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Review article

Soluble MHC class I complexes for targeted immunotherapy

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ABSTRACT

Major histocompatibility complexes (MHC) have been used for more than two decades in clinical and pre-clinical approaches of tumor immunotherapy. They have been proven efficient for detecting anti-tumor-specific T cells when utilized as soluble multimers, immobilized on cells or artificial structures such as artificial antigen-presenting cells (aAPC) and have been shown to generate effective anti-tumor responses. In this review we summarize the use of soluble MHC class I complexes in tumor vaccination studies, highlighting the different strategies and their contradicting results. In summary, we believe that soluble MHC class I molecules represent an exciting tool with great potential to impact the understanding and development of immunotherapeutic approaches on many levels from monitoring to treatment.

1. Introduction

MHC class I and class II molecules have been evolutionarily optimized for the presentation of a variety of peptide antigens (Ag's), which are then recognized by T cell receptors (TCR) present on the surface of T cells. To date over thirty unique TCR-MHC class I and over twenty unique TCR-MHC class II complex structures have been described in detail that result in effective $CD8^+$ and $CD4^+$ T cell stimulation, respectively, when loaded with corresponding Ag's [1].

While both MHC class I and II have been utilized for immunotherapy approaches, this review will focus on the use of MHC class I molecules. MHC class I molecules have been used in many multimeric formulations, from dimeric to dodecameric (reviewed in [2,3]), for detection and analysis of antigen-specific $CD8^+$ T cell responses. Specifically, after immobilization on artificial structures such as paramagnetic beads, liposomes or biodegradable backbones of different sizes and shapes, MHC class I molecules have been used to efficiently stimulate or modulate antigen-specific $CD8^+$ T cell responses *in vitro* and *in vivo* (reviewed in [4–7]). More recently MHC class I molecules have also been utilized for redirection of antigen-specific $CD8^+$ T cells to tumor cells, which they would otherwise not recognize [8–13]. Furthermore, MHC class I molecules have been utilized to deplete antigen-specific $CD8^+$ T cells. In these cases, they were conjugated to alpha emitting epitopes or toxins, or they were immobilized onto a surface of a paramagnetic or biodegradable bead together with a death inducing second signal such as an anti-Fas monoclonal antibody (mAb) (reviewed in [14] and [15–18]). Also noteworthy is that Yoshida et al. show in an elegant way how one can use the significant technological improvements in mass spectrometry based immunopeptidomics and *in silico* methodologies for the identification of tumor-antigens by utilizing transferred secreted human MHC class I molecules presenting peptides derived from intracellular proteins, which are then further processed and used for vaccination [19].

Finally, soluble MHC class I molecules have been used in various vaccination protocols resulting in a wide range of contradicting outcomes, reaching from tolerance induction to induction of anti-tumor responses [20–28]. Here, we will discuss possible reasons and explanations for either favorable or unfavorable immunotherapeutic soluble peptide-MHC-class I complex (pMC) based vaccination strategies. This work wants to contribute to the claim of Hu et al. that the full toolbox of immunotherapeutic approaches to cancer therapy has to be revisited to unleash the immune system's full potential [29].

1.1. Possible mechanism of action for soluble pMC

If a T cell engages a pMC (signal 1), it depends on the presence and type of the co-stimulatory signal (signal 2) if it results in activation, anergy or depletion. While immobilized pMC's have been described to

Abbreviations: MHC, major histocompatibility complex; mAb, monoclonal antibody; APC, antigen presenting cell; aAPC, artificial antigen presenting cell; DC, dendritic cell; Ag's, antigens; pMC, peptide-MHC-class I complex; TCR, T cell receptor

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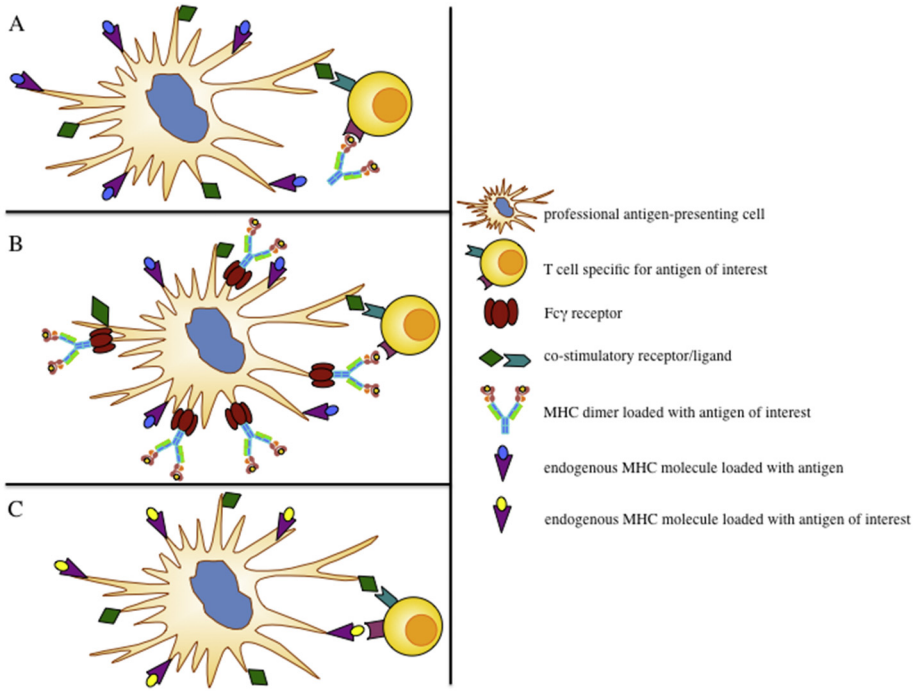

Fig. 1. Schematic of possible mechanisms of action for soluble peptide MHC class I complexes (pMC). (A) Direct interaction of soluble pMC with T cells. (B) Interaction of T cells with Fcγ receptor bound pMC's on professional antigen-presenting cells (APC). (C) Recognition of pMC-antigens as a result of antigen cross-presentation. In general the nature and extent of the induced T cell response will be dependent on a pro-inflammatory environment and co-stimulation provided by APC.

activate naïve $CD8^+$ T cells *in vitro* by a CD28/B7 and LFA-1/ICAM-1 independent mechanism [21] following the "strength-of-signal" hypothesis [30,31], activation is also influenced by an adjuvant induced pro-inflammatory environment in combination with co-stimulatory signals provided by professional antigen-presenting cells (APC) or activated T cells (Fig. 1A).

A second mechanism is the direct stimulation of a TCR by Fcγ-receptor (Fcγ-R) bound pMC on the surface of an APC. It has been demonstrated that antibody Fc functionalized pMC's can bind *via* Fcγ-RI and Fcγ-RIII onto professional antigen-presenting cells which enables them to activate antigen-specific T cell responses. This can be further enhanced through maturation of the APC with immune-stimulatory agents, such as lipo-poly-saccharide (LPS) [24], Poly (I:C) [32], and anti-CD40 mAb [23,33,34]. These agents cause up-regulation of Fcγ-R and expression of co-stimulatory molecules. Thus mature APC can present more pMC and provide better co-stimulation, which results in enhanced T cell stimulation, activation and proliferation (Fig. 1B).

Finally, pMC can be internalized by APC such as immature DC, by a mechanism called phagocytosis and/or pinocytosis. This initial uptake of pMC's initiates a process described as cross-presentation. After internalization the pMC can be exported into the DC cytosol and processed by the proteasome. Subsequently, the dissociated peptide of a pMC will then be loaded onto host MHC class I molecules (reviewed in [35,36]). Alternatively, the pMC will be degraded into various peptides in the phagosome and directly loaded onto MHC class I molecules resulting in the presentation of multiple antigenic peptides, all different from the original loaded peptide of the pMC (reviewed in [37]). Though nature and extent of the immune response will depend on the DC phenotype (Fig. 1C).

While all three mechanisms may contribute to the generation of a pMC induced immune response, to date it is not clear as to which extent each mechanism contributes to the formation of this response.

However, it has been demonstrated that cross-presentation cannot be the only mechanism, as vaccination of TCR transgenic 2C mice that are of $H2^b$ background with soluble QL9-peptide loaded L^d-Ig molecules initiated a 2C T cell response. While 2C cells recognize QL9-peptide in the context of an L^d-MHC molecule in an allo-response, the QL9-peptide cannot be presented on the host K^b-MHC molecules. Therefore, the 2C response must be induced by one of the other two mechanisms [23]. Furthermore, it could be demonstrated that anti-CD40 mAb induced maturation of APC prior to pMC immunization was crucial for an effective immune response. Administration of anti-CD40 mAb together with or after pMC administration did not result in formation of a robust immune response, which further supports that the pMC is presented on the cell surface and not internalized [23].

1.2. Context of stimulation

In general, to ensure a proper $CD8^+$ T cells response upon re-stimulation a co-stimulatory signal during the initial stimulation is required. Furthermore, while primary $CD8^+$ T cell responses can be independent of $CD4^+$ T cell, dependent on antigen levels and presence of danger signals, the generation of a long-lived functional memory $CD8^+$ T cell response requires sufficient $CD4^+$ T cell help (reviewed in [38]).

Recently we demonstrated that pre-treatment with anti-CD40 mAb prior to pMC immunization initiated and significantly increased formation of a long-lived memory $CD8^+$ T cell response *in vivo* [23]. This is in line with findings demonstrating that CD40/CD40L signaling between $CD4^+$ T cells and APC renders the later one into a stimulatory cell for efficient $CD8^+$ T cell priming [39]. Therefore, application of anti-CD40 mAb leads to APC maturation and effective co-stimulation along with pMC resulting in a robust memory $CD8^+$ T cell response. Interestingly, Goldstein et al. demonstrated efficient activation of $CD44^-$ naïve $CD8^+$ T cell by stimulation with immobilized pMC's independent of CD28/B7 and LFA-1/ICAM-1 signaling. This *in vitro* data was in line with the assumption that generation of a primary T cell response does not require an obligatory co-stimulation but whether these T cells developed a memory phenotype was not investigated [21,22]. Another study from Carey and colleagues, co-applying LPS and pMC demonstrated effective $CD8^+$ T cell priming leading to prolonged survival after *in vivo* HSV-1 challenge [24]. Similarly, Sakita et al. and Maile et al. could demonstrate the formation of an *in vivo* anti-pMC T cell response but neither study provided any data regarding the T cell phenotype [25,26]. Furthermore, both studies utilized pMC isolated from *E.coli* inclusion bodies that might bear the risk of LPS contamination or non-specific immune stimulation by a different glycosylation pattern of the pMC [40].

In summary, we feel that more complete, comparative studies are