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REVIEW

Intercellular Exchange of Surface Molecules and its Physiological Relevance

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Abstract For many decades, cellular immunologists have relied on the expression of various cell surface molecules to divide cells into different types and subtypes to study their function. However, in recent years, a large and fast-expanding body of work has described the transfer of surface molecules, including MHC class I and II molecules, between cells, both in vitro and in vivo. The function of this process is still largely unknown, but it is likely to have a significant role in the control of the immune system. It is also likely that this process takes place in a regulated rather than stochastic manner, thus providing another way for the immune system to orchestrate its function. In this review we will summarize the key findings so far, examining the mechanisms of transfer, the consequences of this transfer as shown by in vitro experiments, and possible consequences for the wider immune response.

Keywords Intercellular transfer · MHC · Antigen presentation

Abbreviations

MHC	Major histocompatibility complex
DC	Dendritic cell
APC	Antigen-presenting cell
MICA	MHC (HLA) class I chain-related gene A
ICAM-1	Intercellular adhesion molecule 1
LFA-1	Lymphocyte function-associated antigen 1
NK	Natural killer
SMAC	Supramolecular activation cluster
SMIC	Supramolecular inhibition cluster
TcR	T cell receptor

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Introduction

The function of cells within the immune system is tightly controlled by their surface molecules, which act either as ligands or as receptors. They form a vital component of the communication system between cells. In addition, they enable the body to distinguish between self and non-self. Immunologists have exploited this system to distinguish one cellular subset from another. However, it has become clear that at least some of these molecules, including major histocompatibility complex (MHC) molecules, can be transferred between cells, suggesting that the system is much more fluid than once thought. Although the mechanisms of this transfer are becoming clearer, whether it has any physiological function under normal circumstances and, if so, what its consequences are remain largely unknown. Given the reliance of cells on their surface molecules, it is likely that molecular exchange between cells will have important implications. A greater understanding of this process would further our knowledge of cell-to-cell interactions in the immune system and may provide new therapeutic avenues for intervention.

Transfer of cell surface molecules was first described over 30 years ago when T cells were shown to acquire surface immunoglobulin molecules from B cells (Hudson and Sprent 1976; Hudson et al. 1974) and antigens from macrophages (Bona et al. 1973). It was later shown that both MHC class I and II molecules were transferred passively to T cells (Lorber et al. 1982; Sharrow et al. 1980, 1981). Only much more recently, with the availability of

more sensitive techniques such as flow cytometry, has this process been confirmed and shown to be extensive. In addition, until recently, advances in this field have been hampered by the lack of a physiologically or clinically relevant in vivo model. Therefore, for a long time it was unclear whether this transfer was purely an in vitro phenomenon or whether it took place under normal physiological conditions.

In Vitro Studies

Until the recent development of several in vivo models, almost all studies were carried out in vitro. Molecules shown to be transferred so far include MHC class I and II (Harshyne et al. 2001; Patel et al. 1999; Russo et al. 2000), CD3 (Whale et al. 2006), CD21 (Tabiasco et al. 2003), CD80 (Sabzevari et al. 2001), CD86 (Game et al. 2005), OX40L (Baba et al. 2001), endothelial cell molecules (Brezinschek et al. 1999), natural killer (NK) receptors (Domaica et al. 2009; Sjostrom et al. 2001; Vanherberghen et al. 2004), chemokine receptors (Mack et al. 2000), and GPI-anchored proteins (Anderson et al. 1996; Liu et al. 2002) (Table 1). Sjostrom et al. (2001) used Western blotting to determine that the transferred protein was the same size as the full-length protein, and therefore the acquired molecule was likely to be intact. Many cell types have been implicated in this process to different extents. In the case of T cells, uptake of MHC class II is carried out much more efficiently by activated cells than by naïve cells (Tsang et al. 2003). However, for antigen-presenting cells (APCs), transfer occurs readily in the steady state (Patel and Mannie 2001).

Mechanisms of Transfer

Transfer at the Immunological Synapse

The first immunological synapses described (Monks et al. 1998) are now known to be monocentric (stable) synapses which are made up of two main domains: central and peripheral. Monocentric synapses result between interacting T cells and APCs, where adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) are found in the peripheral supramolecular activation cluster (SMAC) and MHC-peptide complexes are found in the central SMAC. This arrangement is mirrored by the cognate ligands on the interacting T cell. Conversely, inhibitory immunological synapses that form during immune surveillance of target cells expressing MHC class I by NK cells have been found to contain MHC class I complexes in the peripheral supramolecular inhibition cluster (SMIC) and the adhesion molecule LFA-1 in the central SMIC. As the interface between two cells, the immunological synapse is clearly an important feature of intercellular communication. This, and the prolonged cell contact involved, suggests that the intercellular transfer of surface molecules may also occur during the immunological synapse.

The importance of the formation of the immunological synapse in the transfer of cell surface molecules has been shown by the finding that T cells acquire molecules much more efficiently from syngeneic APCs, i.e. where synapses can be formed (Arnold et al. 1997). Both the T cell receptor (TcR) and CD28 can acquire their respective ligands during a synapse (Huang et al. 1999; Hwang et al. 2000; Wetzel et al. 2005). Bystander molecules can also be acquired during the synapse, with MHC class I complexes transferred onto $CD4^+$ T cells from APCs due to their presence in the immunological synapse (He et al. 2007). Synapses between other cell types are also associated with the uptake of receptor ligands. Tumor cells can transfer molecules through the synapse (Poupot and Fournie 2003). B cells take up antigen from T cells during the synapse between the two cells (Batista et al. 2001). Cytotoxic T cells acquire fragments of plasma membrane from target cells (Hudrisier et al. 2001; Stinchcombe et al. 2001), as do $\gamma\delta$ T cells (Espinosa et al. 2002), and NK cells also transfer molecules through the synapse (Carlin et al. 2001; Roda-Navarro et al. 2006; Tabiasco et al. 2002).

The transfer of cell surface molecules can begin within minutes after the formation of the synapse (Huang et al. 1999; Tabiasco et al. 2002; Wetzel et al. 2005). Adsorption of receptor ligands onto the cell surface is in most cases followed by internalization of the ligand–receptor pair, but it is clear that in some cases the adsorbed molecule either remains on or is returned to the cell surface in a functional form.

Wetzel and colleagues visualized the transfer of MHC molecules to T cells during the dissolution of the immunological synapse, but also observed the transfer of these molecules after cell contact without the formation of a mature synapse (Wetzel et al. 2005). Therefore, transfer of molecules through the synapse is not the only method of molecular transfer. Cell surface molecules, with their strong anchors in the plasma membrane, are not in all likelihood removed alone. A portion of membrane, including proteins, is transferred as a whole, a process known as trogocytosis (Joly and Hudrisier 2003). Dendritic cells (DCs) have also been shown to acquire membrane from surrounding cells in this way, a process that may involve the class A scavenger receptor present on DCs (Harshyne et al. 2001, 2003). In addition, T cells acquire membrane fragments, including cell surface proteins, from endothelial cells during transendothelial migration (Brezinschek et al. 1999).

Table 1 Summary of transferred molecules and the cells involved described to date

Transferred molecule	Donating cell	Receiving cell	References
MHC class I	DC	DC	Herrera et al. (2004); Smyth et al. (2008)
MHC class I	Endothelial cell	DC	Herrera et al. (2004)
MHC class I	Tumor cell	DC	Russo et al. (2000)
MHC class I	APC	T cell ($CD4^+$)	Hao et al. (2007); He et al. (2007); Xiang et al. (2005)
MHC class I	DC	T cell ($CD8^+$)	Huang et al. (1999); Xia et al. (2006)
MHC class I	Not defined	NK cell	Sjostrom et al. (2001)
MHC class II	DC	DC	Herrera et al. (2004)
MHC class II	Tumor cell	DC	Russo et al. (2000)
MHC class II	Endothelial cell	DC	Herrera et al. (2004)
MHC class II	Epithelial cell	DC	Millet et al. (2008)
MHC class II	Epithelial cell	Epithelial cell	Millet et al. (2008)
MHC class II	APC	T cell ($CD4^+$)	Arnold and Mannie (1999); Game et al. (2005); Tsang et al. (2003); Undale et al. (2004); Wetzel et al. (2005); Xiang et al. (2005)
MHC class II	APC	T cell ($CD8^+$)	Undale et al. (2004)
T cell receptor/CD3	T cell ($CD4^+$)	DC	Busch et al. (2008)
B cell receptor	B cell	B cell	Quah et al. (2008)
IgM	B cell	T cell	Hudson and Sprent (1976); Hudson et al. (1974)
CD80	APC	T cell ($CD4^+$)	Game et al. (2005); Hwang et al. (2000); Sabzevari et al. (2001); Tatari-Calderone et al. (2002); Xiang et al. (2005)
CD80	APC	T cell ($CD8^+$)	Hwang et al. (2000); Xia et al. (2006)
CD86	APC	T cell ($CD4^+$)	Game et al. (2005); Hwang et al. (2000)
CD86	APC	T cell ($CD8^+$)	Hwang et al. (2000)
OX40L	Not defined	T cell ($CD4^+$)	Baba et al. (2001)
CD2	T cell ($CD4^+$)	DC	Busch et al. (2008)
MICA	Target cell	NK cell	McCann et al. (2007)
NKG2D	NK cell	Target cell	Roda-Navarro et al. (2006)
CCR5	PBMC	Monocytes	Mack et al. (2000)
CD31	Endothelial cell	T cell ($CD4^+$)	Brezinschek et al. (1999)
CD49d	Endothelial cell	T cell ($CD4^+$)	Brezinschek et al. (1999)

DC dendritic cell, *APC* antigen-presenting cell

Transfer Through Exosomes

In addition to being transferred during cell contact, molecules can also be transferred between cells by the release of vesicles called exosomes from one cell and the uptake of these by another cell. Exosomes (reviewed in Fevrier and Raposo 2004; Simons and Raposo 2009; Thery et al. 2009) are 50- to 90-nm vesicles contained within multivesicular bodies within the cell and are secreted when the multivesicular body fuses with the cell membrane. Exosomes are formed from the plasma membrane of the cell and thus express many of the cell surface molecules present on the cell they derive from.

Exosomes are secreted from APCs (Arnold and Mannie 1999), including DCs (Zitvogel et al. 1998) and B cells (Raposo et al. 1996), and from activated T cells (Blanchard et al. 2002), and intestinal epithelial cells (van Niel et al. 2001), amongst others. The directions of exosome transfer demonstrated so far include DC to DC (van Niel et al. 2001), APC to T cell (Arnold and Mannie 1999), and tumor cell to DC (Wolfers et al. 2001). Exosomes are released from both immature and mature DCs, with the phenotype of the exosome reflecting the maturation status of the parent cell (Segura et al. 2005a).

Exosomes have been shown to include in their repertoire MHC (both class I and II) and co-stimulatory molecules (Zitvogel et al. 1998) and have been shown to stimulate $CD8^+$ T cell responses (Hwang et al. 2003; Zitvogel et al. 1998), although there is evidence to suggest that these exosomes in $CD4^+$ T cell responses do not directly activate T cells but instead act to deliver MHC class II to DCs through integration into the DC membrane (Thery et al. 2002). This integration of exosomes into the plasma membrane occurs following capture through the integrin LFA-1 on the recipient cell binding to ICAM-1 on the

exosome (Nolte-'t Hoen et al. 2009; Segura et al. 2007; Segura et al. 2005b). Cells with high levels of the active form of LFA-1 (e.g. $CD8^+$ DCs and activated T cells) therefore acquire exosomes more effectively than other cell types. Macrophages appear to capture exosomes through phosphatidylserine receptors such as Tim1 and Tim4, which bind phosphatidylserine present on exosomes (Miyanishi et al. 2007; Zakharova et al. 2007). As well as being incorporated into the membrane of recipient DCs, exosomes can be endocytosed, processed, and presented in the normal manner (Morelli et al. 2004).

Transfer Along/through Nanotubes

In addition to being secreted by cells, vesicles may travel between cells within nanotubes. Nanotubular networks (reviewed in Davis and Sowinski 2008) are newly discovered connections between various cell types, including DCs (Watkins and Salter 2005), macrophages (Onfelt et al. 2006), T cells (Sowinski et al. 2008), and NK cells (Onfelt et al. 2004).

Nanotubes may be formed in two ways. They can form between cells after the demise of the immunological synapse as the cells dissociate (Onfelt et al. 2004), possibly resulting from membrane bridges observed during the cytotoxic T cell/target-cell synapse (Stinchcombe et al. 2001). Alternatively, they can be formed through an extension of membrane from one cell fusing with a neighboring cell membrane (Rustom et al. 2004). As well as carrying vesicles and other cytoplasmic components between cells, cell surface molecules can travel along the membranes of the nanotubes and onto the connected cell (Onfelt et al. 2004; Rustom et al. 2004). Although most of the work on nanotubes has been performed in vitro, these structures have recently been observed in vivo between MHC class II^+ cells in the murine cornea, and the incidence of nanotube formation was shown to increase during inflammation, suggesting a possible physiological role (Chinnery et al. 2008).

The different mechanisms of transfer of cell surface molecules are not mutually exclusive. During interactions between DCs and T cells, DCs have been shown to acquire CD2 from T cells in a cell contact-dependent manner and acquire several other T cell surface molecules, including CD3/TcR and OX40, through exosomes (Busch et al. 2008). CD2 is transferred early after contact and without the need for T cell activation, possibly by trogocytosis, while the exosome-delivered molecules are acquired much later, following activation of the T cells.

Duration of Surface Expression

For a transferred molecule to be functional, it would need to remain on the cell surface for a substantial period of time. The stability of transferred molecules has been investigated in vitro. MHC molecules have been found to remain on recipient cells for as long as 2 days following transfer (Dolan et al. 2006b), providing ample opportunity for interaction of this molecule with its ligand. Not all molecules have stable expression after transfer, however. The co-stimulatory molecules CD80 and OX40L are present for only 4 and 12 h, respectively (Baba et al. 2001; Hwang et al. 2000). The difference in the duration of surface expression of a transferred molecule may depend on the mechanism of transfer. Busch et al. (2008) lowered the pH of recipient cells and showed that CD2, transferred through cell contact, was not removed, whilst molecules such as CD3, OX40, and PD-1, transferred via exosomes, were removed, suggesting that molecules become more firmly established through transfer by cell contact. This stability in the membrane, related to the mechanism of transfer, may be reflected in the length of time the molecule is expressed.

Functionality of Transferred Molecules

The transfer of molecules between cells is only important if the molecule remains functional on its host cell and influences its function or the way that it interacts with other cells. This has been shown to be the case in many circumstances. DCs can stimulate allogeneic T cells after acquisition of foreign MHC (Russo et al. 2000) and can effectively stimulate both $CD8^+$ and $CD4^+$ T cells through acquired MHC class I and II, respectively (Dolan et al. 2006a, b; Xiang et al. 2005). MHC class II/peptide complexes transferred from T cells to DCs and B cells are also able to stimulate a $CD4^+$ T cell response (Nolte-'t Hoen et al. 2004). The functionality of MHC and co-stimulatory molecules such as CD80, CD86, and OX40L transferred to T cells was demonstrated by these cells' subsequent ability to stimulate naïve T cells and thus dispense with the services of APCs (Baba et al. 2001; Game et al. 2005; Sabzevari et al. 2001; Tatari-Calderone et al. 2002; Zhou et al. 2005). Presentation of acquired MHC class II/peptide complexes by T cells can also induce hyporesponsiveness (Tsang et al. 2003) and confer regulatory ability upon these cells (LeMaoult et al. 2007). NK cell ligands acquired by $CD4^+$ T cells from tumor cells bind to and activate NK cells (Domaica et al. 2009). Inhibitory NK receptors, GPI-anchored proteins, and MHC class II taken up by polymorphonuclear cells have all been found to be functional following transfer (Anderson et al. 1996; Sjostrom et al. 2001; Whale et al. 2006). The consequences of surface molecule acquisition confirm the transfer of intact molecules that can subsequently bind to their ligand at the cell surface and signal through their intracellular tail.

Indeed, phosphotyrosine has been found in association with transferred NK cell receptors, suggesting the induction of a signaling cascade (Vanherberghen et al. 2004). This functional viability of cell surface molecules following transfer suggests that they may have a physiological role.

Consequences

The consequences of transfer appear to be many and varied, at least under the in vitro conditions where this process has been investigated. The most basic consequence of this process may be that it allows cells in an immune synapse to dissociate, with the transfer of a receptor from one cell to the other removing the bond between the two cells. This is especially true of high-avidity interactions.

APC-to-APC Transfer

B cells appear to use transfer to amplify the immune response, as activated B cells can transfer their B cell receptors to surrounding B cells, enabling uptake of that specific antigen by non-antigen-specific neighboring B cells (Quah et al. 2008). This allows a significant immune response to be generated despite the very low numbers of B cells of each specificity. Cross-linking of the acquired B cell receptor did not result in activation of the cell, which was therefore acting only as an APC, and did not amplify the B cell response to the antigen.

Antigen spreading is also the result of MHC transfer in the thymus, between thymic epithelial cells, and from thymic epithelial cells to DCs. This may allow rare antigens to be more widely expressed and increase the chances of contact with a developing T cell, which can then be positively or negatively selected as appropriate (Millet et al. 2008). It has also been suggested that different populations of DCs may be responsible for the tasks of antigen processing and stimulation of T cells. Thus DCs in the periphery may transfer MHC to allow antigen to be presented by the correct cell type in the correct place (Smith and Fazekas de St Groth 1999).

Regulatory T Cells

MHC transfer has been shown to increase the suppressive activity of regulatory T cells. $CD4^+$ Tr1 cells acquired peptide/MHC class I complexes from the DCs used in their generation. This uptake resulted in greater suppression of antigen-specific $CD8^+$ T cell responses in comparison with those Tr1 cells which did not acquire peptide/MHC class I. In this situation, MHC transfer may be a means to down-regulate an ongoing immune response (Hao et al. 2008).

APC-to-T Cell Transfer

For T cells it appears that the transfer of MHC class II/peptide complexes and co-stimulatory molecules can allow either continuation of an immune response or its down-regulation, presumably depending on the environmental conditions. It is thought that MHC class I uptake can render T cells sensitive to killing by surrounding T cells with the same specificity, i.e. fratricide (Chai et al. 1998; Cox et al. 2007; Huang et al. 1999). The transfer of MHC from APCs to T cells may also act to down-regulate the immune response by removing the stimulus available to other T cells (Kedl et al. 2002), although this may have a further consequence of affinity maturation. However, activated $CD4^+$ T cells that have acquired peptide MHC class I complexes via exosomes can then go onto stimulate a naïve (Hao et al. 2007; Xiang et al. 2005) or memory (Shi et al. 2006) $CD8^+$ T cell response. This is not unique to the mechanism of transfer, as T cells that have acquired MHC class II from APCs through cell contact can also go onto stimulate a $CD4^+$ T cell response (Undale et al. 2004). Acquisition of CD80 also allows the continuation of the co-stimulatory signal for 24 h after the dissolution of the synapse (Zhou et al. 2005).

The outcome of transfer probably depends on the balance between all these different effects, with either up- or down-regulation of the immune response occurring as appropriate to the conditions. For example, a T cell may acquire peptide MHC complexes from an APC, allowing it to stimulate a neighboring T cell. If this occurs in the early stages of an immune response, T cells of the same specificity will be rare and the dispersal of the peptide MHC complex may amplify the immune response. If, however, the immune response is well developed, the proliferation of antigen-specific T cells may result in the T cell expressing peptide/MHC being surrounded by other T cells, leading to death through fratricide (Huang et al. 1999).

The complex nature of MHC transfer is further demonstrated by the transfer of peptide/MHC class I complexes from APCs to $CD8^+$ T cells. The consequences of this process appear to be twofold. Firstly, the $CD8^+$ T cell bearing peptide/MHC class I can stimulate antigen-specific $CD8^+$ memory T cells to enhance the immune response. However, these peptide/MHC class I-carrying cells cause the death of antigen-specific APCs and other $CD8^+$ T cells that have acquired peptide MHC class I complexes, which acts to down-regulate the immune response (Xia et al. 2006). Similar results have been found with $CD4^+$ T cells that have acquired MHC class I and II (Umeshappa et al. 2009). In addition, DCs that acquire CD3/TcR complexes from $CD4^+$ T cells become less able to stimulate a $CD4^+$ T cell response, apparently due to the masking of MHC class II complexes on the DC surface, but retain the ability to

stimulate a $CD8^+$ T cell response (Busch et al. 2008). Although this seems contradictory, these differing outcomes may be carefully controlled to allow the stimulation of the correct immune response (in these cases, cytotoxic T-lymphocyte responses), whilst removing the stimulus from APCs and so preventing the response from becoming out of control, a situation which could easily arise given the ability of MHC to move between cells. These data reveal that MHC transfer is a complicated and structured process rather than a random redistribution of cell surface molecules among cells.

Regulation of Molecular Transfer

There are many examples of the regulation of MHC transfer. B cell receptors can only be transferred to other B cells (and these bystander B cells do not acquire all of the functions of the transferred molecule) (Quah et al. 2008) and, in a similar way, exosomes can only be captured by cells expressing certain receptors (Miyanishi et al. 2007; Nolte-'t Hoen et al. 2009; Segura et al. 2007; Segura et al. 2005b; Zakharova et al. 2007). Exosome transfer is further regulated by the make-up of these vesicles. Busch et al. found that several co-stimulatory molecules, such as CD28 and CD4, were not transferred through exosomes from T cells to DCs, suggesting that an active sorting process takes place (Busch et al. 2008), and the increased levels of tetraspan proteins on B cell exosomes, compared with, for example, the transferrin receptor, a marker for plasma membranes, provides further evidence for this (Escola et al. 1998).

Nanotubes often form between cells that have been in cell contact (the duration of which must be over 4 min (Sowinski et al. 2008)), and therefore the sharing of information is restricted by this initial contact, as in the case of molecular transfer during a synapse. The direction of transport along nanotubes can also be controlled, with unidirectional (Rustom et al. 2004) or bidirectional (Onfelt et al. 2006) transfer being observed depending on the cell types involved.

The stability of expression of the transferred molecules can also provide a means for regulation. As described above, MHC molecules have been found to remain on recipient cells much longer than co-stimulatory molecules following transfer (Baba et al. 2001; Dolan et al. 2006b; Hwang et al. 2000). After loss of co-stimulatory molecules, cells that have acquired MHC molecules will no longer be able to stimulate T cells and may instead down-regulate the immune response through the induction of anergy (Smyth et al. 2007).

In contrast to the tight regulation of co-stimulatory molecules, NK cells acquire MICA from target cells, and this molecule can then be transferred between NK cells, during which time it remains functional (McCann et al. 2007). Again, the differences seen regarding the transfer of different surface molecules suggest a complex and organized process.

In Vivo Relevance of Intercellular Transfer of Molecules

Most of the experimental evidence discussed above has been obtained in vitro or under artificial conditions in vivo such as injection of allogeneic cells. This has led to skepticism as to whether intercellular molecular exchange takes place under normal physiological conditions. Millet and colleagues transplanted bone marrow from MHC-null mice into allogeneic wild-type recipients and showed that in the thymus, donor DCs had acquired MHC class II from recipient epithelial cells, which was expressed at 5% of normal levels. When the strain combination was reversed, recipient MHC-deficient epithelial cells did not acquire MHC class II from wild-type donor cells, demonstrating the unilateral nature of this transfer (Millet et al. 2008).

Transplantation is the only example where foreign MHC molecules are deliberately introduced. Our laboratory has demonstrated that following allogeneic heart or kidney transplantation in mice, cells can be found within the recipient spleen which express both donor and recipient MHC class II molecules. This transfer was extensive and bidirectional; recipient cells can acquire MHC molecules from donor cells and vice versa (Brown et al. 2008). A possible mechanism for this was suggested by Montecalvo et al. (2008), who showed that graft-infiltrating leukocytes contain exosomes which are released ex vivo. The bidirectional nature of DC-to-DC transfer of MHC class II molecules had previously been shown upon injection of allogeneic DCs (de Heusch et al. 2007). One interesting observation is that it takes place only within the spleen of the recipient, but not within the graft itself. The reason for this is still unclear.

Physiological Significance of the Intercellular Transfer of Molecules

The physiological significance of MHC transfer is yet to be elucidated, but this process may have consequences for transplantation, autoimmunity, and the antitumor response. The extent of molecular transfer, with the large number of molecules transferred and the wide variety of cells able to participate in this process, suggests a physiological consequence.

In transplantation, the expression by recipient APCs of not only recipient MHC class II-presenting donor peptides

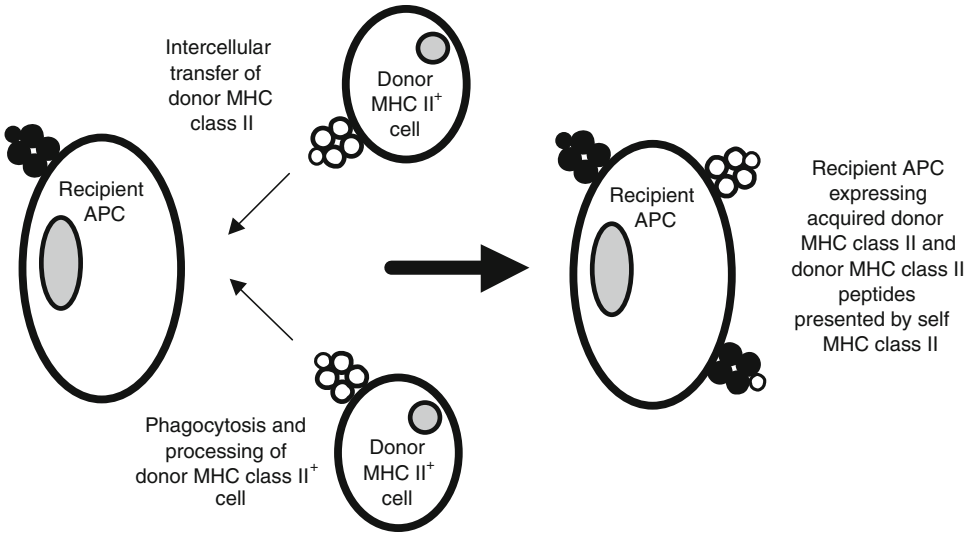

Fig. 1 In the context of transplantation, transfer of MHC class II molecules from donor APCs would allow recipient APCs to present antigen through the direct antigen-presentation pathway as well as the conventional indirect pathway, whereby donor cells are processed and donor MHC peptides are presented by recipient MHC class II molecules. This has been termed the "semi-direct" pathway of alloantigen presentation

but also donor-derived MHC class II/peptide complexes would allow the stimulation of both the direct and indirect alloresponse. This has been termed the "semi-direct" antigen-presentation pathway (Herrera et al. 2004) (Fig. 1). In HIV infection it has been shown that the chemokine receptor CCR5, which is the point of entry into the cell for the virus, can be transferred between cells, allowing infection of cells that would not otherwise be susceptible (Mack et al. 2000). The unraveling of the physiological effects of MHC transfer will increase our understanding of the immune system and may open a new avenue for therapeutic intervention in the above conditions.

MHC Transfer as an Immunological Tool

The TcR-dependent nature of the acquisition of peptide/MHC complexes by T cells has resulted in the use of MHC transfer as a tool to study antigen-specific T cell populations. Cells expressing GFP-tagged MHC class I molecules were pulsed with peptides and incubated with peripheral blood mononuclear cells. Those $CD8^+$ T cells with TcRs specific for the peptide/MHC complex acquired these molecules and became GFP positive, allowing further phenotypic and functional analysis (Tomaru et al. 2003). This technique to identify antigen-specific lymphocytes is similar to tetramer staining, but with the additional advantage of not requiring prior knowledge of the peptide involved. Similar techniques using fluorochrome-labeled APCs or APCs labeled with membrane markers (Beadling and Slifka 2006; Daubeuf et al. 2006; Machlenkin et al. 2008; Puaux et al. 2006) have also been developed and used to identify antigen-specific $CD8^+$ T cells (Beadling and Slifka 2006; Daubeuf et al. 2006; Machlenkin et al. 2008; Puaux et al. 2006; Tomaru et al. 2003), $CD4^+$ T cells (Puaux et al. 2006), and B cells (Puaux et al. 2006) in the context of virus (Beadling and Slifka 2006; Daubeuf et al. 2006; Tomaru et al. 2003) and tumor (Machlenkin et al. 2008) immunity.

Conclusions

Intercellular molecular transfer appears to be a complex phenomenon. Although circumstantial evidence suggests that it is a controlled process, the process of this control and the feedback mechanisms, if any, are poorly understood. Although most work has been carried out in vitro so far, there is emerging evidence to suggest that this transfer also takes place in vivo. The challenge now is to determine to what extent intercellular molecular transfer take place in vivo and its functional relevance under normal and pathological conditions. It is likely that this process forms a novel mechanism of interaction in the immune system. Understanding the fundamental principles that govern it will have implications on diverse fields in immunology such as infection, autoimmunity, transplantation, and tumor immunity.

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