# UPDATES AND DEVELOPMENTS IN ONCOLOGY

Major histocompatibility complex class I and tumour immuno-evasion: how to fool T cells and natural killer cells at one time

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Cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells lyse tumours expressing and lacking, respectively, properly conformed class I molecules of the major histocompatibility complex [MHC-I (Figure 1)]. In keeping with the "missing self" hypothesis [1], a logical extrapolation would be to postulate that the primary goal of a tumour is to elude both defense lines.
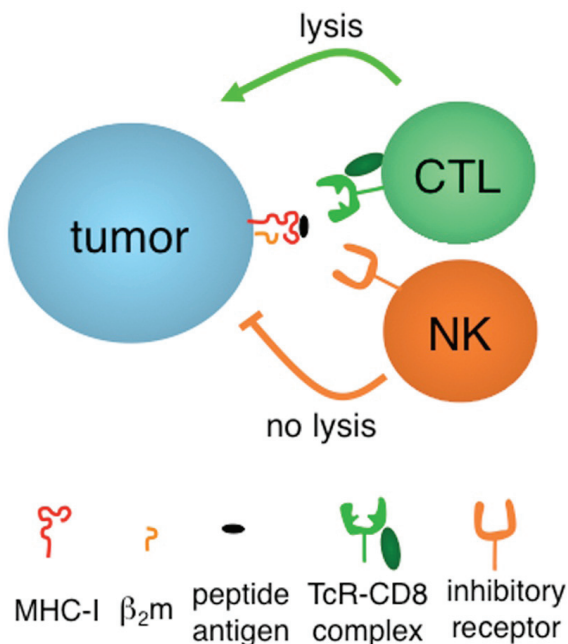
FIGURE 1 *Activation–inhibition and molecules of major histocompatibility complex, class I (MHC-I). Tumours are killed either when they are able to express MHC-I molecules containing tumour peptide antigens recognized by the rearranging T-cell receptor (TCR) of cytotoxic T lymphocytes (CTLs), or when self–MHC-I molecules are lacking or unable to properly engage non-rearranging inhibitory receptors, mainly (but not exclusively) expressed by natural killer (NK) cells. Peptide antigens must be processed and tailored before they can stabilize MHC-I assemblies with β_2-microglobulin (β_2m). Only folded MHC-I molecules serve as ligands of CTLs and NK cells.*

With regard to CTL evasion, tumour losses of MHC-I have been thoroughly studied (our group has more than 200 papers on file) and have, in most instances (although not invariably), been associated with poor outcome (reviewed in Garrido *et al.* [2]). Interestingly, the principle of MHC-I loss also applies to the members of the so-called antigen-processing machinery, such as the transporter associated with antigen processing (TAP), the endoplasmic reticulum aminopeptidase associated with antigen processing (ERAAP in mice and ERAP1 and ERAP2 in humans), and tapasin. These are in charge of, respectively, translocation (into the endoplasmic reticulum), final trimming, and editing of peptide antigens (Figure 1) before loading onto MHC-I. After our initial observation of linked expression patterns between MHC-I and members of the antigen-processing machinery [3], coordinated downregulation of some of these molecules was shown to correlate with poor prognosis [4].

Immunotherapeutic approaches, including the massive administration of dominant tumour antigens in peptide-based T-cell therapy (mostly pursued in melanoma and incorrectly called "vaccination"), impose an even greater selective pressure, possibly leading to an increased advantage for tumour cell variants lacking the antigen-presenting MHC-I molecule or the protein antigen that contains the immunogenic peptide epitope (or both) [2,5]. Particularly when irreversible, MHC-I loss in cancer patients has been claimed to negatively affect prognosis [2].

Assuming that spontaneous and immunotherapy-induced MHC-I losses are drivers and not passengers of tumour progression, it remains to be explained why they do not incite recognition and tumour lysis by NK cells (Figure 1). Porgador *et al.* [6] described a very high prevalence (5 in 13 cases) of irreversible complete MHC-I losses in patients treated with various immunotherapeutic regimens. Despite the cells being very sensitive targets of autologous NK cells *in vitro,* clinical outcome was reported to be poor. Likewise, Pende *et al.* [7] observed that long-term tumour

cell lines, even when established from patients not undergoing immunotherapy, do not express enough MHC-I to protect themselves from NK recognition. Why, then, can these tumours evade in the face of a brisk *in vitro* NK response?

A possible interpretation is that simple cytotoxicity readouts do not reflect the lytic behaviour of immune effectors *in vivo*. After all, if antitumour T-cell counts and activity *in vitro* are not entirely predictive of clinical responsiveness to vaccination [8], why should NK cell responses *in vivo* be faithfully recapitulated in an *in vitro* assay? Alternatively, it might be hypothesized that NK cells have nothing to do with tumour immune surveillance, at least in humans. Indeed, lymphoid cell infiltrates contain many more T cells than NK cells, and only T cells are positively associated with a favorable outcome [9]. Whatever the interpretation, a drastic objection is that certain subsets of NK cells may be important at early stages, but may be long gone by the time the tumour becomes clinically evident and hits the pathology slide.

If NK cells are indeed important, tumours low in MHC-I may elude them either by exploiting certain "gaps" in the inhibitory NK receptor repertoire [10] or, analogous with viral immuno-evasion strategies [11], by "replacing" MHC-I self-inhibitory signals with other inhibitory ligands such as the non-classical MHC-I human leukocyte antigens G (HLA-G) and E (HLA-E) [12–14]. However, at least HLA-E behaves not only as an inhibitory, but also as a triggering ligand [15]. In addition, HLA-E expression may not be restricted to tumours with MHC-I loss as required by the "replacement" model [16,17]. Finally, and quite surprisingly, HLA-E is associated with a good prognosis, at least in certain tumour histotypes [18–20]. It will be of considerable interest to find out if and how tumours use NK-decoy tactics.

Although there are simpler ways to explain MHC-I–driven tumour evasion from both CTL and NK cells, those explanations have received considerably less attention than the foregoing mechanisms. A straightforward assumption is that, besides MHC-I losses adopted by CTL-sensitive tumours, there are mechanisms of MHC-I gains, and those mechanisms are preferred by another set of tumours that are particularly sensitive to NK lysis. It might be envisaged that the opposing influences of CTL and NK cells prevent any major change in MHC-I expression, making less-aggressive tumours resemble their normal counterparts. By contrast, aggressive tumours may escape by adopting whichever immuno-evasion strategy is the most advantageous in the context of the immune response mounted by an individual host. Indeed, a Gaussian distribution of MHC-I expression around "normal" values was observed *in vitro* and *in vivo* in a variety of solid tumours [3,21], MHC-I losses and MHC-I gains both being associated with poor prognosis in colorectal carcinoma [22].

Given the opposing effects of MHC-I molecules on CTL and NK cells (Figure 1), an MHC-I phenotype efficiently triggering both effectors is a contradiction in terms. For instance, in the classical paper that pioneered the "missing self" hypothesis, a TAP-defective mutant of the murine lymphoma RMA, called RMA-S, was shown to be rejected essentially by NK cells [1].

Recently, RNA interference of the same RMA cells for ERAAP (just downstream of TAP in the antigen-processing machinery pathway [23]) similarly resulted in tumour rejection [24], but in addition to NK cells, T cells (CD4 and CD8 alike) were also involved. It appears that poorly folded MHC-I molecules synthesized in the absence of ERAAP can be "seen" as abnormal by several immune effectors. Quite interestingly, only a few human tumours express low ERAP1 and ERAP2 levels [25,26], suggesting that the spontaneous occurrence of this altered, two-edge phenotype is counterselected *in vivo*.

In conclusion, it is fairly clear what tumours look like when they are "out of the hands" of the immune system, but we know much less of "real" tumours under immunologic scrutiny and during immuno-editing *in vivo*. If CTL and NK cells must both be "tuned in" to reject tumours, many more immuno-evasive MHC-I (and non-MHC-I [27]) phenotypes remain to be discovered.

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CONFLICT OF INTEREST DISCLOSURES

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