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## Review

# Role of ion channels in ionizing radiation-induced cell death<sup>☆</sup>



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## ABSTRACT

Neoadjuvant, adjuvant or definitive fractionated radiation therapy are implemented in first line anti-cancer treatment regimens of many tumor entities. Ionizing radiation kills the tumor cells mainly by causing double strand breaks of their DNA through formation of intermediate radicals. Survival of the tumor cells depends on both, their capacity of oxidative defense and their efficacy of DNA repair. By damaging the targeted cells, ionizing radiation triggers a plethora of stress responses. Among those is the modulation of ion channels such as Ca<sup>2+</sup>-activated K<sup>+</sup> channels or Ca<sup>2+</sup>-permeable nonselective cation channels belonging to the super-family of transient receptor potential channels. Radiogenic activation of these channels may contribute to radiogenic cell death as well as to DNA repair, glucose fueling, radiogenic hypermigration or lowering of the oxidative stress burden. The present review article introduces these channels and summarizes our current knowledge on the mechanisms underlying radiogenic ion channel modulation. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

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## Contents

1. Introduction . . . . .	2657
2. Radiotherapy . . . . .	2658
3. Radiosensitizing ion channels . . . . .	2658
4. Ion channels conferring intrinsic radioresistance . . . . .	2659
5. Ion channels in acquired radioresistance . . . . .	2660
6. Concluding remarks . . . . .	2661
Acknowledgment . . . . .	2662
References . . . . .	2662

## 1. Introduction

Ionizing radiation kills or inactivates cells mostly by damaging the nuclear DNA and cell survival critically depends on successful repair of the DNA damage [1]. Ionizing radiation may lead to necrotic as well as apoptotic cell death depending on cell type, dose and fractionation protocols [2]. The major death pathway in this scenario in normal tissue cells is apoptosis. However, cancer cells which often have developed strategies to evade apoptosis [3] may either undergo (regulated) necrosis or reenter the cell cycle with accumulated DNA damages. During the

subsequent cell divisions those cells will not be able to segregate the chromosomes and end up as multinucleated giant cells in mitotic catastrophe. Mitotic catastrophe again leads either to apoptotic or necrotic cell death. Another possible mechanism of radiation-induced death in cells with disturbed apoptosis machinery is excess autophagy. While autophagy is a survival strategy [4] excess autophagy overdigests the cytoplasm and cell organelles forcing the cell into apoptosis or necrosis [5].

Meanwhile, the evidence is overwhelming that ion channels fulfill pivotal functions in cell death mechanisms such as apoptosis (for review see the article by Annarosa Arcangeli in this special issue on “Membrane channels and transporters in cancers”) as well as in stress response and survival strategies. Notably, tumor cells have been demonstrated to express a set of ion channels which is different to that of the parental normal cells. These channels may fulfill specific oncogenic functions in neoplastic transformation, malignant progression or tissue

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invasion and metastasis (for review see [1]). In addition, they may contribute to the cellular stress response for instance during fractionated radiation therapy and may confer radioresistance.

The present review intends to sum up data on ion channel function in the stress response to ionizing radiation. In particular, ion channels that may induce cell death in tumor cells and facilitate radiogenic cell killing are introduced. In addition, data on ion channels which, in contrast to the before mentioned, confer radioresistance are reviewed. Finally, ion channels of tumor cells that might contribute to acquired radioresistance, e.g. by promoting radiogenic hypermigration or transition into relatively radioresistant cancer stem (cell)-like cells (CSCs) are described. Prior to that, a brief introduction into radiotherapy and its radiobiological principles is given in the next paragraphs.

## 2. Radiotherapy

Radiation therapy together with surgery and systemic chemotherapy is the main pillar of anti-cancer treatment. About half of all cancer patients receive radiation therapy, half of all cures from cancer include radiotherapy [6]. Despite modern radiation techniques and advanced multimodal treatments, local failures and distant metastases often limit the prognosis of the patients, especially due to limited salvage treatments [7].

Ionizing radiation impairs the clonogenic survival of tumor cells mainly by causing double strand breaks in the DNA backbone. The number of double strand breaks increases linearly with the absorbed radiation dose. The intrinsic capacity to detoxify radicals formed during transfer of radiation energy to cellular molecules such as H<sub>2</sub>O (giving rise to hydroxyl radicals,  $\cdot$ OH) and the ability to efficiently repair DNA double strand breaks by non-homologous end joining or homologous recombination determines the radiosensitivity of a given tumor cell. Irradiated tumor cells which leave residual DNA double strand breaks un-repaired lose their clonogenicity meaning that these cells can not restore tumor mass (for review see [8]).

In addition to these intrinsic resistance factors, the microenvironment may lower the radiosensitivity of tumor cells. Hypoxic areas are frequent in solid tumors reaching a certain mass. Tumor hypoxia, however, decreases the efficacy of radiation therapy [9]. Ionizing radiation directly or indirectly generates radicals in the deoxyribose moiety of the DNA backbone. In a hypoxic atmosphere, cellular thiols can react with those DNA radicals resulting in chemical DNA repair. At higher oxygen partial pressure, in sharp contrast, radicals of the deoxyribose moiety are chemically transformed to strand break precursors [10]. By this mechanism, hypoxia increases radioresistance by a factor of two to three (oxygen enhancement ratio) [11].

Fractionated treatment regimens which improve recovery of the normal tissue after irradiation but not of the tumor have been established in radiotherapy [12]. In addition to limit normal tissue toxicity, killing of tumor mass by initial radiation fractions has been demonstrated to reoxygenate and thereby radiosensitize solid tumors during further fractionated radiotherapy. Beyond that, fractionated radiation regimens aim to redistribute tumor cells in a more vulnerable phase of the cell cycle in the time intervals between two fractions [13]. Accelerated repopulation of the tumor after irradiation is a frequently reported phenomenon. Possible mechanisms of accelerated repopulation include induction of CSCs: It has been proposed that radiation therapy induces CSCs to switch from an asymmetrical into a symmetrical mode of cell division; i.e., a CSC which is thought to normally divide into a daughter CSC and a lineage-committed progenitor cells is induced by the radiotherapy to divide symmetrically into two proliferative CSC daughter cells. This is thought to accelerate repopulation of the tumor after end of radiotherapy. Importantly, CSCs are thought to be relatively radioresistant possibly due to i) high oxidative defense and, therefore, low radiation-induced insults, ii) activated DNA checkpoints resulting in fast DNA repair, and iii) an attenuated radiation-induced cell cycle redistribution [14].

Finally, fractionated radiation therapy, which applies fractions of sublethal radiation doses (usually 2 Gy per fraction), has been demonstrated in a variety of tumor entities *in vitro* and in animal models to stimulate hypermigration and hypermetastasis of tumor cells as well as infiltration of the tumor by CD11b-positive myeloid cells and subsequent vasculogenesis. It is tempting to speculate that radiogenic hypermigration boosts cellular interaction of tumor cells with non-tumor cells, e.g. endothelial cells. It has been proposed that CSCs lodge within perivascular niches where a complex regulatory network supports CSC survival [15]. As a matter of fact, CSCs but not non-CSCs gain radioresistance when transplanted orthotopically in mice [16] supporting the idea of a tumor microenvironment-dependent acquired radioresistance. Ion channels contribute to both, intrinsic and acquired radioresistance of tumor cells as discussed in the next paragraphs

## 3. Radiosensitizing ion channels

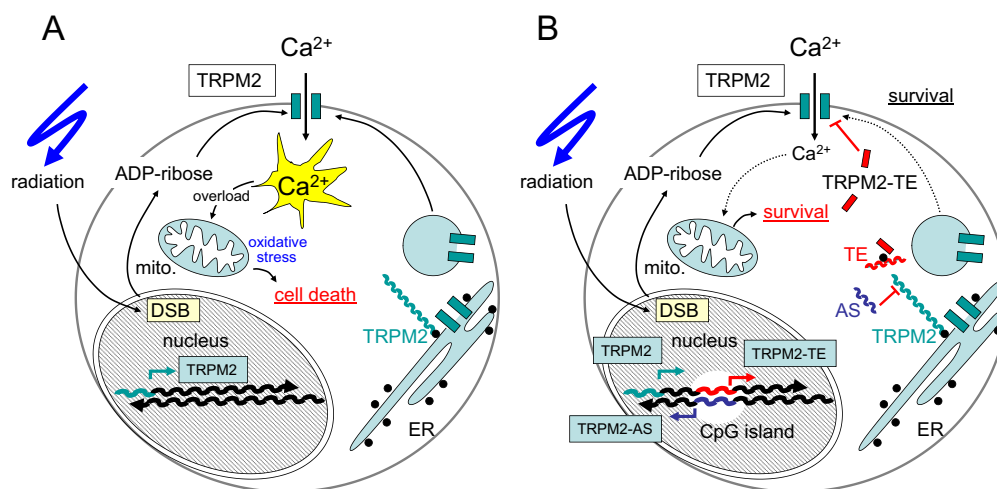
Member 2 of the melastatin family of transient receptor potential channel (TRPM2) is a Ca<sup>2+</sup>-permeable nonselective cation channel. Heterologous expression of TRPM2 in human embryonic kidney cells [17] or A172 human glioblastoma cells [18] facilitates oxidative stress-induced cell death. Reactive oxygen species (ROS) have been demonstrated to trigger TRPM2 activation [19,20]. The principal activator, however, of TRPM2 is ADP-ribose (ADPR) that binds to a special domain located at the C-terminus of the channel [21,22]. Sources of ADPR are the mitochondria [23] or ADPR polymers. The latter are formed, e.g., during DNA repair by poly (ADP-ribose) polymerases (PARPs). ADPR is released from the ADPR polymers by glycohydrolases [21,24].

Expression of TRPM2 has been demonstrated in several tumor entities such as insulinoma [25], hepatocellular carcinoma [25], prostate cancer [26], lymphoma [27], leukemia [28] and lung cancer cell lines [29]. TRPM2 activity increases the susceptibility to cell death [30] probably by overloading cells with Ca<sup>2+</sup> (Fig. 1A).

Remarkably, cancer cells may evade TRPM2-mediated cell death. In lung cancer cells, de-methylation of a CpG island within the TRPM2 gene gives rise to new promoters that regulate transcription of a non-functional truncated TRPM2 channel [29] and to a TRPM2 specific antisense RNA. This antisense RNA inhibits TRPM2 translation. Moreover, the truncated channel is non-functional and acts dominant negative, thus switching off the tumor-suppressing function of the full-length TRPM2 protein [29] (Fig. 1B).

The initially described member of the vanilloid family of TRP channels, the nociceptive and heat receptor TRPV1, is reportedly expressed in several tumor entities such as uveal melanoma [31], pancreatic [32] and prostatic neuroendocrine tumors [33], glioblastoma [34] and urothelial cancer of human bladder [35]. At least in the latter two tumor entities, TRPV1 exerts anti-oncogenic effects [35,36]. TRPV1 expression inversely correlates with glioma grading [34]. Remarkably, neural precursor cells have been demonstrated to induce ER stress-mediated cell death of glioblastoma cells by activating glioblastoma TRPV1 channels through secretion of endogenous vanilloids [37]. Along those lines is the observation that a TRPV1 antagonist promotes tumorigenesis in mouse skin [38].

Notably, targeting of TRPM2 and TRPV1 by RNA interference has been demonstrated to decrease gamma irradiation-induced formation of nuclear  $\gamma$ H2AX foci and further DNA damage response in A549 lung adenocarcinoma cells [39]. Since  $\gamma$ H2AX foci are used as a surrogate for DNA double strand breaks, one might speculate that TRPM2 or TRPV1 may amplify ionizing radiation-induced insults (Fig. 1). Another interpretation which has been favored by the author of the study [39] would be that activity of TRPM2 and TRPV1 is required for the formation of DNA repair complexes. In combination, the data hint to the possibility of radiosensitizing cancer cells by pharmacologically activating TRPM2 or TRPV1 channels. Whether this might become a promising new strategy of tumor radiosensitization has to await animal studies.



**Fig. 1.** Speculative mechanism of a putative TRPM2-mediated radiosensitization (A) and reported strategy [29] of lung cancer cells to avoid TRPM2-mediated susceptibility to cell death (B), for details see text. TRPM2-TE (TE): truncated TRPM2, TRPM2-AS (AS): TRPM2 antisense RNA, mito.: mitochondrion).

#### 4. Ion channels conferring intrinsic radioresistance

DNA repair involves cell cycle arrest, chromatin relaxation and formation of repair complexes at the site of DNA damage. Moreover, radiation-induced formation of radicals requires activated radical detoxification pathways and increased oxidative defense to constrain the radiation-induced insults. All these processes of stress response lead to elevated ATP consumption which requires intensified energy supply. Recent *in vitro* observations suggest that these processes depend at least partially on radiation-induced ion channel activation.

Studies of our laboratory indicate that survival of irradiated human leukemia cells critically depends on Ca<sup>2+</sup> signaling involving radiogenic activation of TRPV5/6-like nonselective cation and K<sub>v</sub>3.4 voltage-gated K<sup>+</sup> channels [40,41]. The nonselective cation channels in concert with K<sub>v</sub>3.4 generate radiogenic Ca<sup>2+</sup> signals that contribute to G<sub>2</sub>/M cell cycle arrest by CaMKII-mediated inhibition of the phosphatase cdc25B. Activity of the latter is required in these cells for release from radiation-induced G<sub>2</sub>/M arrest via dephosphorylation and thereby activation of cdc2, a component of the mitosis promoting factor. Experimental interference with the radiogenic Ca<sup>2+</sup> signals, e.g. by pharmacological inhibition or knock-down of K<sub>v</sub>3.4 overrides cell cycle arrest resulting in increased apoptosis and decreased clonogenic survival of irradiated leukemia cells [40,41]. This radiosensitization by K<sub>v</sub>3.4 targeting demonstrates the pivotal role of radiogenic K<sub>v</sub>3.4 channel activation for cell cycle arrest and DNA repair.

Similar to leukemia cells, A549 lung adenocarcinoma cells reportedly respond to ionizing radiation with activation of K<sub>v</sub> channels [42] and transient hyperpolarization of the plasma membrane. Later on, the membrane potential of the irradiated A549 cells strongly depolarizes. This depolarization is dependent on external glucose and inhibited by phlorizin, a sodium glucose cotransporter (SGLT) blocker. In parallel, irradiation induces phlorizin-sensitive <sup>3</sup>H-glucose uptake within few minutes after irradiation [43]. Combined, these data suggest that radiogenic activation of SGLT transporters and K<sub>v</sub> K<sup>+</sup> channels cooperate in glucose fuelling of the irradiated A549 cells, the former by generating the glucose entry routes, the latter by increasing and maintaining the driving force for Na<sup>+</sup>-coupled glucose entry. Glucose uptake by SGLTs is mainly driven by the inwardly directed electrochemical driving force for Na<sup>+</sup> which in turn is highly dependent on the K<sup>+</sup> channel-regulated membrane potential. SGLTs allow efficient glucose uptake even from a glucose-depleted microenvironment which is typical for malperfused solid tumors [44]. It is therefore not surprising that several tumor entities such as colorectal, pancreatic, lung, head and neck, prostate, kidney, cervical, breast, bladder and prostate cancer as well as chondrosarcomas and leukemia upregulate SGLTs [45–53].

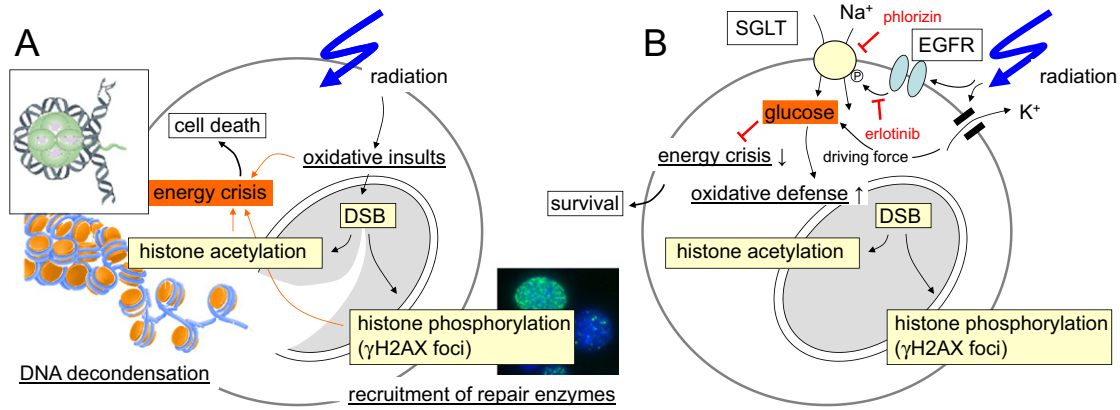
SGLT has been shown to be in complex with the EGFR [50,53] and radiogenic SGLT activation depends on EGFR tyrosine kinase activity [43]. Importantly, radiogenic increase in glucose fuelling seems to be required for cell survival since the SGLT inhibitor phlorizin radiosensitizes A549 lung adenocarcinoma and FaDu head and neck squamous carcinoma cells [43].

Intracellular ATP concentration has been reported to drop in irradiated A549 cells indicative of an irradiation-caused energy crisis. Notably, recovery from radiation-induced ATP decline is EGFR/SGLT-dependent and associated with improved DNA-repair leading to increased clonogenic cell survival. This is evident from the fact that EGFR or SGLT blockade delays recovery of intracellular ATP concentration and histone modifications necessary for chromatin remodeling during DNA repair. *Vice versa*, inhibition of the histone H3 modification prevents chromatin remodeling as well as energy crisis [8]. Together, these data suggest that irradiation-associated interactions between SGLT1 and EGFR result in increased glucose uptake, which counteracts the energy crisis in tumor cells caused by chromatin remodeling required for DNA repair (Fig. 2) [8,43].

Besides plasma membrane ion channels, mitochondrial transport pathways have been shown to contribute to cellular stress response. Stress-induced upregulation of uncoupling proteins (UCPs) conveys hyperpolarization of the membrane potential across the inner mitochondrial membrane ( $\Delta\Psi_m$ ) and thereby formation of reactive oxygen species [54]. UCPs are reportedly upregulated in a number of aggressive human tumors (leukemia, breast, colorectal, ovarian, bladder, esophagus, testicular, kidney, pancreatic, lung, and prostate cancer) in which they are proposed to contribute to malignant progression (for review see [54]).

In addition to malignant progression, UCPs may alter the therapy sensitivity of tumor cells. UCP-2 expression has been associated with paclitaxel resistance of p53 wildtype lung cancer, CPT-11 resistance of colon cancer and gemcitabine resistance of pancreatic adenocarcinoma, lung adenocarcinoma, or bladder carcinoma. Accordingly, experimental targeting of UCPs has been demonstrated to sensitize tumor cells to chemotherapy *in vitro* (for review see [54]).

Notably, ionizing radiation induces up-regulation of UCP-2 expression in colon carcinoma cells [55] and in a radiosensitive subclone of B cell lymphoma [56], as well as UCP-3 expression in rat retina [57]. Radioprotection might result from lowering the radiation-induced burden of reactive oxygen species. As a matter of fact, multi-resistant subclones of leukemia cells reportedly show higher UCP-2 protein expression, lower  $\Delta\Psi_m$ , lower radiation induced formation of reactive oxygen species, and decreased DNA damage as compared to their parental sensitive cells [58].



**Fig. 2.** Radiation-caused energy crisis (A) and functional significance of SGLT1-mediated glucose fueling for DNA repair and cell survival (B) of irradiated A549 lung adenocarcinoma cells (DSB: double strand breaks).

In summary, these data indicate that ion transports through channels may regulate processes that mediate intrinsic radioresistance. Only few laboratories worldwide including ours are working on the radiophysiology of tumor cells. The investigation of ion transports in irradiated cells therefore is at its very beginning and the few data available are mostly phenomenological in nature. The molecular mechanisms that underlie e.g. radiogenic channel activation are still ill-defined. Nevertheless, the data prove functional significance of ion transports and electrosignaling for the survival of irradiated tumor cells and might have translational implications for radiotherapy in the future.

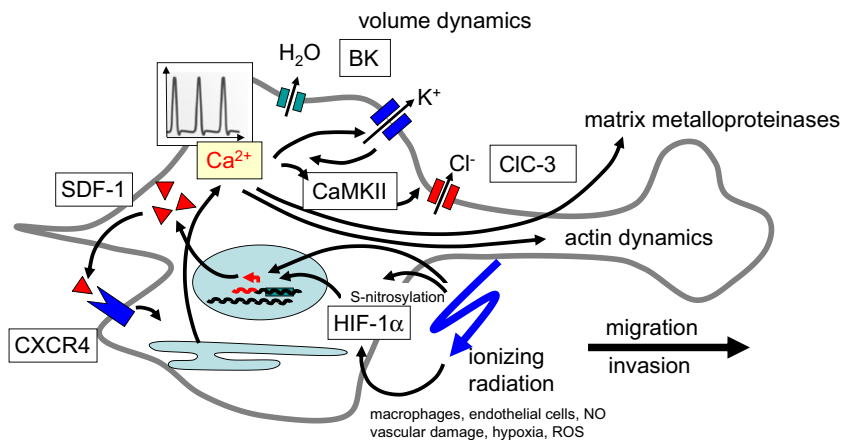
### 5. Ion channels in acquired radioresistance

Microenvironmental stress such as hypoxia, interstitial nutrient depletion or low pH has been proposed to switch tumor cells from a “Grow” into a “Go” phenotype. By migration and tissue invasion “Go” tumor cells may evade the locally confined stress burden and resettle in distant and less hostile regions. Once resettled, tumor cells may readapt the “Grow” phenotype by reentering cell cycling and may establish tumor satellites in more or less close vicinity of the primary focus (for review see [54]).

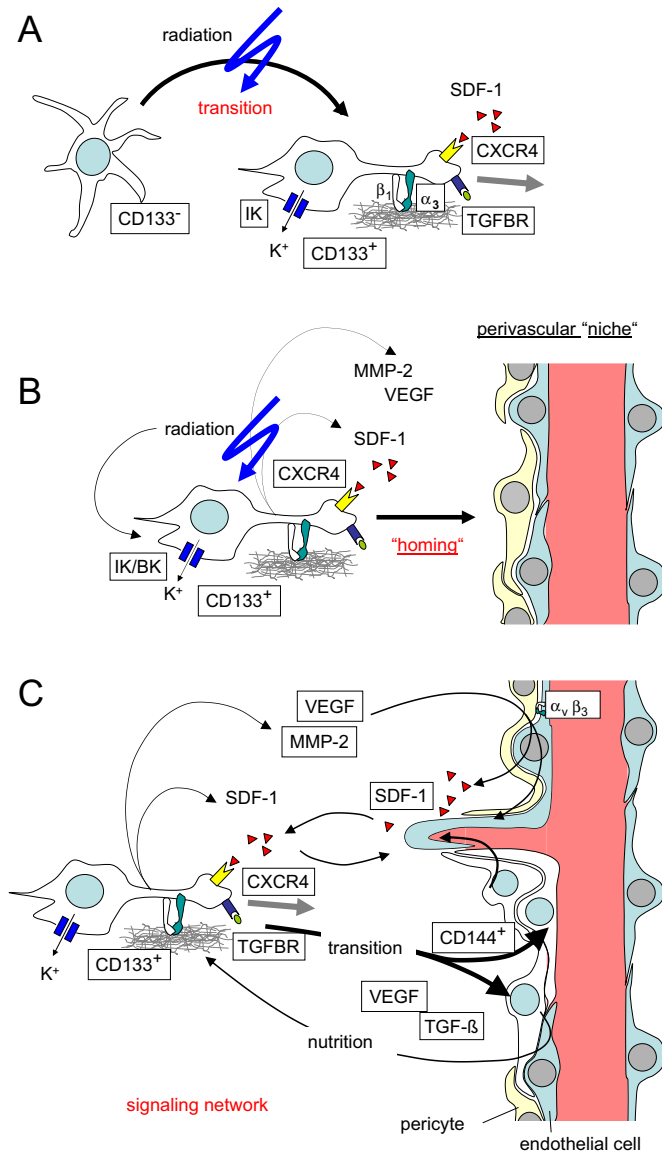
In accordance with this hypothesis, sublethal ionizing irradiation as applied in single fractions of fractionated radiotherapy has been

demonstrated *in vitro* and/or in rodent tumor models to induce migration, invasion and metastasis or spreading of cervix carcinoma [59], head and neck squamous cell carcinoma [60], lung adenocarcinoma [61,62], colorectal carcinoma [62], breast cancer [62–64], meningioma [65], medulloblastoma [66] and glioblastoma. In particular, in glioblastoma the experimental evidence for such radiogenic hypermigration is meanwhile overwhelming [67–80]. Glioblastoma cells show a highly migrative phenotype that may “travel” large distances through the brain [81]. At least in theory, radiogenic hypermigration might, therefore, contribute to locoregional treatment failure by promoting emigration of tumor cells from the target volume during fractionated radiation therapy.

Migration and radiogenic hypermigration are well documented in glioma cells. They invade the surrounding brain parenchyma primarily by moving along axon bundles and the vasculature. During brain invasion along those tracks cells have to squeeze between very narrow interstitial spaces which requires effective local cell volume decrease and reincrease. Glioblastoma cells are capable of losing all unbound cell water [82]. The electrochemical driving force for this tremendous cell volume decrease is provided by an unusually high cytosolic  $\text{Cl}^-$  concentration (100 mM) [83,84] which is utilized as an osmolyte. During local regulatory volume decrease, extrusion of  $\text{Cl}^-$  and  $\text{K}^+$  along their electrochemical gradients involves  $\text{ClC-3 Cl}^-$  channels [85,86],  $\text{Ca}^{2+}$ -activated high conductance BK- [74,87,88] and intermediate



**Fig. 3.** Hypothetical signaling underlying radiogenic hypermigration of glioblastoma cells. SDF-1 is a HIF-1 $\alpha$  target gene and hypoxia is a strong inducer of SDF-1 expression [111]. Beyond that, ionizing radiation reportedly stimulates the generation of NO in tumor-associated macrophages leading to HIF-1 $\alpha$  stabilization by S-nitrosylation [100]. Finally, radiation may directly stabilize HIF-1 $\alpha$  as deduced from *in vitro* experiments (own unpublished results). SDF-1 induces  $\text{Ca}^{2+}$  signals through CXCR4 chemokine receptor that in turn contribute to the programming and mechanics of migration (for details see text) and possibly invasion, e.g., via calpain-dependent [112] activation of matrix metalloproteinases [113,114].



**Fig. 4.** Synopsis of the signaling network in glioblastoma conferring radioresistance and speculative role of ionizing radiation herein. A. Irradiation induces secretion of SDF-1 [80,95–97] and transition of CD133<sup>-</sup> “differentiated” glioblastoma cells to CD133<sup>+</sup> GSCs with up-regulated CXCR4 [106],  $\beta_1/\alpha_3$  integrins [108], TGF $\beta$ 2 receptor [115], TGF- $\beta$  responsiveness [115], and IK Ca<sup>2+</sup>-activated K<sup>+</sup> channel-dependent highly migratory and invasive phenotype [109]. B. Irradiation promotes “homing” of GSCs to perivascular niches by stimulating cell migration. C. The reciprocal interaction between glioblastoma and endothelial cells strongly depends on matrix metalloproteinase-2 (MMP-2) expression by glioblastoma [114] and SDF-1 signaling of endothelial cells [110]. Importantly, irradiation induces upregulation of MMP-2 in glioblastoma cells (B) which is required for tissue invasion [67,71,72,79,114] and VEGF secretion (B) [71,75] which reportedly may promote angiogenesis [116]. In addition, transition of glioblastoma cells into endothelial cells [117] and pericytes [15] reconstruct the glioblastoma vasculature which supports both, vessel function and tumor growth.

conductance IK K<sup>+</sup> channels [86,89]. Inhibition of either of these channels attenuates glioblastoma cell migration or invasion [83,90–94] confirming their pivotal function in these processes.

Ionizing radiation has been demonstrated in our laboratory to activate BK K<sup>+</sup> channels in glioblastoma cells *in vitro* [74]. Radiogenic BK channel activity, in turn, is required for Ca<sup>2+</sup>/calmodulin kinase II (CaMKII)- [74] and consecutive CaMKII-dependent CIC-3 channel activation (own unpublished observation and [85]). Inhibition of BK or CaMKII abolishes radiogenic hypermigration [74] indicating BK channel activation as key event of radiogenic hypermigration of glioblastoma cells. Radiogenic hypermigration is paralleled by radiogenic expression

of the chemokine SDF-1 (stromal cell-derived factor-1, CXCL12) in different tumor entities including glioblastoma [80,95–97]. Glioblastoma cells reportedly express CXCR4 chemokine receptors and SDF-1 stimulates glioblastoma cell migration via CXCR4-mediated Ca<sup>2+</sup> signaling [93]. CXCR4 receptors reportedly signal through phospholipase C and BK channels have been shown to be functionally coupled with IP<sub>3</sub> receptors in the ER [98] suggesting (and confirmed by own unpublished observations) that radiogenic SDF1/CXCR4 signaling is upstream of BK channel activation. SDF-1, in turn, is a target gene of the transcription factor HIF-1 $\alpha$  which reportedly becomes stabilized, e.g. by S-nitrosylation, upon irradiation [95,99–101] (Fig. 3). Together, this gives a good example of radiogenic signaling which integrates biochemical signaling, electrosignaling (i.e., BK-dependent regulation of membrane potential) and Ca<sup>2+</sup> signaling modules (more details are given in the legend to Fig. 3).

Ionizing radiation has been demonstrated to select stem (cell)-like glioblastoma cells or even induce transition of “differentiated” cancer cells to GSCs/CSCs in glioblastoma [102–104] and other tumor entities [14]. Notably, “stemness” is associated with SDF-1 secretion [105] and markedly increased CXCR4 chemokine expression [106]. Importantly, CXCR4 upregulation is required to maintain “stemness” of non-small cell lung cancer [107] and glioblastoma cells [105]. In accordance to CXCR4 upregulation, GSCs show a highly migratory/invasive phenotype [108,109]. Most importantly, this phenotype is highly dependent on the Ca<sup>2+</sup>-activated IK K<sup>+</sup> channel [89,109]. Furthermore, IK channels have been demonstrated to be overexpressed in about one third of the glioma patients with IK protein expression correlating with poor patient survival [89].

Unexpectedly, a previous report demonstrated that *xenografted* CD133<sup>+</sup> stem-like subpopulations of glioblastoma exhibit a higher radioresistance than *xenografted* CD133<sup>-</sup> cells while radiosensitivity of both subpopulations does not differ *in vitro* [16]. This clearly indicates a function of the brain microenvironment for radioresistance. In particular, endothelial cells have been postulated to promote glioblastoma therapy resistance [110]. Part of the reported reciprocal interaction between glioblastoma cells and endothelial cells as well as of the complex signaling network in perivascular “niches” is schematically summarized in Fig. 4.

Albeit merely speculative, the idea that radiogenic hypermigration might promote “homing” of (CXCR4-highly-expressing stem-like) glioblastoma cells to perivascular niches is highly attractive. The subsequent reciprocal modifications of glioblastoma and endothelial cells might eventually induce radioresistance of glioblastoma cells. Together, these data suggest that radiogenic hypermigration might contribute to the apparently high radioresistance of glioblastoma cells either by promoting evasion from the radiation target volume or by stimulating the chemotaxis of glioblastoma cells to “radioprotective” perivascular niches.

## 6. Concluding remarks

The radiation physiology of cancer cells is yet a neglected research field. While the number of reports on ion channel function in neoplastic transformation, malignant progression or metastasis of cancer cells increases constantly only little is known about the role of ion channels in radiotherapy. The few data available strongly suggest that ionizing radiation-induced ion channel modifications are a common phenomenon. Importantly, these modifications impact on the stress response and survival of irradiated tumor cells. By modulating intracellular Ca<sup>2+</sup> signals radiosensitive ion channels may directly crosstalk with the biochemical signaling of the DNA damage response. By driving local cell volume changes radiogenic ion channel modifications may promote cell migration and stress evasion of irradiated tumor cells. By stabilizing the membrane potential ionizing radiation-induced K<sup>+</sup> channel activity might facilitate Na<sup>+</sup>-coupled glucose uptake providing the energy for DNA-repair. Finally, mitochondrial channels upregulated

by ionizing radiation might lower the oxidative insults associated with ionizing radiation. Given the aberrant and partly specific ion channel expression of tumor cells, a more profound understanding of the mechanisms underlying radiogenic ion channel modifications might be harnessed in the future to develop new strategies for the radiosensitization of tumors.

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