretreatment with a NO scavenger, 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide (c-PTIO), abolished excess MN formation. In another study, Han et al. revealed that stimulated cell proliferation and increased MN and DNA DSBs were observed simultaneously in the bystander cell population, which were co-cultured with cells irradiated by low-dose α-particles (1–10 cGy) [33]. NO played an essential role in simulation of these effects in the bystander cell population. Low concentrations of NO, generated by the NO-donor spermidine, were shown to induce cell proliferation, DNA DSBs, and MN simultaneously [33].

4. RIBE as an inflammatory-type response

Different factors can stimulate NO production in target cells and increase DNA damage in bystander cells. Generation of NO and reactive nitrogen species (NO/RNS) by iNOS is a critical feature of the inflammatory environment [34]. It has been shown that macrophage activation and inflammatory-type responses in the hemopoietic system are early consequences of exposure to ionizing radiation in vivo [35]. Irradiation, as well as stimulation of RAW 264.7 cells (a mouse leukemic monocyte macrophage cell line) by lipopolysaccharide-induced iNOS activity and NO generation, increased DNA damage in bystander cells [36,37]. Pretreatment of target macrophages or bystander cells with the competitive NOS inhibitor L-NAME significantly reduced the induction of gene expression and DNA damage in bystander cells.

How does NO stimulate DNA damage in the bystander cells? NO produced in inflamed or irradiated tissues mediates cellular regulation through posttranslational modification of a number of regulatory proteins. The best studied of these modifications are S-nitrosylation [38–40] and tyrosine nitration [41–43]. Tyrosine nitration is well-accepted marker of tissue inflammation and is gaining attention because of its impact on carcinogenesis and tumor growth. This protein posttranslational modification is mediated by reactive nitrogen species such as peroxynitrite anion ($ONOO^-$) and nitrogen dioxide ($\bullet NO^2$), formed as secondary products of NO metabolism in the presence of oxidants including superoxide radicals ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and transition metal centers [42,44]. Tyrosine nitration can up- or down-regulate the functions of many proteins [43,45–47]. Ionizing irradiation stimulates expression and activity of iNOS along with accumulation of tyrosine nitration within cellular proteins in a dose-dependent manner [48]. These effects are inhibited by N-[3-(aminomethyl) benzyl] acetamidine dihydrochloride, a specific inhibitor of iNOS. Exposure to ionizing radiation increased the production of tyrosine nitration in irradiated bone marrow cells in vivo and in co-cultured/non-irradiated clonal-dependent hematopoietic progenitor cell line. The induction of iNOS expression and iNOS-dependent release of nitric oxide in bone marrow stromal cells was observed within 24 h after irradiation and was similar in magnitude to that observed in cultures incubated with IL-1β and TNF-α [48].

Some authors hypothesize that moderate increases of NO stimulate proliferation and shorten the cell cycle in bystander cells, thus reducing the time to repair DSBs. Increased cell division might increase the probability of carcinogenesis in bystander cells because cell proliferation increases the probability of mutations from mis-repaired DSBs [33]. However, other researchers have shown that accumulation of bystander DNA damage is not dependent on the length of the cell cycle. Their results indicate that accumulation of bystander DNA damage is possible in non-proliferative cells with high transcription rates [49,50]. There is also evidence that radiation-induced genomic instability (GI) can be induced by indirect mechanisms [51,52] and that in both hemopoietic tissue [53] and mammary epithelium [54], there is genotype-dependent expression of the instability phenotype. Taken together, the data support the hypothesis that there is an inverse relationship between effective recognition of damage and expression of an instability phenotype.

Interactions between irradiated and non-irradiated hemopoietic cells stimulate GI in the last ones both in vitro and in vivo [51,52]. Activated macrophages are known to produce clastogenic factors, via the intermediacy of superoxide and NO, and are able to induce gene mutations, DNA base modifications, DNA strand breaks, and cytogenetic damage in neighboring cells [55]. One possible mechanism is NO-induced reduction of homologous recombination repair (HRR). I recently demonstrated that NO,

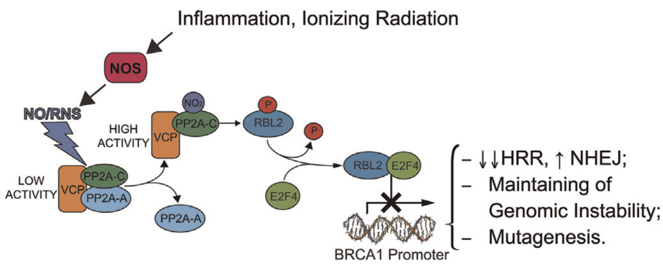

Fig. 1. Schematic representation of NO/RNS-dependent stimulation of genomic instability.

generated in macrophages, inhibits expression of breast cancer type 1 susceptibility protein (BRCA1) in co-cultured bystander cell lines [37]. BRCA1 protein contributes to cell viability in multiple ways, including HRR of DSBs, cell-cycle checkpoint control, mitotic spindle assembly, and regulation of chromosome segregation [56–58]. The loss of BRCA1 protein function predisposes individuals to the development of breast and ovarian cancers [59]. The key step of this mechanism is the NO-induced tyrosine nitration and activation of PP2A. Activated PP2A stimulates dephosphorylation of the RBL2 protein and the subsequent formation of the RBL2/E2F4 inhibitory complex, which binds to the proximal *BRCA1* promoter and represses BRCA1 protein expression [37] (Fig. 1). The same effects seen with the activation of PP2A and stimulation of RBL2/E2F4 inhibitory complex formation were shown after treating prostate carcinoma cells with ionizing radiation [60]. This inhibition of BRCA1 expression significantly reduces the ability of cells to repair DNA DSBs through HRR with a moderate increase in error-prone non-homologous end-joining (NHEJ) [37]. Hence, NO stimulates GI by inhibiting BRCA1 protein expression and shifting DNA DSB repair from high-fidelity HRR to error-prone NHEJ.

5. RIBE propagation

NOS activation and overproduction of NO after ionizing radiation not only affects cells with activated NOS with bystander cells, but also can stimulate specific mechanisms of the signaling amplification. When a few cells in the population are individually irradiated, signaling factors including NO are released from irradiated cells and react with adjacent non-irradiated cells. In turn, these cells are induced to release NO or other factors that facilitate the propagation of the initial event. With such a series of cascade reactions, the original signaling factors generated from the directly irradiated cells may be magnified so that a measurable RIBE can be propagated relatively far from the area of irradiation. This is similar to the field effect described in cancer biology. Recently, Martinez-Outschoorn et al. (2010) suggested that such field effect could be mediated and propagated by oxidative and nitrative stress in cancer-associated fibroblasts [61]. It was revealed that MCF7 (breast cancer) cells induce the downregulation of Cav-1 (an endogenous endothelial NOS (eNOS) inhibitor) in adjacent fibroblasts with subsequent overexpression of eNOS. Then, the eNOS-overexpressing fibroblasts downregulate Cav-1 in the next adjacent fibroblasts that do not express eNOS. As such, the effect of eNOS stimulation can be laterally propagated from cell-to-cell like a virus and even amplified [61]. This would then provide a ***"mutator field"*** resulting in widespread NO/RNS overproduction with subsequent propagation of GI.

If we accept NO/RNS-dependent mutagenesis as a completely stochastic process, we can postulate that the efficacy of mutagenesis (ME) and carcinogenesis in ***"mutator fields"*** depends on the area of the field with NO/RNS-stimulated genomic instability (FA), the strength of NO/RNS maintained genomic instability (SGI), and the duration of this field maintenance (FD). This can be illustrated by the equation below:

$$ME = FA^{*} \times FD \times SGI^{**}$$

This is a simplified equation: *it is obvious that number of actively divided cells involved in the FA cannot be always constant; **SGI can demonstrate a different strength along the mutagenic field. It is also obvious, that if any of the factors of the equation (FA, FD, or SGI) is inappreciable, then the efficacy of the mutagenesis is inappreciable too. Hence, all these factors are equally important for the development and maintenance of the mutagenesis. For example, acute inflammation can produce a very high concentration of NO/RNS and, as a result, very high level of SGI in the affected area. However, relatively short duration of this effect (FD) leads to a very low level of ME. On another hand, chronic inflammation demonstrates moderate level of SGI, but with the long duration of this condition (high FD) can simulate the high ME. Hence, according with the equation (for the same level of FA) chronic inflammation would demonstrate higher level of ME compared with the acute inflammation. This conclusion is supported by numerous studies of the different research groups [62–65].

6. Conclusion

This mini-review has attempted to introduce the role of NO in the stimulation and propagation of RIBE. Hydrophobic properties of NO, which permit its diffusion through the cytoplasm and plasma membranes, allow this signaling molecule to easily spread from irradiated cells to bystander cells without the involvement of GJIC. Propagation of NO and its effects from irradiated cells to bystander cells is not limited by the distance of NO diffusion. The ability to downregulate Cav-1 expression in bystander cells allows NO to stimulate eNOS and produce additional NO. Hence, bystander cells become secondary sources of NO generation with the creation of a wide ***"mutator field"***. Further research is needed to determine the mechanisms and the role of the NO in the development of a ***"mutator field"***. It could be assumed that pretreatment with NOS-inhibitors or NO-scavengers could significantly attenuate the strength and propagation of RIBE.

The mechanisms of RIBE-activated GI are similar to the mechanisms of GI during inflammation. Excessive generation of NO in irradiated cells can stimulate the GI in these cells as well as in the bystander cells. One of these mechanisms involves NO-dependent inhibition of BRCA1 expression with a subsequent downregulation of DNA HRR and shift to the error-prone NHEJ (Fig. 2). Hence, accumulation of DNA errors in bystander cells is most likely a result of decreasing the ability of these cells to properly repair DNA errors that constantly arise during normal DNA replication.

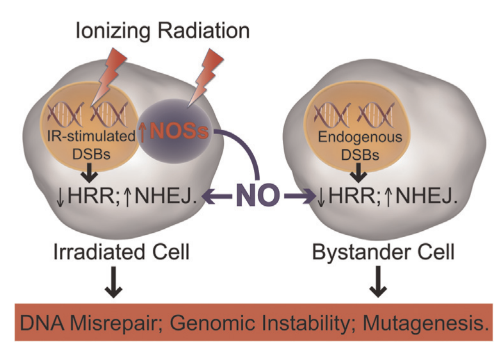

Fig. 2. Activation of NOSs in irradiated cells leads to NO-dependent down-regulation of HRR/NHEJ ratio with subsequent maintenance of genomic instability in both irradiated and bystander cells.

Additional research is needed to clarify whether the NO-dependent promotion of survival and proliferation of bystander cells further stimulates accumulation of DNA errors in these cells.

Acknowledgments

This work was supported by the American Cancer Society Grant IRG-73-001-37 and by the National Institutes of Health Grant 5R01CA090881. The author thanks Heidi Sankala for editorial assistance with the manuscript.

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