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Review article

Immunomodulation of classical and non-classical HLA molecules by ionizing radiation

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ABSTRACT

Radiotherapy has been employed for the treatment of oncological patients for nearly a century, and together with surgery and chemotherapy, radiation oncology constitutes one of the three pillars of cancer therapy. Ionizing radiation has complex effects on neoplastic cells and on tumor microenvironment: beyond its action as a direct cytotoxic agent, tumor irradiation triggers a series of alterations in tumoral cells, which includes the *de novo* synthesis of particular proteins and the up/down-regulation of cell surface molecules. Additionally, ionizing radiation may induce the release of "danger signals" which may, in turn lead to cellular and molecular responses by the immune system. This immunomodulatory action of ionizing radiation highlights the importance of the combined use (radiotherapy plus immunotherapy) for cancer healing. Major histocompatibility complex antigens (also called Human Leukocyte Antigens, HLA in humans) are one of those molecules whose expression is modulated after irradiation. This review summarizes the modulatory properties of ionizing radiation on the expression of HLA class I (classical and non-classical) and class II molecules, with special emphasis in non-classical HLA-I molecules.

Contents

1. Introduction

Despite all the advances achieved in oncology field, radiotherapy (RT) remains as one of most widely used and successful treatments for cancer. In fact, over half of all cancer patients receive RT, alone or associated with chemo or immunotherapy [1,2]. The

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ability of RT to kill cancer cells by a direct cytotoxic mechanism has been well established [3–5]. However, a large body of evidence indicates that the effects of RT are more complex than the simple elimination of radiosensitive cancer cells. Ionizing radiations (IR) have the ability of modify tumor microenvironment and exert an important impact on the immune system [6–10]. In some cases, this effect is more evident with hypofractionated regimes [11,12].

Cell death induced by radiation increase the generation of "danger signals" that promote the ability of professional antigen presenting cells (i.e. dendritic cells, DCs) to present released antigens to T lymphocytes, inducing antigen-specific immune responses [13]. Additionally, local RT occasionally inhibits the growth of distant metastatic tumors which have not been irradiated. This phenomenon has been called the abscopal effect and can be attributed to the induction and enhancement by IR of the endogenous anti-tumor innate and adaptive immune responses [13,14]. There is accumulating evidence that adaptive immunity significantly contributes to the efficacy of RT: irradiated tumors are often more infiltrated by leukocytes than unirradiated tumors [11,15–17]. In addition, IR also increase the immunogenicity of tumor cells by enhancing interferon-γ (IFN-γ) production, which in turns alters the expression of adhesion molecules on vasculature and induces the release of chemokines, creating a microenvironment beneficial for T cell infiltration and recognition of tumor cells by cytotoxic T lymphocytes [3,18]. Other immunomodulatory actions of IR include the up-regulation of tumor-associated antigens [3,19], for example cancer-testis antigens [20,21], the induction of matrix metalloproteinases [22] and secretory molecules [11,23]. These immunomodulatory properties of IR emphasize the use of RT in combination with immunotherapy to improve the efficiency of cancer treatments [14,23–26]. The immunomodulatory effects of IR are summarized in Fig. 1.

Within the immune-related molecules that undergo changes in their surface expression after RT we could mention the major histocompatibility complex (MHC) molecules. In humans they are also called Human Leukocyte Antigen (HLA) molecules, as they were first discovered through antigenic differences between white blood cells from different individuals [27].

2. MHC/HLA molecules: a brief overview

The function of MHC molecules is to bind peptide fragments derived from pathogens and display them on the cell surface for recognition by the appropriate T cells. The consequences are almost always deleterious to the pathogen: virus-infected cells are killed, macrophages are activated to kill bacteria living in their intracellular vesicles, and B cells are activated to produce antibodies that eliminate or neutralize extracellular pathogens.

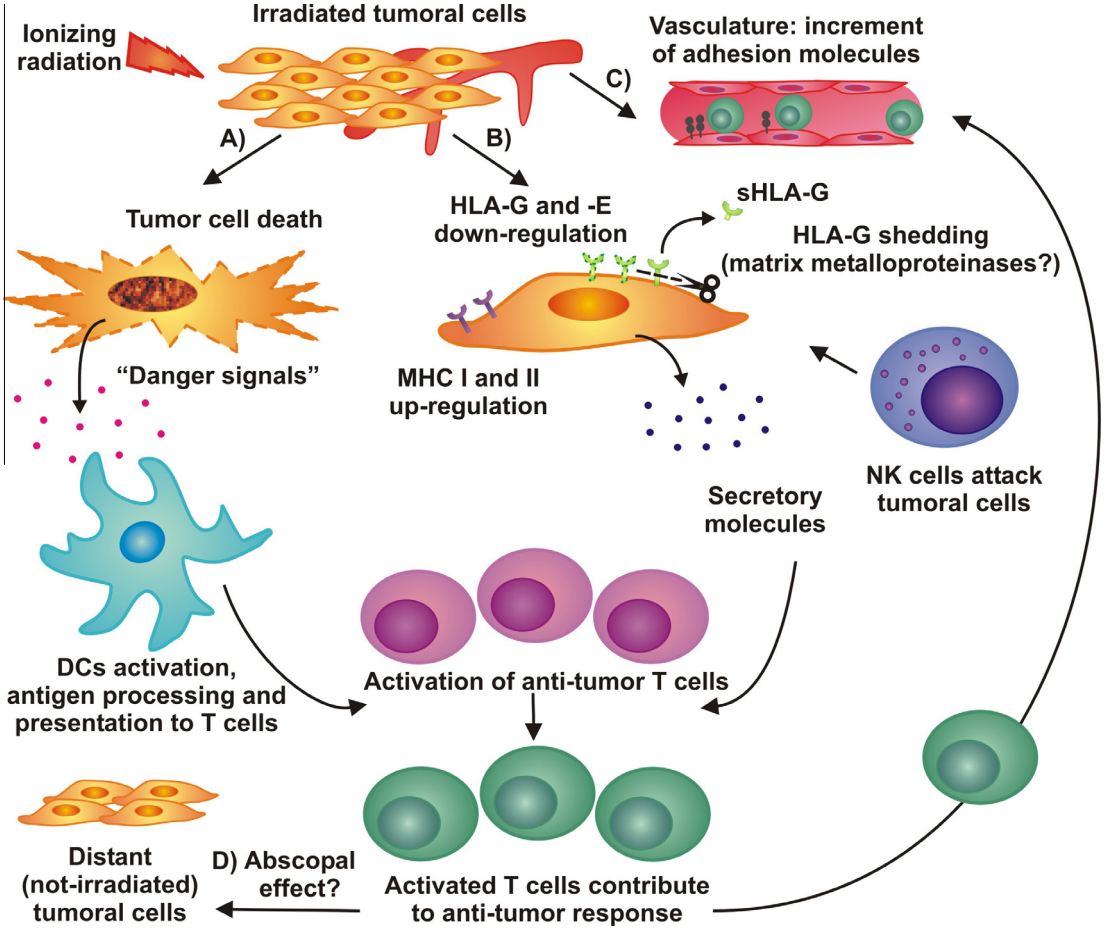

Fig. 1. Immunomodulatory action of radiotherapy. (A) Tumor cells killed by IR constitute a very good source of antigens for DCs uptake and presentation to T cells. (B) Radiation up-regulates the release of secretory molecules (cytokines, inflammatory mediators) by tumoral cells providing signals for T cells to come to the areas of tumor. The expression of immunomodulatory surface molecules (MHC I and II, death receptors) is also up-regulated, making it easier for T cells to recognize and kill tumor. In addition, IR could down-regulate the surface expression of non-classical HLA class I molecules such as HLA-G and HLA-E, contributing to the anti-tumor immune response. The decrease in cell surface HLA-G induced by IR could occur through the shedding of this molecule, probably by activation of matrix metalloproteinases, causing the release of sHLA-G. (C) IR can contribute to the anti-tumor response, by enhancing the expression of adhesion molecules on vasculature, facilitating the access of activated T cells to the tumor site. (D) Additionally, IR could inhibit the growth of distant metastatic tumors that have not been irradiated (abscopal effect).

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The MHC molecules could be divided in two major classes: MHC class I and MHC class II. The MHC class I are constitutively expressed by virtually all somatic nucleated cells. They present endogenous peptides to antigen-specific cytotoxic T lymphocytes, resulting in cell killing [28]. The MHC class II proteins are only present on specialised antigen-presenting immune cells, including B lymphocytes, macrophages and DCs. MHC II proteins present antigens from foreign bodies such as bacteria. Once at the cell surface, the membrane-bound MHC II protein displays the antigen for recognition by T helper lymphocytes.

The HLA class I family is sub-divided into classical and non-classical subfamilies. Classical HLA class I includes the HLA-A, -B and -C molecules, whereas the sub-group of non-classical HLA class I is represented by HLA-E, -F and -G molecules. On the other hand, the HLA class II family in humans includes HLA-DR, -DP and -DQ molecules.

3. Modulation of HLA expression by ionizing radiation

The effects of IR on the expression of HLA molecules are contradictory. Several studies reported that gamma-radiation down-regulates the expression of HLA class II [29–31]. In particular, a decrease in HLA-DR expression has been reported on CD3+ and CD8+ cells after 24, 48 and 72 h of exposure to gamma irradiation [32]. Similarly, Cao and Xiao [33] reported the diminution of HLA-DR expression (together with CD86 and CD80 reduction) after exposure of DCs to 25–30 Gy of gamma-radiation.

On the other hand, up-regulation in the expression of MHC class I/II molecules after irradiation with a gamma-radiation source has been widely demonstrated. In human tumoral cells and in a mouse models, IR increased MHC class I and activated cytotoxic T cells [26,34]. Gamma irradiation up-regulated HLA class I molecules in different tumoral cell lines and primary tumors in a dose dependent manner [25,35,36]. Similarly, Ma et al. [37] observed that low-dose irradiation of human renal cell carcinoma induced an increase in the membrane expression of MHC I and MHC II which was dose dependent. The up-regulated expression of HLA class I seems specific for ionizing radiation, as similar changes in gene expression were not observed upon other treatments that induce DNA-damage such as hypoxia or hyperthermia, and also appears to be a specific feature of malignant cells, since that phenomenon was not observed in normal primary cells [3].

Deficiency of MHC class I antigen presentation is very frequent in tumors [38,39], and blunted antigen presentation through reduced expression of MHC class I molecules on the surface of cancer cells represents a mechanism of tumor immune escape. For this reason, IR-mediated enhancement of MHC class I expression could be a potential tool for cancer treatment.

The up-regulation in MHC class I expression after exposure to IR is mediated by the release of soluble factors such as IFNs. The influence of IFN-γ signalling (generated after irradiation) on surface MHC class I expression has been studied [11]. These authors used murine B16/OVA melanoma cells engineered to overexpress a dominant negative mutant of the IFN-γ receptor (B16/OVA/DNM). Following irradiation, the expression of surface MHC class I was increased in B16/OVA, but not in B16/OVA/DNM cells, suggesting that IFN-γ acts directly on tumor cells to induce MHC class I up-regulation. More recently, Wan et al. [40] showed that the transfer of conditioned media from irradiated ZR-75-1 human breast cancer cells to non-irradiated cells increased the expression of both cell surface and total HLA class I in the recipient cells. This observation suggests that HLA I elevation in the recipient cells could be due to secreted soluble factors from the irradiated donor cells. To corroborate this hypothesis, the authors added a neutralizing antibody against IFN-β to the conditioned media from irradiated cells, and they observed a reduced expression of HLA I in non-irradiated recipient cells, suggesting that enhanced HLA I expression after IR exposure was mediated by IFN-β secretion from the irradiated donor cells.

In RT, patient irradiation protocols consist in the administration of fractionated doses in order to not cause damage to normal tissues [41,42]. In this regard, Sharma et al. [3] compared the effects of irradiation with a single dose of 20 Gy or with a fractionated irradiation protocol (2 Gy during 10 days) and they observed an increment in the expression of HLA I with both irradiation protocols.

4. Non-classical HLA class I molecules. Effects of IR on its surface expression

Neoplastic cells have developed a variety of strategies to escape immune control [43]. Alteration of HLA expression and/or function is one of the most frequent mechanisms used by tumor cells to avoid cytotoxic T lymphocyte recognition and destruction. In addition, expression of non-classical HLA class I antigens (HLA-E, -F and/or -G) are often induced in tumors. Thus, alterations in the expression of classical and non-classical HLA class I provide tumor cells with different mechanisms to evade host immune surveillance.

4.1. HLA-G

In contrast to classical HLA class I genes, which are very polymorphic and ubiquitously expressed, the HLA-G gene has a very low level of polymorphism and highly restricted distribution under non-pathological situations: trophoblast [44], thymus [45], cornea [46], pancreas [47], and erythroid and endothelial precursors [48]. Apart from its expression in adult immune privileged organs and in cells of the hematopoietic lineage, induction of HLA-G protein expression can be frequently observed in certain pathological situations such as cancer, transplantation, and viral infectious diseases [49–53]. Indeed, HLA-G has been detected in nearly thirty types of malignancies of distinct origin including melanoma, carcinoma (breast, renal, ovarian, lung, and colorectal), lymphoma and leukemia [54,55]. Recently, de Figueiredo Feitosa et al. [56] evaluated the expression of HLA-G in histologically normal and tumoral thyroid tissues, and they found that HLA-G was weakly expressed in normal thyroid glands and colloid goiters, whereas in papillary thyroid carcinoma, follicular thyroid carcinomas and follicular adenomas the percentage of cell staining was significantly higher. Moreover, the level of HLA-G expression was correlated with the size and aggressiveness of the tumor. Besides to its expression by tumoral cells, it has been shown that HLA-G could be expressed also by tumor associated macrophages/monocytes in lung cancer, melanoma, breast cancer and neuroblastoma [57–60] and by glioblastoma infiltrating microglia [61]. Interestingly, it has also been demonstrated that membrane patches containing HLA-G molecules could be transferred from cancer cells to activated NK cells, through a phenomenon known as trogocytosis [62–64]. As a result, the NK cells that receive the HLA-G molecules stop proliferating and inhibit the cytotoxic effector functions of neighbouring NK cells.

The HLA-G molecule can be expressed as seven different isoforms, four membrane bound (HLA-G1 to -G4) and three soluble (HLA-G5 to -G7) generated by alternative splicing of the HLA-G primary transcript [65]. Among these isoforms, the HLA-G1 and HLA-G5 are the most frequently observed [55]. A soluble form of the HLA-G1 molecule (sHLA-G1) also exists which is generated by proteolitic cleavage of the membrane-bound HLA-G1 at the cell surface [66]. Similar to classical HLA class I molecules, HLA-G forms

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heterodimers with β2 microglobulin [67]. Association with β2 microglobulin is required for cell surface expression of HLA-G1 and its interaction with ILT-2 receptor [55]. In addition, HLA-G can form homodimers and homotrimers. These HLA-G oligomers bind to HLA-G inhibitory receptors with increased affinity than monomers [67,68]. IFN-β and IFN-γ (two cytokines frequently present in the tumor microenvironment) increase the formation of HLA-G1 dimers [55]. Moreover, soluble HLA-G5 dimers and multimers have also been detected in ascitic fluid from ovarian carcinoma patients [55].

As we mentioned above, HLA-G exhibits low level of allelic polymorphism, with 31 HLA-G alleles acknowledged in the coding region to date [69]. HLA-G polymorphism has also been reported in the 5′-upstream regulatory region (5′ URR) and in the 3′-untranslated region (3′ UTR) of the gene, which may contribute to the regulation of HLA-G expression [70]. Among them, a 14 bp insertion/deletion polymorphism has been described in the 3′ UTR in exon 8 [71]. This 14-bp insertion/deletion polymorphism is associated with HLA-G mRNA stability and splicing pattern, which could affect HLA-G protein expression [70,72].

HLA-G is a potent immunosuppressive molecule and mediates this inhibitory action by binding to inhibitory receptors present on immune cells [65,73]. Three HLA-G-recognizing immunoglobulin-like receptors have been identified: ILT-2, ILT-4 and KIR2DL4 [74–76]. These receptors are differentially expressed by immune cells: B and T lymphocytes express the ILT-2 receptor, decidual and peripheral NK cells express KIR2DL4 and ILT-2 receptors, whereas monocytes/macrophages/DCs express the ILT-2 and ILT-4 receptors [73]. By binding to these receptors, HLA-G inhibits cytotoxicity of CD8+ T lymphocytes and NK cells, the alloproliferative response of CD4+ T cells [77–80] and the production of Th1 (IFN-γ, IL-2) and Th2 (IL-10) citoquines by CD4+ T lymphocytes [81]. Furthermore, HLA-G can induce apoptosis of activated CD8+ T cells and NK cells and affects the function of DCs, in particular their maturation, migration, trafficking, antigen presentation as well as their cross-talk between T and NK cells [49]. sHLA-G can also induce apoptosis in T lymphocytes and NK CD8+ cells [82] and downregulates the expression of the chemokine receptor in T cells, impairing chemotaxis [83]. Peripheral sHLA-G antigens, which could be derived from the release of membrane-bound HLA-G isoforms (sHLA-G1 from HLA-G1 shedding) and from the secretion of sHLA-G isoforms, (HLA-G5 in particular) may affect anti-tumor immune response both locally at the tumor site and systemically via the circulation [54]. Plasma levels of sHLA-G are often significantly increased in patients with malignant diseases such as melanoma, glioma, breast and ovarian carcinoma, lung cancer, papillary thyroid carcinoma, and leukaemia [84–87]. In this regard, determination of sHLA-G levels has been applied as a diagnostic tool to distinguish between malignant and benign tumors or health controls, and as a prognostic marker in prediction of the disease outcome [88–91].

It has been shown that certain stimulus, such as cytokines (IL-10 and IFN-γ), heat shock, hypoxia, oxidative stress and radiation could modulate the expression of HLA-G [83]. Previous data from our laboratory indicate that the exposure of the naturally expressing HLA-G1 FON cell line (from human melanoma) to high doses (10–20 Gy) of gamma-radiation decreases the surface expression of this molecule. The fractionated 20 Gy irradiation protocol (2 Gy × 10) was also effective in decreasing surface HLA-G1 levels [92]. Our results are in agreement with a previous work of Urosevic et al. [93]. In this study, the authors analysed a series of basal cell carcinomas (BCCs) of the skin treated with superficial radiotherapy for HLA-G expression. Immunohistochemistry of these tumors revealed HLA-G expression in 90% of the tumors, and in nearly 20% of BCC cases, HLA-G was also expressed in tumor-infiltrating mononuclear cells (TIMC). The expression of HLA-G on TIMC was associated with longer recurrence-free period in those patients whose tumors recurred. After comparing primary BCCs and BCCs relapsed after radiotherapy, the authors observed a decrease in HLA-G expression on tumor cells and the loss of HLA-G expression on TIMC. They conclude that radiotherapy may change the immunobiology of BCC resulting in downregulation of HLA-G expression on tumor and on tumor-infiltrating cells.

In addition, we could demonstrate that the down-regulation of surface HLA-G1 in melanoma FON cells by gamma radiation, was accompanied by a significant decrease in total HLA-G1 (evaluated by Western Blot), and by the concomitant increase in the levels of sHLA-G1 in the culture medium (measured by ELISA assay). Taking together, these results strongly suggest that the way by which IR decrease HLA-G1 cell-surface expression could be through the shedding of membrane-bound HLA-G1 to the medium [92]. Recently, we evaluate if the expression of HLA-G1 intervenes in the survival response to gamma radiation of human tumoral cells cultured in vitro. For that purpose, we compared the survival frequency of HLA-G1 positive and HLA-G1 negative cell lines from melanoma (M8 cells) and erythroleukemia (K562 cells). We could determine that HLA-G1 confers a significant reduction in cell survival after gamma irradiation to those cell lines that express the HLA-G1 molecule with respect to HLA-G1 negative cells, postulating HLA-G1 as a possible tumoral radiosensitivity marker [94]. In summary, considering the evidence obtained so far, one of the effects of IR on tumoral HLA-G1 expressing cells could be the promotion of the shedding of this molecule increasing the levels of sHLA-G1. This could decreasing surface HLA-G, making tumoral cells more susceptible to the attack of the immune system. On the other hand, those cells that express HLA-G seemed to be more sensitive to IR.

4.2. HLA-E

HLA-E is ubiquitiously expressed in several tissues. It is found in extra villous trophoblast cells, kidney, skin, liver, thyroid, bladder, stomach, endometrium, spleen, lymph nodes as well as in endothelial cells, B and T lymphocytes, monocytes, macrophages and megakaryocytes [83,95]. In fact, HLA-E is expressed in all human tissues where classical HLA class I molecules are expressed [83,96]. Similar to HLA-G, HLA-E forms a complex with β2 microglobulin [67]. HLA-E was first described as a non-polymorphic ligand of the CD94/NKG2 family of receptors expressed mainly by NK cells and some subsets of CD8+ T cells [97,98] so its role was confined to the regulation of NK cell function. The CD94/NKG2 receptors are comprised of both activating (2C, 2E and 2H) and inhibitory (2A and 2B) members [99]. Therefore, interaction of HLA-E with these receptors can result in either inhibition or activation of NK cells. However, there is convincing evidence that HLA-E can also present peptide antigens for T-cell receptor recognition. Thus, HLA-E may play a relevant role in both innate and adaptive immunity [100,101]. HLA-E is also expressed by tumor cells of different types of cancers such as colorectal, laryngeal, ovarian, and breast cancer, melanoma, lymphoma and glioma [52,83,102–107]. Due to its capacity to bind to the CD94/NKG2A receptor, HLA-E expression by tumors might also result in their escape from immune surveillance [107,108]. Indeed, in malignant cells the physiological correlation of HLA class I antigens and HLA-E is disturbed (down-regulation of classical HLA class I together with up-regulation of HLA-E antigens) as a strategy for avoiding T cell immune recognition [83]. In addition, HLA-E could be released by melanoma cells as soluble forms (sHLA-E) by proteolytic cleavage of surface molecules [104] and serum levels of sHLA-E were found to be significantly increased in melanoma patients in comparison with healthy donors [109]. Similarly to HLA-G, there is a correlation between HLA-E expression and tumor

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progression. Indeed, the expression of HLA-E in HLA class I-negative breast carcinoma patients is associated with a poor relapse-free period [106], and Talebian Yazdi et al. [110] have recently reported that in non-small cell lung cancer, CD8+ T cell infiltration strongly contributes to a better prognosis when the tumor cells retain the expression of classical HLA class I and do not express HLA-E.

With regard to the influence of IR on HLA-E expression, we could observed that together with HLA-G1 surface decrease, the HLA-E surface expression, as well as surface HLA-I levels were down-regulated in FON cells exposed to 10 and 20 Gy of gamma-radiation [92]. Given that HLA-G stabilizes the surface expression of HLA-E [97], the decrease in HLA-E observed in irradiated FON cells could be an indirect effect of HLA-G1 diminution induced by IR. In contrast to our results, Riederer et al. [111] reported that irradiation of macrovascular endothelial cells (ECs) with 4 Gy of gamma-radiation induced HLA-E up-regulation, conferring protection against killing by activated NK cells.

The difference between both series of results could be due to the selected dose of radiation and to the cell type: Michelin et al. [92] employed melanoma FON cells that were exposed to high doses of gamma-radiation, whereas in [111] the authors used sub-lethal doses of gamma-radiation on non-tumoral EC.

4.3. HLA-F

HLA-F was discovered in 1990 [112] and remains the least studied of the non-classical HLA class I molecules. HLA-F expression seems to be limited to the tonsils, spleen, thymic tissue, and placenta, and overall transcription of this gene appears to be higher in lymphoid cells compared with non-lymphoid cells [113]. Similar to HLA-G molecules, HLA-F can form a complex with β2 microglobulin [67], and has been shown to bind to the inhibitory receptors ILT-2 and ILT-4, suggesting a potential role of HLA-F in regulating immune cell function [113,114]. The cytoplasmic expression of HLA-F was found in different tumor cell lines and/or tumor lesions derived from bladder, liver and non-small cell lung cancer as well as glioblastoma [83]. Furthermore, HLA-F expression appears of clinical significance and has been suggested as an unfavourable prognostic factor in patients affected by non-small cell lung cancer [115], and by oesophageal squamous cell carcinoma [116]. In this regard, Ishigami et al. [117] have recently reported that the expression of HLA-F (and HLA-E) in gastric cancer specimens, significantly correlate with depth of invasion, nodal involvement, lymphatic invasion, and venous invasion. In breast cancer cells HLA-F positivity was significantly associated with tumor size [118]. Additionally, anti-HLA-F IgG was found in the sera of patients with various types of cancer, but not in the sera of healthy donors [119].

So far no data have been reported on HLA-F and radiation.

5. Concluding remarks

Ideally, the finding of an anti-neoplastic treatment that favour at the same time up-regulation of classical and reduction of non-classical HLA class I molecules on the surface of tumoral cells, could at least in theory, induce optimal conditions to increase the susceptibility of cancer cells to be recognized and eliminated by NK cells and cytotoxic T lymphocytes. In this regard, and as summarized in Table 1, several publications reported that gamma-radiation augments the surface levels of classical HLA class I molecules [3,120] and decreases surface levels of HLA-G and HLA-E [92,93]. On the other hand, gamma irradiation was also reported to increase the levels of the non-classical HLA-E [111]. Therefore, a single completely effective radiotherapy for the treatment of cancer has not been found so far and there is still much research to be done in order to take advantage on the knowledge of the regulation of HLA molecules by IR for increasing tumor susceptibility to be attacked by the immune system.

Table 1
Effect of gamma irradiation on the surface expression of classical and non-classical MHC molecules.

Molecule	Dosis of gamma irradiation (Gy)	Cell type	Effect on molecule expression	Reference
MHC class I/II	100	Melanoma cells	Up-regulation	[121]
MHC class I/II	100–180	Human multiple myeloma cell lines	Up-regulation	[25]
MHC class I	1–25	Mice and cell lines	Up-regulation	[26]
MHC class I	50 (in 25 fractions)	Melanoma cells (B16)	Up-regulation	[122]
MHC class I	25, 50 and 100	Cervical cancer cells	Up-regulation	[123]
MHC class I	10 and 20	Human carcinoma cell lines	Up-regulation	[34]
MHC class I	20	Cancer cell lines/ biopsies	Up-regulation	[3]
HLA class I	2–20	Brain tumors	Up-regulation	[35]
HLA-DR	30	DCs	Down regulation	[30]
HLA-DR	25–30	DCs	Down-regulation	[33]
HLA-DR	–	CD3+ and CD8+ cells	Down-regulation	[32]
HLA-DR	5	Monocyte derived DCs	Down-regulation	[31]
HLA-G	10–20	Human melanoma cells (FON)	Down-regulation	[92]
HLA-G	–	Basal cell carcinoma/ tumor-infiltrating cells	Down-regulation	[93]
HLA-E	10–20	Human melanoma cells (FON)	Down-regulation	[92]
HLA-E	4	Macrovascular endothelial cells	Up-regulation	[111]

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