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Radiation-induced Bystander Effect and Its Possible Countermeasures

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Abstract

Ionizing radiation has been indispensable to medical diagnosis. In cancer, radiation therapy or radiotherapy (RT) offers patients a better chance of survival. It destroys cancer by depositing high-energy radiation on the cancer tissues, though it may directly damage a few normal cells. Therefore, the total radiation dose is administered in fractionated modalities over weeks or months. However, experimental evidence indicates that the irradiated cancer cells subsequently release cytokines in the blood that enter into nearby unirradiated nuclei/cells through several signaling pathways and cause radiation-induced bystander effects (RIBEs) such as DNA damage, chromosomal instability, mutation, and apoptosis in them as side effects of RT. Recently, many combined therapeutic protocols consisting of a few natural and synthetic products have been proposed to minimize RIBEs. This article reviews the present understanding of RIBEs and their possible countermeasures. Besides, a new protocol of combined therapy of nanoparticle-based ion treatment (NIT) and RT to minimize RIBEs has been proposed.

Keywords: Cancer, Radiation, RIBEs, Combined therapy, Nanoparticles, Ions

Introduction

Cancer continues to be a pervasive disease, and its management is a rising concern in an aging population [1,2]. Radiation therapy or radiotherapy (RT) is an effective treatment for cancer and management, conferring survival and palliative benefits [3-5]. For years, the belief was that the significant biological effects, or death, induced by ionizing radiation (IR) in mammalian cells were the direct consequence of radiation-induced unrepaired or misrepaired DNA damage in the irradiated cells [6], and no effect in cells that receive no direct radiation traversal. However, in 1992, an experiment revealed that 1% of cells irradiated with α-particles led to chromatid exchange in more than 30% of cells. It occurs due to the inter-relationship between irradiated and unirradiated cells and is called the radiation-induced bystander effect (RIBE) [7]. RIBE is the biological alterations manifested in unirradiated cells, called bystander cells, induced by signals from nearby irradiated cells within an irradiated volume [8]. Both bystander and irradiated cells exhibit genetic damage, chromosome aberrations, and possibly cancer formation [9].

The RIBE can be described in medium transfer experiments [10,11], in which a cell culture medium is harvested from irradiated cells to treat unirradiated cells. Unirradiated cells (either healthy or cancerous) that received the irradiated cell-conditioned medium (ICCM) show lethal mutations and marked cell death [12]. The mechanism of bystander signal transmission has become a fascinating topic of research. For example, Ariyoshi *et al.* reported that exosome-like vesicles (ELV) mediate the radiation-induced bystander signal from irradiated cells [13]. They observed DNA damage in normal human fibroblast cells cultured with ICCM ELV and mouse serum ELV irradiated with a 4 Gy of X-ray dose. Another report indicated that irradiated MCF-7 breast cancer cells could induce bystander death in unirradiated MCF-7 and hFOB 1.19 (human osteoblast) bystander cells where the bystander signal was mediated by the reactive oxygen species (ROS) generation during the irradiation with HDR brachytherapy [14]. Chen *et al.* reported that the up-regulation of ROS by mitochondria-dependent bystander signaling (γ-H2AX) contributes to the genotoxicity of bystander effects [15].

In addition to the bystander signaling mechanisms, investigation of the dependence of signal strength on various irradiation parameters such as dose and post-irradiation aging of targeted cells is also necessary. Mukherjee *et al.* studied the effect of dose-varied ICCM, collected at different post-irradiation times, on DNA damage and apoptosis of bystander cells [16]. In their study, different sets of culture media of human hepatocellular carcinoma HepG2 cells had undergone irradiation by γ-rays with doses of 2, 5, and 8 Gy; the respective ICCM was collected in the early and late post-irradiated stages (1, 2, and 24 h) to transfer to unirradiated cells. This study showed that compared to control (the directly irradiated cells), bystander cells had an increased level of H2AX phosphorylation, mitochondrial membrane depolarization, and elevation of intrinsic apoptotic pathway mediators such as p53, Bax, cas9, cas3, and PARP cleavage. These intrinsic apoptotic pathways in a nearby unirradiated cell (bystander cell), mediated by the bystander signals released from irradiated cell, is shown by the sketch in the scenario (1) in **Figure 1** following reference [16]. The highest expression of the apoptosis markers was observed in 8 Gy irradiation-induced bystander cells, and the ICCM collected at the early time (1 or 2 h), though the 24 h ICCM induced the highest increase of H2AX and p53 phosphorylation and Bax levels.

Possible routes of the bystander effect involve gap-junction intercellular communications, soluble signal molecules, oxidative metabolism, plasma membrane-bound lipid rafts, and calcium fluxes [17-20]. Exposure to radiation causes unrepairable DNA damages, especially double-stranded breaks (DSBs), leading to the accumulation of p53 [21], a protein that stimulates the expression of pro-apoptotic mediators, thereby disrupting the intricate balance between cellular anti-apoptotic and pro-apoptotic proteins [16].

The transmission of bystander effects among cancer cells involves the activation of inflammatory cytokines, death ligands, and reactive oxygen/nitrogen species (ROS/RNS). Besides bystander effects, two other non-target effects (NTEs) in radiotherapy are the cohort and abscopal effects. In cohort effects, irradiated cells can produce signals that reduce the survival of neighbouring cells within an irradiated volume suggesting the importance of cellular communication under irradiation with non-uniform dose distribution. In abscopal effects, the NTEs typically occur in distant non-irradiated cells from an irradiated target, mediated primarily by immune cells such as T cells [22].

The availability of micro-beams that can deposit energy

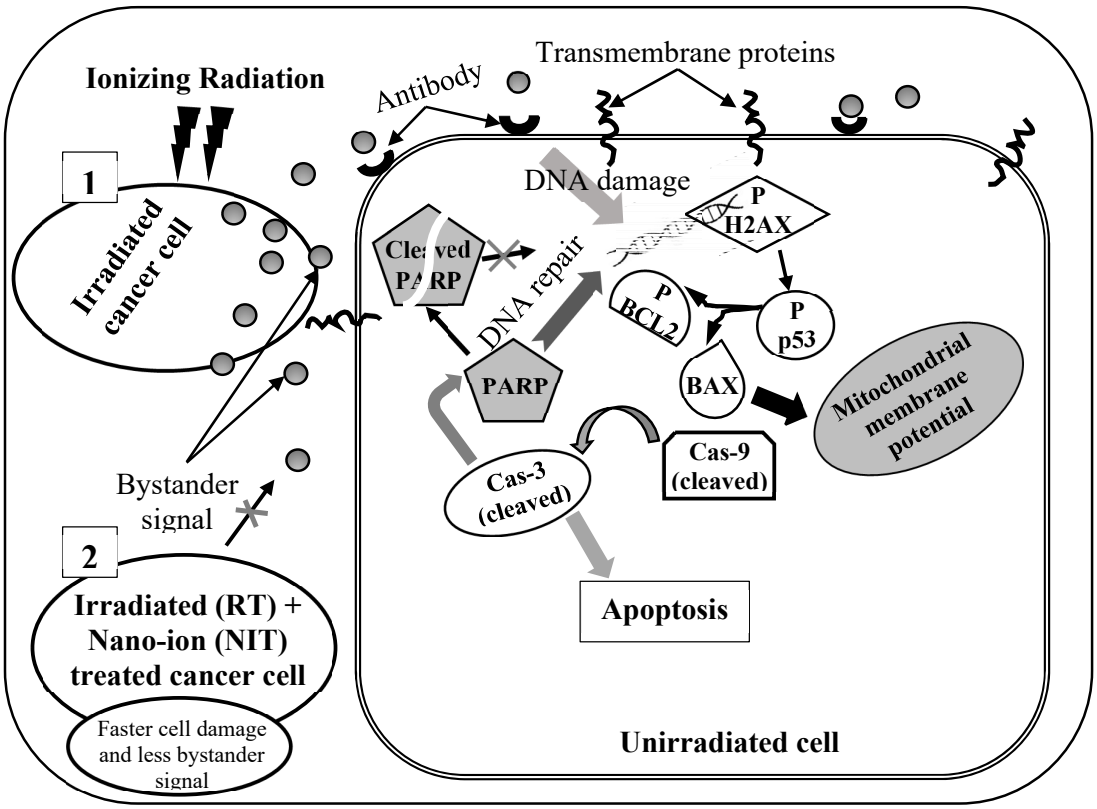

Figure 1. (1) These intrinsic apoptotic pathways in a nearby unirradiated cell (bystander cell), mediated by the bystander signals released from irradiated cell, reference [16], **(2)** irradiated (RT) and ion-treated (NIT) cell release less or no bystander signal.

precisely to a part of the cell (such as the cytoplasm or nucleus) makes it possible to investigate the damage caused by irradiation of the nuclei versus the cytoplasm in a different manner [23]. It has been generally accepted in radiation biology that genotoxic effects, such as mutations and carcinogenesis, attributed to ionizing radiation exposure mainly result from direct damage to the nuclei. The extra-nuclear, i.e., cytoplasmic, irradiation may result in mutations in the nuclei. It has shown that cytoplasmic irradiation of human–hamster-hybrid (A_L) cells with eight alpha particles led to around a threefold increase in CD59 mutations while inflicting minimal cytotoxicity [24]. More recent studies demonstrated that cytoplasmic irradiation is associated with mitochondrial dysfunction [25] and autophagy [26]. Cytoplasmic irradiation can also induce a bystander effect, exhibiting genotoxic effects such as a mutation in directly and indirectly irradiated cells [27].

Cell Signaling Pathways of RIBE and Their Inhibition

Figure 1 shows the sketch of a few signaling pathways of RIBE in nearby bystander cells, as reported by Mukherjee *et al.* [16]. Although gap junction communication and the presence of soluble mediator(s) are both known to play crucial roles in the bystander response, the specific cell signaling molecules are yet to identify. Researchers at Columbia University showed that the cyclooxygenase-2 (COX-2, also known as prostaglandin endoperoxide synthase-2) signaling cascade plays an essential role in the bystander process using the charged particle beam [28]. Also, the Cox-2 activity gets suppressed when bystander cells are treated with NS-298, an anti-inflammatory agent [29]. It reduces the bystander effect drastically.

Multiple signal transduction pathways stimulated by IR are mediated by the mitogen-activated protein kinase (MAPK) superfamily, including extracellular signal-regulated kinase 1/2 (ERK 1/2), c-Jun NH_2-terminal kinase (JNK) and p38 [20]. Various signals reaching the cell membrane activate MAPK pathways [30]. Radiation-induced oxidative stress induces multiple effects on cellular macromolecules and signaling cascades. Mukherjee *et al.* studied the consequences of ICCM, from γ-irradiated hepatocellular carcinoma (HepG2) cells, on the oxidative stress induction in bystander HepG2 and normal liver cells (BRL-3A) and their interactions with critical cell signaling mediators [31]. The experimental outcome revealed that the levels of pro-survival signaling factors (p-PI3K, p-Akt, p38-MAPK, p-JNK, and p-NF-κB) increase in bystander HepG2 cells but significantly decrease in bystander BRL-3A cells. Enhanced ROS levels down-regulate the activation of PI3K, Akt, JNK, and NF-κB in BRL-3A cells but add to the activation of DNA damage sensor ATM (ataxia telangiectasia mutated) kinase and cell cycle inhibitor p21.

Yin *et al.* reported that α-particle irradiation activates the TGF-β1-Smad2 (tumor growth factor β1-mothers against decapentaplegic homolog 2) pathway and consistently decreases the miR-21 level in HaCaT keratinocyte cell lines, which subsequently induces bystander micronucleus formation in unirradiated WS1 fibroblasts after co-culture. On the other hand, X-ray irradiation did not prompt a bystander effect in unirradiated WS1 cells and did not trigger the Smad2 pathway or decrease the miR-21 level in irradiated HaCaT cells [32]. IR activates TGF-β-Smad pathways [33]. Smad2 and Smad7 play a significant role in radiation-induced double-strand break (DSB) signaling [34].

Chen *et al.* investigated the bystander effect due to different types of irradiation, including gamma and lithium-ion, in the model human neuroblastoma cell line (SH-SY5Y) [35]; the gamma and lithium-ion irradiations cause several bystander effects in the unirradiated SH-SY5Y cell lines; for example, promotion of cell proliferation through activation of the ERK and AKT signaling pathways by the gamma irradiation, with minimal effect on the cell cycle of unirradiated SH-SY5Y cells. In contrast, lithium-ion irradiation inhibited cell proliferation, arrested the cell cycle, and activated the process of pro-apoptosis [35].

MAPK pathways link to the growth factor-mediated regulation of cellular events such as proliferation, senescence, differentiation, and apoptosis. Activation of multiple MAPK pathways, such as the ERK, JNK, and p38, has been shown to occur after exposure of cells to radiation and a variety of other toxic stresses. Lyng *et al.* investigated MAPK signaling pathways in bystander cells exposed to ICCM and the role of oxidative metabolism and calcium signaling in the induction of bystander responses [36]. These authors had irradiated HPV-G keratinocyte cell lines with varying doses, in the range of 0.005–5.0 Gy, using a cobalt-60 teletherapy unit, and then the media were harvested for 1-hour post-irradiation and, subsequently, transferred to the recipient HPV-G cells. It activated JNK and ERK proteins in bystander cells after exposure to ICCM. On the other hand, inhibition of the ERK pathway increases bystander-induced apoptosis, while inhibition of the JNK pathway decreases apoptosis.

Countermeasures for RIBE

Radiation-induced bystander signals cause various side effects (i.e., RIBEs), which commonly appear as changes in the skin (such as itching, peeling, and blistering) and fatigue; other side effects, such as diarrhea, nausea, hair loss, and vomiting depend on the exposed area of the body. Although most side effects tend to subside within a few weeks or months of completing radiation therapy, some may last for a longer time.

Many natural herbs help manage RIBEs to some extent. For example, curcumin (an antioxidant and anti-inflammatory compound found in turmeric) may help protect against radiation-induced skin damage, and *Ginkgo biloba* (a Chinese tree) may help shield against organ damage. Other natural antioxidants such as caffeine, melatonin, flavonoids,

polyphenols, and phytochemicals (e.g., albana) help decrease radiation-induced damage in either plasmid or cellular DNA through scavenging of oxygen radicals and/or peroxides [37-42]. Several investigations revealed that those who take probiotics throughout their radiotherapy for various types of cancer are less likely to experience radiation-induced diarrhea [43-45].

In a review article, Zhang *et al.* discussed the radioprotective properties of antioxidants and what those properties tell about the DNA and other cellular targets of radiation [46]. The radiation-induced DNA damage causes genotoxicity; preventing this damage requires an antioxidant during irradiation [47]. Two ways it may work, either (1) react with all the oxygen-related free radicals and detoxify them to radicals that are not themselves genotoxic, and/or (2) effectively compete with oxygen in chemically repairing the DNA damage through reactions with free radicals. For example, thiol-based compounds are especially capable of scavenging oxygen radicals and affecting the chemical restoration of some forms of DNA damage with the subsequent formation of sulphur-based radicals, which are non-reactive to DNA [48]. The incorporation of one or more positive charges on the thiol-based antioxidant has the effect of changing the proximity of the compound to the DNA [49,50]. The resulting counter-ion condensation between the positive charge of thiol and the negatively charged sugar-phosphate backbone of the DNA binds the thiol close to the DNA, facilitating the competition of the thiol with oxygen in reactions with DNA radicals, thereby reducing the DNA damage and increasing the cell survival [50,51].

A review article has discussed the advantages of using mesenchymal stem cells (MSCs) in combination with radiation therapy to treat rectal cancer [52]. This combined therapy on xenotumors, implanted in a murine model, showed the existence of a synergic mechanism that enhances the local and systemic actions of the radiation both on the treated tumor and its possible metastasis. These authors remarked that the physicochemical tropism of MSCs and the widespread functions of macromolecules, proteins, and exosomes released from activated MSCs have the effect of counteracting the pro-tumorigenic and pro-metastatic signals that contribute to the growth, spread, and resistance of the tumor cells in this combined therapy.

Application of Nanoparticles

Further research reveals that radiosensitizer agents made of high atomic number (Z) materials selectively increase the toxicity of radiation to the cancerous area and lessen the effect on healthy tissue [53-55]. Metallic/metal oxide nanoparticles such as gold nanoparticles (Au NPs), platinum nanoparticles (Pt NPs), iron oxide nanoparticles (Fe_3O_4 NPs), and bismuth oxide nanoparticles (Bi_2O_3 NPs) work as radiosensitizers and can increase the effect of radiation on cancerous areas by increasing the dose deposition in the target amount [56-59]. Recently, Rahman *et al*. explored the cellular outcomes of bismuth oxide nanoparticles (Bi_2O_3 NPs) on human breast cancer (MCF-7) and human fetal osteoblast (hFOB 1.19) cells due to the RIBE after irradiation with 6 MV clinical photon beam [60]. Bi_2O_3 NPs work as a radiosensitizer that increases the survival rate of the treated bystander cells (MCF-7 and hFOB 1.19) up to approximately 3–8% following a short and long-term incubation with ICCM treated with Bi_2O_3 NPs. Radiation causes the emission of more secondary electrons when metallic nanoparticles are present in the cells. The interaction of radiation with nanoparticles creates hydrolysis of water molecules within the cells and generates free radicals, which interact with DNA and cause excessive damage to them and cell death. Thus, it enhances the radiation treatment efficacy [61].

Functional nanomaterials have also been investigated for several other cancer therapeutic applications, such as photodynamic (PDT) and photothermal therapy (PTT) [62]. In PDT, the photosensitizer accumulates in cancerous sites; when irradiated with light, singlet oxygen and other cytotoxic reactive oxygen species (ROS) are generated that cause apoptosis and/or necrosis [63]. PTT uses materials with high photothermal conversion efficiency to elevate the temperature of targeted cancerous areas, leading to cancer cell death. Superparamagnetic iron oxide nanoparticles (SPION) have been investigated for cancer hyperthermia treatment due to their smaller size, higher targeting specificity, controllable releasing speed, and immune evasion capability [64].

Ion-conjugated Charged Nanoparticles (ICNPs): A New Proposal

Ion-conjugated charged nanoparticles (ICNPs) are surface-coated with counterion-conjugated charged molecules such as surfactants, citrates, or phosphates. The surface charge helps electrostatically binding ICNPs with oppositely charged biomolecules such as proteins and, subsequently, the release of counterions that intercalate into the bound molecules and irreversibly denature them [65-68]. This type of mechanism has the name 'reverse charge parity counterion' (RCPC) interaction [69], where the charge density (charge/volume) of counterions is an important parameter [70]. The denatured proteins lose their bio-functionalities [71]. Earlier, our *in vitro* experiment showed that the RCPC interaction causes cell membrane rupture and subsequent necrotic collapse of the cancer cell lines in the culture medium [72]. It gives hope that nanoparticle-based ion therapy (NIT) can be developed for cancer treatment to avoid using drugs, radiation, or surgery.

In this article, the author propose a new protocol in the following steps for a combined therapy using NIT and RT to minimize RIBE:

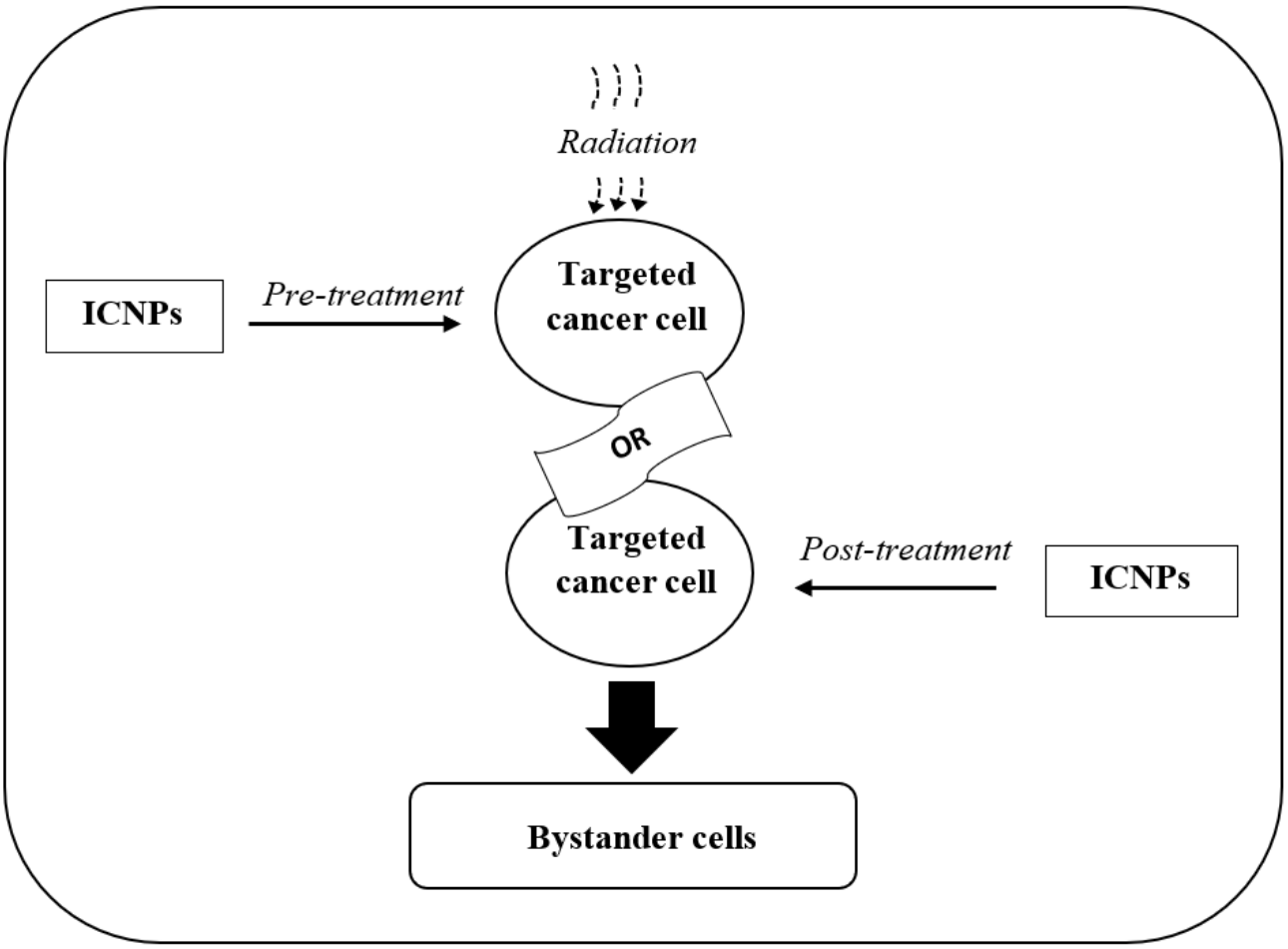

Figure 2. Schematic presentation of the proposed combined (NIT+RT) therapy.

(i) Pre-treat the target cancer cells with ICNPs before radiation treatment (RT), or post-treat target cancer cells with ICNPs after RT, or simultaneous NIT and RT, and

(ii) Incubation of NIT+RT treated cells with bystander cells.

NIT has its way of damaging target cells besides that due to RT. Consequently, target cells will die earlier than a pure RT; thus, the release of bystander signals will reduce. It is shown by the sketch in the scenario (2) in **Figure 1**.

A schematic presentation of the above protocol is shown in **Figure 2**. Work on this new protocol of combined therapy (NIT + RT) is undergoing, and the outcome will be published soon. On successful completion, a clinical test will follow. For clinical applications, a model ICNP has been proposed in our earlier review article [73].

Conclusion and Future Proposal

The author has reviewed research articles on the radiation-induced bystander effects (RIBEs) in unirradiated cells. Radiation causes several damages, such as unrepairable DNA damage in the nuclei of the targeted cells, which, in turn, induces apoptosis in the irradiated cells. However, nearby unirradiated cells (called bystander cells) get equally affected by the signals (called bystander signals) released from the irradiated cells; this is called RIBE. Recent reports suggest some combined therapies to countermeasure RIBE using herbal agents, antioxidant agents, mesenchymal stem cells (MSCs), or nanoparticles in addition to radiotherapy (RT). In this review article, the author has proposed a new therapeutic protocol to countermeasure RIBE using a nanoparticle-based ion treatment (NIT), with ion-conjugated charged nanoparticles (ICNPs), of the targeted cancer cells, either before or after RT. This protocol involves a nano-bio interaction model called

'reverse charge parity counterion' (RCPC) interaction, which causes necrotic death of the targeted cancer cells. In RT, a combination of NIT can inhibit bystander signal release in the medium.

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