

Review Article

Human Leukocyte Antigen (HLA) Molecules and Ionizing Radiation

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Abstract

Despite all the advances achieved in molecular oncology field, radiotherapy remains as one of most widely used and successful treatments for cancer healing. Ionizing radiation has complex effects 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. 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 immunomodulatory 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.

INTRODUCTION

Radiotherapy (RT) has been employed for the treatment of oncological patients for nearly a century, and is presently considered as one of the most successful components of anti-neoplastic treatments [1-3]. Indeed, more than 50% of tumors received radiotherapy, alone or associated with chemo or immunotherapy [4]. The ability of RT to kill cancer cells by a direct cytotoxic mechanism has been well established [1,5]. However, a large body of evidence indicates that RT effects are more complex than the simple elimination of radiosensitive cancer cells. Radiation may induce immunomodulatory activities by up-regulating tumor-associated antigens [6,7], adhesion molecules [8,9], and secretory molecules [10,11], increasing immunogenicity of tumor cells. In this way, RT can improve the efficiency of tumor immunotherapy [2,12-16]. Ionizing Radiation (IR) can also inhibit the growth of distant tumors after local RT, a phenomenon known as the abscopal effect [2]. These immunomodulatory properties of RT emphasize the use of RT in combination with immunotherapy for the treatment of cancer.

Within the immunomodulator molecules that undergo changes in their surface expression after RT we could mention the Major Histocompatibility Complex (MHC) molecules, or Human Leukocyte Antigen (HLA) molecules in humans. These

MHC molecules could be divided in two major classes: MHC class I and MHC class II. The MHC class I heterodimers are constitutively expressed by virtually all somatic nucleated cells. They present endogenous peptides to antigen-specific cytotoxic T lymphocytes, resulting in cell killing [17]. The MHC Class II proteins are only present on specialised antigen-presenting immune cells, including B lymphocytes, macrophages and Dendritic Cells (DCs). MHC II proteins present exogenous antigens that originate extra cellularly 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 in humans 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.

The effects of IR on the immune system have been extensively documented [18,19]. Exposure to IR often leads to immunosuppression, particularly following high-dose irradiation. Immunosuppression is most often ascribed to lymphocytes being highly radiosensitive, owing to their proclivity to undergo radiation-induced apoptosis. In addition to these cytotoxic

effects, IR may induce “danger signals”, which may in turn influence cell responses in the immune system. Such evidence has led to the emerging notion that IR is better considered an immunomodulatory agent rather than an immunosuppressive one [20,21]. The immunomodulatory effects of IR are summarized in Figure 1.

In this review, we will focus on the effects of IR on the expression of HLA class I and class II molecules, highlighting in particular the effects exerted on the expression of non-classical HLA class I molecules, such as HLA-G and HLA-E.

CLASSICAL HLA MOLECULES AND IR

The immunosuppressive effects of IR are well known [22]. Gamma irradiation down-regulates the expression of HLA class II [23-25]. In particular, a decrease in HLA-DR expression has been reported on CD3+ cells and on CD8+ cells after 24, 48 and 72 h of exposure to gamma irradiation [26]. Similarly, Cao and Xiao [27] reported the diminution of HLA-DR expression (together with CD86 and CD80 reduction) after exposure of DCs to 25-30 Gy of gamma radiation.

There is accumulating evidence that adaptive immunity significantly contributes to the efficacy of RT [28]. Under certain circumstances, irradiation can augment the local immune response, for example, irradiated tumors in human patients and in mice are more often infiltrated by leukocytes than the unirradiated tumors [11,29,30] and recent studies in preclinical models showed that the efficacy of RT depends on adaptive immunity [31].

Gamma radiation induce a variety of alterations in tumor cells [12], that includes de novo synthesis of particular proteins and up-regulation in the expression of MHC class I/II molecules [1-3,12-14,16,32-34]. In human tumoral cells and in a mouse models, irradiation increased MHC class I and activated cytotoxic T cells [2,35]. Gamma irradiation up-regulated HLA class I molecules in multiple myeloma cell lines and primary tumors in a dose dependent manner [16]. Similarly, Ma et al. [34] observed that low-dose radiation of human renal cell carcinoma cells induced an increase in the membrane expression of MHC I and MHC II which was dependent of the dose. The up-regulated expression of HLA class I seem specific for gamma radiation, as similar changes

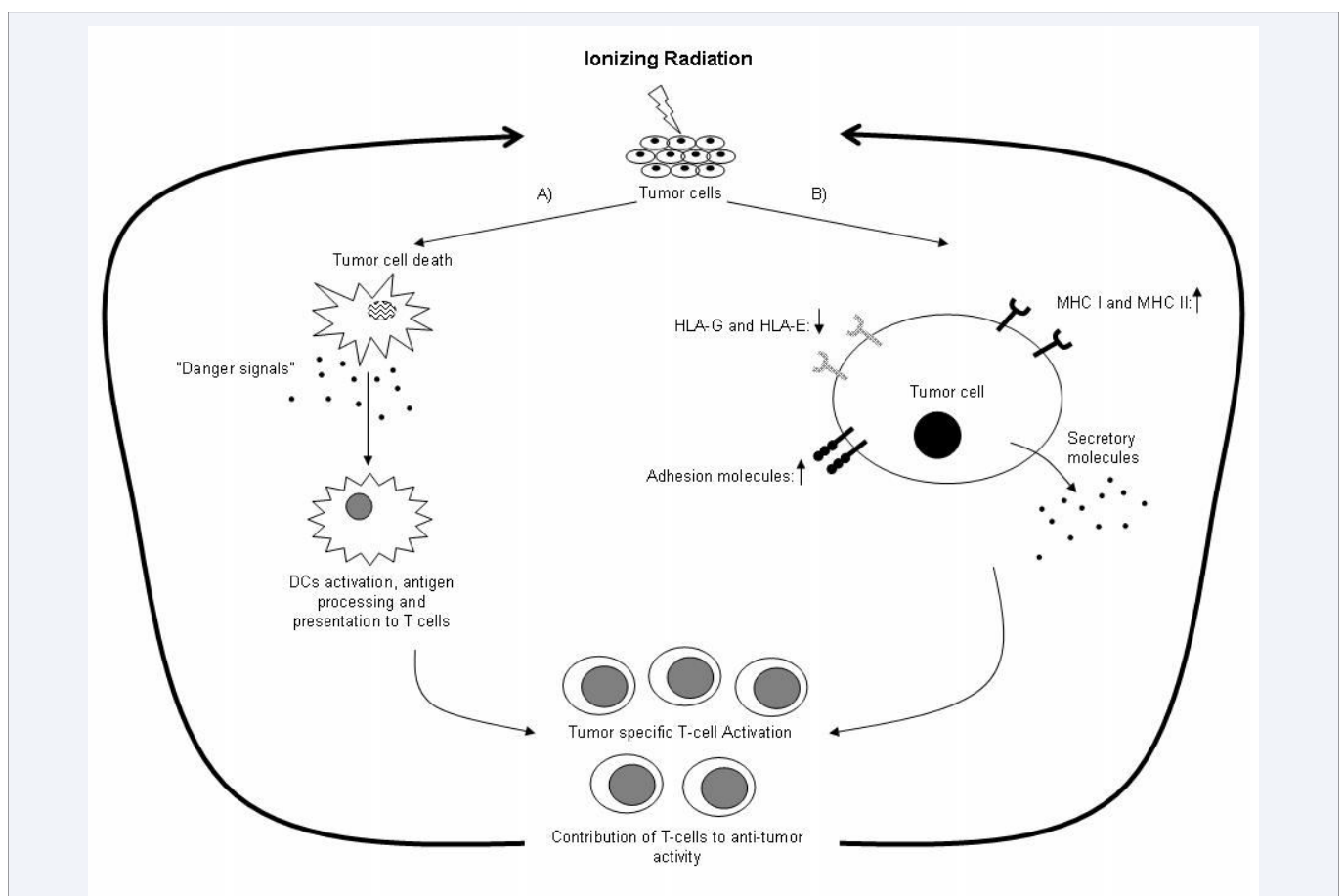


Figure 1 Immunomodulatory action of radiotherapy. A) Tumor cells killed by IR constitute a very good source of antigens for DCs uptake and presentation to T cells. Optimal activation of T cells by DCs presenting tumor antigens can be achieved only in the presence of “danger” signals. B) Radiation up-regulates 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, adhesion molecules, 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.

in gene expression were not observed upon other treatments that induce DNA-damage, hypoxia or hyperthermia [1]. Deficiency of MHC class I antigen presentation is very frequent in tumors [36], and blunted antigen presentation through reduced expression of MHC class I molecules on the surface of cancer cell 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. In addition, gamma radiation increases tumor cell recognition by CD8+T lymphocytes, so the combination of RT with treatments that support tumor specific immunity may result in an increased therapeutic efficacy [1].

The up-regulation of HLA class I after gamma irradiation seems to be a specific feature of malignant cells, since that phenomenon was not observed in normal primary cells [1].

Recently, Wan et al. [37] showed that the transfer of conditioned media from irradiated ZR-75-1 human breast cancer cells to non-irradiated recipient cells increased the expression of both total cellular and cell surface HLA class I in the recipient cells. This observation suggests that HLA I elevation in the recipient cells is due to secreted soluble factors such as cytokines 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 is mediated by IFN- β secretion from irradiated cells. Another inducer of surface MHC class I up-regulation after irradiation is IFN- γ . Lugade et al. [11] tested the influence of IFN- γ signalling (generated after irradiation) on surface MHC class I expression. For this purpose, the authors used murine B16/OVA melanoma cells engineered to over express 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.

In RT, patient irradiation protocols consist in the administration of fractionated doses in order to not cause damage of normal tissues [38,39]. In this regard, Sharma et al. [1] 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.

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

Neoplastic cells have developed a variety of strategies to escape immune control [40]. Alteration of HLA expression and/or function is one of the most frequent mechanisms used by tumor cells to avoid Cytotoxic T Lymphocyte (CTL) 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.

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 [41], thymus [42], cornea [43], pancreas [44], and erythroid and endothelial precursors [45]. Apart from its expression in adult immune privileged organs and in cells of the hematopoietic lineage, induction of HLA-G protein expression could be frequently observed in certain pathological situations such as cancer, transplantation, and viral infectious diseases [46-50]. 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 [51,52]. Recently, de Figueiredo Feitosa et al. [53] 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 tumour associated macrophages/monocytes in lung cancer, melanoma, breast cancer and neuroblastoma [54-57] and by glioblastoma infiltrating microglia [58]. Interestingly, it has also been shown that membrane patches containing HLA-G molecules could be transferred from cancer cells to activated NK cells, through a phenomenon known as trogocytosis [59-61]. As a result, the NK cells that receive the HLA-G molecules stop proliferating and inhibit the cytotoxic effector functions of neighboring 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 [62]. Among these isoforms, the HLA-G1 and HLA-G5 are the most frequently observed [52]. A soluble form of the HLA-G1 molecule (sHLA-G1) also exists which is generated by proteolytic cleavage of the membrane-bound HLA-G1 at the cell surface [63]. Similar to classical HLA class I molecules, HLA-G forms heterodimers with β 2 microglobulin [64]. Association with β 2 microglobulin is required for cell surface expression of HLA-G1 and its interaction with ILT-2 receptor [52]. In addition, HLA-G can form homodimers and homotrimers. These HLA-G oligomers bind to HLA-G inhibitory receptors with increased affinity than monomers [64,65]. IFN- α and IFN- γ (two cytokines frequently present in the tumor microenvironment) increase the formation of HLA-G1 dimers [52]. Moreover, soluble HLA-G5 dimers and multimers have also been detected in ascitic fluid from ovarian carcinoma patients [52].

As we mentioned above, HLA-G exhibits low level of allelic polymorphism, with 31 HLA-G alleles acknowledged in the coding region to date [66]. 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 [67]. Among them, a 14 bp insertion/deletion polymorphism has been described in the 3' UTR in exon 8 [68]. This 14-bp insertion/deletion polymorphism is associated with HLA-G mRNA stability and splicing pattern, which could affect HLA-G protein expression [67, 69].

HLA-G is a potent immunosuppressive molecule and mediates this inhibitory action by binding to inhibitory receptors present on immune cells [62,70]. Three HLA-G-recognizing immunoglobulin-like receptors have been identified: ILT-2, ILT-4 and KIR2DL4 [71-73]. 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 [70]. By binding to these receptors, HLA-G inhibits cytotoxicity of CD8+ T lymphocytes and NK cells, the alloproliferative response of CD4+ T cells [74-77], and the production of Th1 (IFN- γ , IL-2) and Th2 (IL-10) cytokines by CD4+ T lymphocytes [78]. 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 [46]. sHLA-G can also induce apoptosis in T lymphocytes and NK CD8+ cells [79] and it has been recently demonstrated that sHLA-G downregulates the expression of the chemokine receptor in T cells, impairing chemotaxis [80]. 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 [51]. sHLA-G plasma levels are often significantly increased in patients with malignant diseases such as melanoma, glioma, breast and ovarian carcinoma, lung cancer, papillary thyroid carcinoma, and leukaemia [81-84]. 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 [85, 86].

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 [80]. 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 x 10) was also effective in decreasing surface HLA-G1 levels [87]. Our results are in agreement with a previous work of Urosevic et al. [88]. 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 tumours, and in nearly 20% of BCC cases, HLA-G was also expressed in Tumour-Infiltrating Mononuclear Cells (TIMC). The expression of HLA-G on TIMC was associated with longer recurrence-free period in those patients whose tumours recurred. After comparing primary BCCs and BCCs relapsed after radiotherapy, the authors observed a decreased 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 down regulation 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 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 effect of IR in decreasing HLA-G1 cell-surface expression could be through the shedding of membrane-bound HLA-G1 to the medium [87]. Recently, we evaluate if the expression of HLA-G1 intervenes in the survival response to ionizing radiation of human tumoral cells cultured in vitro. For that purpose, we compared the survival frequency after gamma irradiation 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 [89].

HLA-E

HLA-E is ubiquitously 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 [80,90]. In fact, HLA-E is expressed in all human tissues where classical HLA class I molecules are expressed [80,91]. Similar to HLA-G, HLA-E forms a complex with β 2 microglobulin [64]. HLA-E is also expressed by tumour cells of different types of cancers such as colorectal, laryngeal, ovarian, and breast cancer, melanoma, lymphoma and glioma [49,80,92-97]. In addition, HLA-E could be released by melanoma cells as soluble forms (sHLA-E) by proteolytic cleavage of surface molecules [94] and serum levels of sHLA-E were found to be significantly increased in melanoma patients in comparison with healthy donors [98]. Similarly to HLA-G, there is a correlation between HLA-E expression and tumor progression. Indeed, de Kruijff et al. [96] found that the expression of HLA-E in HLA class I-negative breast carcinoma patients was associated with a poor relapse-free period. 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 [99,100] 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 [101]. 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 [102,103]. 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 [97,104]. 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 [80].

With regard to the influence of IR on HLA-E expression, we could observe 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 [87]. Given that HLA-G stabilizes the surface expression

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	[32]
MHC class I/II	100-180	Human multiple myeloma cell lines	Up-regulation	[16]
MHC class I	1-25	Mice and cell lines	Up-regulation	[2]
MHC class I	50 (in 25 fractions)	Melanoma cells (B16)	Up-regulation	[12]
MHC class I	25, 50 and 100	Cervical cancer cells	Up-regulation	[14]
MHC class I	10 and 20	Human carcinoma cell lines	Up-regulation	[35]
MHC class I	20	Cancer cell lines/ biopsies	Up-regulation	[1]
HLA class I	2-20	Brain tumors	Up-regulation	[13]
HLA-DR	30	DCs	Down regulation	[24]
HLA-DR	25-30	DCs	Down- regulation	[27]
HLA-DR	--	CD3+ and CD8+ cells	Down- regulation	[26]
HLA-DR	5	Monocyte derived DCs	Down- regulation	[25]
HLA-G	10-20	Human melanoma cells (FON)	Down-regulation	[87]
HLA-G	--	Basal cell carcinoma/tumor- infiltrating cells	Down-regulation	[88]
HLA-E	10-20	Human melanoma cells (FON)	Down-regulation	[87]
HLA-E	4	Macrovascular endothelial cells	Up-regulation	[105]

of HLA-E [99], 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. [105] reported that irradiation of macrovascular Endothelial Cells (ECs) with sublethal dosis (4 Gy) of gamma radiation induced HLA-E up-regulation, conferring protection against killing by activated NK cells. Irradiation had no effect on HLA-E expression on microvascular ECs and the sensitivity of these cells to NK cells remained unaffected. The difference between both series of results could be due to the dose, since in [87] the cells were exposed to high dosis of gamma radiation, whereas in [105] the authors used sub-lethal dosis of gamma radiation.

HLA-F

HLA-F was discovered in 1990 [106] 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 [107]. Similar to HLA-G molecules, HLA-F can form a complex with $\beta 2$ microglobulin [64], 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 [107,108]. 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 [80]. 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 [109], and by oesophageal squamous cell carcinoma [110]. In addition, anti-HLA-F IgG is present in the sera of patients with various types of cancer, but not in the sera of healthy donors [111]. So far no data have been reported on HLA-F and radiation.

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 the 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 [1,33] and decreases surface levels of HLA-G and HLA- E [87,88]. On the other hand, gamma irradiation was also reported to increase the levels of the non- classical HLA-E [105]. 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 to take advantage on the knowledge of the regulation of HLA molecules by IR for increase tumor susceptibility to be attacked by the immune system.

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