Lipid Metabolism and Tumor Antigen Presentation

11

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Abstract

Tumors always evade immune surveillance and block T cell activation in a poorly immunogenic and immunosuppressive environment. Cancer cells and immune cells exhibit metabolic reprogramming in the tumor microenvironment (TME), which intimately links immune cell function and edits tumor immunology. In addition to glucose metabolism, amino acid and lipid metabolism also provide the materials for biological processes crucial in cancer biology and pathology. Furthermore, lipid metabolism is synergistically or negatively involved in the interactions between tumors and the microenvironment and contributes to the regulation of immune cells. Antigen processing and presentation as the initiation of adaptive immune response play a critical role in antitumor immunity. Therefore, a relationship exists between antigen-presenting cells and lipid metabolism in TME. This chapter introduces the updated understandings of lipid metabolism of tumor antigen-presenting cells and describes new directions in the manipulation of immune responses for cancer treatment.

Keywords

Lipid metabolism · Antigen presentation
Immune response · Tumor microenvironment

11.1 Introduction

Among the most important biological components, lipids participate in many key biological functions, including maintaining steady-state levels of membrane biosynthesis, serving as energy storage sources, and playing pivotal roles as inflammatory mediators in immunity and cancer [1]. Cellular lipid metabolism importantly facilitates the functions of immune cells [2]. Increasing evidence suggests that tumor metabolism, including lipid metabolism, inhibits the antitumor response. Over the past decade, studies have demonstrated the importance of the immune system in affecting the outcome of cancer. Tumor antigen processing and presentation play vital roles in the antitumor immune response, and several studies reported that antigen-presenting cells, especially dendritic cells (DCs), are influenced by lipid metabolism, resulting in tumor progression. In this chapter, we summarize the current reports and recent advances in lipid metabolism and tumor antigen presentation.

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11.2 Antigen Presentation

Antigen processing and presentation refer to the ability of an antigen-presenting cell (APC) to process and present antigenic peptides to antigen-specific T cells, which is a complex biological process with many molecular contributors and involves phagocytosis, antigen processing, peptide loading, localization of major histocompatibility complex (MHC) molecules to the cell surface, and T cell binding. Antigen processing can be depicted in a simplistic manner as the degradation of large antigens into smaller fragments, which are compatible with binding to antigen-presenting molecules [3]. In addition, the MHC/peptide complex together with costimulatory molecules and secretion of pro-inflammatory cytokines induce an appropriate immune response via interactions with T cells [4]. Antigenic peptides present antigens to T cells in two ways: on the one hand, they present endogenous antigens to $CD8^+$ T cells through endogenous pathways of MHC Class I (MHC-I); on the other hand, they bind to MHC Class II (MHC-II) molecules through exogenous pathways and present them to $CD4^+$ T cells (Fig. 11.1).

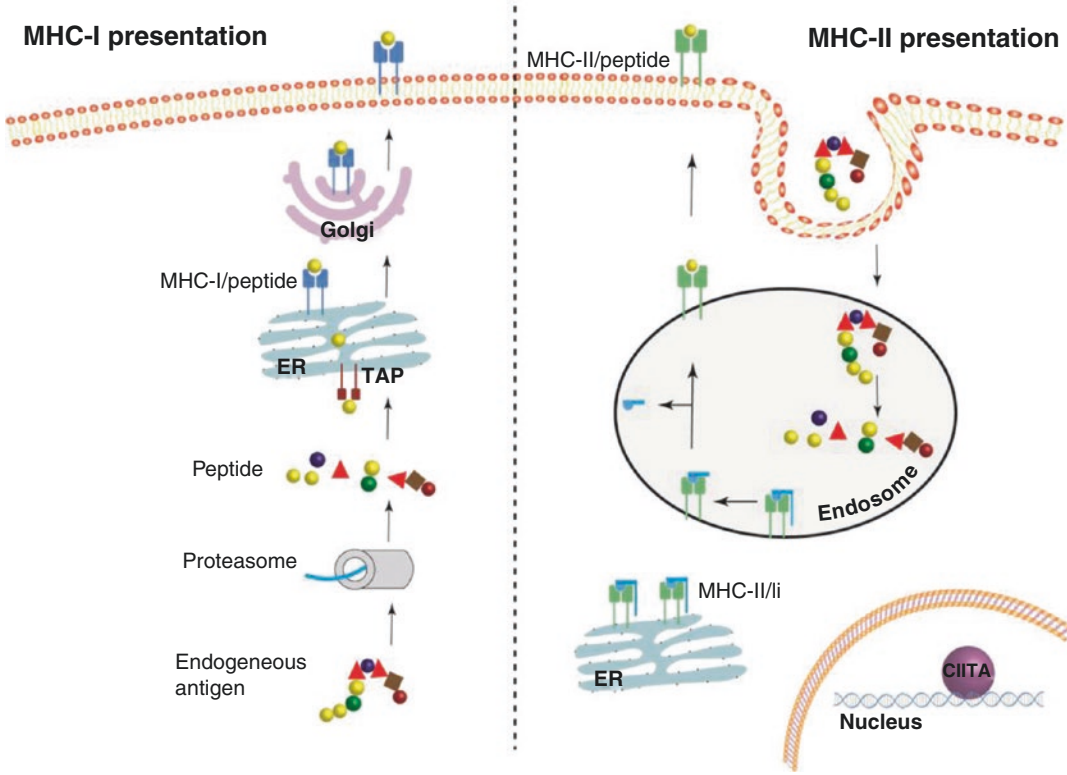

Fig. 11.1 Classical antigen presentation. (1) Classical MHC class I (MHC-I) presentation: endogenous antigen is degraded into peptides by proteasomes in the cytosol, transporter-associated with antigen processing (TAP) translocates the peptides into the endoplasmic reticulum (ER) and combines the peptides with MHC-I, and then the MHC-I/peptide complex is transported to the antigen-presenting cell (APC) membrane through the Golgi complex. (2) Classical MHC class II (MHC-II) presentation: exogenous antigens are internalized by professional APC, degraded into peptides in endosomes, and bound to MHC-II provided by ER. Then, MHC class II/peptide complexes are delivered to the cell surface and interact with the T cell. In addition, MHC-II molecule expression is promoted by the MHC class II transactivator (CIITA), and invariant chain (li) is proteolyzed by cathepsin and replaced by peptide

11.2.1 MHC Class I Presentation

MHC-I presentation refers to that in the cytosol, endogenous antigens are degraded into small molecular antigenic peptides by proteasomes, and the treated peptides are translocated by endoplasmic reticulum (ER), after modified by aminopeptidases, peptides bind to newly synthesized MHC-I molecules to form an antigen–peptide–MHC-I molecular complex, which is recognized by $CD8^+$ T lymphocytes on the cell surface. Endogenous antigens, including tumor antigens, are processed in this manner. If self-peptides are produced by tumor cells, they trigger an antitumor response. In contrast, if self-peptides are produced in normal host cells, it can lead to autoimmunity or tolerance [5].

MHC-I molecules are expressed in most nucleated cell types. Peptides binding to MHC-I molecules are produced through a two-step proteolytic mechanism: they are produced by cytoplasmic proteases, and then modified by aminopeptidase. These peptides are joined with MHC-I molecules in the ER. The degradation of most intracellular proteins and endogenous antigens in cells is accomplished by proteasome. After cytoplasmic protein is dissolved, following cytosolic proteolysis, antigenic peptides are recruited into the ER and translocated into the endoplasmic reticulum lumen via the transporter associated with antigen processing (TAP), which is composed of TAP1 and TAP2 [6]. The proteins ERp57, tapasin and the calnexin–calreticulin system certainly compose of peptide-loading complex (PLC) with TAP. Peptides loaded onto MHC-I molecules are only 8- to 11-amino acid residues long, while peptides can be much longer after the TAP translocation.. Finally, high-affinity peptide/MHC-I complexes are transported to the cell membrane via the Golgi body, triggering an antigen-specific $CD8^+$ T cell response.

11.2.2 MHC Class II Presentation

Unlike the MHC-I molecules expressed in most nuclear cell types, MHC-II molecules are constitutively expressed in a small number of immune cells, such as DCs, macrophages, and B lymphocytes. MHC-II molecules can also be expressed in restricted types of endothelial and epithelial–mesenchymal cells under inflammatory conditions. Transcriptional control of the MHC-II locus depends on the activity of the MHC-II transactivator (CIITA) [7]. In addition, interferon γ (IFN-γ) is the main cytokine that drives the synthesis of CIITA and induces the expression of MHC-II. Other important immunological molecular stimuli, such as Toll-like receptor (TLR) or transforming growth factor β (TGFβ) signaling, also contribute to this process. APCs take up antigens through phagocytosis, micro- or macropinocytosis, and endocytosis using Fc receptors, integrins, C-type lectin receptors, apoptotic cell receptors, and scavenger receptors. After uptake, exogenous antigens are internalized into phagosomes or endosomes [8, 9], and then, APCs process antigens into peptides that bind to MHC-II molecules to form the peptide/MHC-II complex. Invariant chain (Ii) protein, HLA-DM, HLA-DO, and other proteases are involved in this process. Peptide/MHC-II molecular complexes are very stable and can continuously present antigens, increasing the chance of matching with $CD4^+$ T lymphocytes. Finally, peptide/MHC-II complexes are transported to the plasma membrane and trigger T cell-mediated immune responses [5].

11.2.3 Cross-Presentation

Antigen cross-presentation combines both MHC-I and MHC-II pathways, and this process has received considerable attention during the last 20 years. Antigenic peptides cross-present antigens in two ways: on the one hand, they bind endogenous antigens to $CD8^+$ T cells through endogenous pathways of MHC-I; on the other hand, they bind to MHC-II molecules through exogenous pathways and present them to $CD4^+$ T cells [10, 11]. DCs are the most efficient cross-presenting cell type; however, different subtypes of DC cells have different cross-presentation abilities [12]. Two major pathways of antigen

cross-presentation have been described: the cytosolic pathway and the vacuolar pathway [9]. Proteins that are endocytosed or phagocytosed enter the cytosol. In the cytosolic pathway, antigens are transferred to the cytoplasm, processed in the proteasome, and then loaded onto the newly formed MHC class I molecules. This process may involve the participation of the ER machinery. Similar to direct presentation, this approach relies on TAP. In contrast, the vacuolar pathway is TAP independent, and exogenous proteins are degraded into peptides by lysosomal proteases within the phagolysosome or endosome in this pathway. These peptides are then loaded onto MHC-I molecules that recycle through the endocytic compartments by peptide exchange. The vacuolar pathway is less defined but is thought to occur in the endocytic compartments because antigens are resistant to proteasome inhibitors but sensitive to lysosomal proteolysis inhibitors. In addition, this pathway depends on cathepsin [13]. The use of each pathway may depend on the type of antigen and the mechanism of its uptake. Both of these two antigen presentation pathways are important in the process of cross-presentation, and existing evidence suggests that cytoplasmic pathways also play an important role [5].

11.2.4 Nonclassical MHC Presentation

The recognition of lipids and glycolipids is restricted by a family of MHC-like molecules called CD1 that have evolved from MHC by acquiring a very hydrophobic groove capable of accommodating the acyl chains of a large number of lipids. Lipid antigen is captured by the four types of human CD1 antigen-presenting molecules: CD1a, CD1b, CD1c, and CD1. At the cell surface, CD1a and CD1c readily capture exogenous lipids, whereas CD1b and CD1d do this to a lesser degree [14]. Lipid antigen binding to CD1 can stimulate natural killer T (NKT) cells. NKT cells are very important lymphocytes in both rodents and humans as these cells exhibit the unique property of recruiting natural killer (NK) cells, CD4 and CD8 T cells and B cells at the site of initial insult, coordinating the early events of DC maturation.

11.3 Antigen-Presenting Cells

APCs are cells that can intake and process antigens and present their information to T cells. Common APCs include DCs, mononuclear/macrophage cells, and B lymphocytes that express MHC-II molecules. These cells are also called professional APCs. Nonprofessional APCs include endothelial cells, fibroblasts, epithelial cells, mesothelial cells, and eosinophilic granulocytes, which also express MHC-II molecules and costimulating molecules under the stimuli of inflammatory or cytokines. Nonprofessional APCs exhibit weaker phagocytosis, processing, and presentation of antigen information abilities compared with professional APCs. In addition, all nucleated cells that express MHC-I can process endogenous antigens, including virus-related antigens and tumor antigens. These cells then present antigens to $CD8^+$ T cells called target cells. Thus, most cells are capable of acting as APCs to $CD8^+$ T cells, but only professional APCs can present antigens to $CD4^+$ T cells. DCs exhibit the strongest antigen-presenting function among APCs at present. DCs stimulate the activation and proliferation of naive T cells, which play an important role in adaptive immune responses.

11.3.1 Dendritic Cells

Dendritic cells play a pivotal role in the mediation of innate immune responses and maintenance of adaptive immune responses. DCs are divided into immature (imDCs) and mature (mDC). imDCs exhibit a high capability of phagocytosis but low expression of MHC molecules. Moreover, imDCs lack costimulatory molecules (CD40, CD80, CD86) and cannot effectively activate T cells. In contrast, mDCs exhibit high expression of MHC molecules and costimulatory molecules and activate T cells.

However, these cells do not effectively phagocytize antigens. DCs are particularly adept at initiating T cell responses, inducing T cell polarization, and presenting exogenous and endogenous antigens on either MHC-I or MHC-II [15].

DC maturation is critical for T cell expansion and differentiation, allowing T cells to become activated by making contact at the immunological synapse. DCs also activate naive and memory B cells through their ability to stimulate $CD4^+$ T cells. DCs accumulate in blood and lymphoid tissues; however, these cells are found throughout the body, i.e., skin Langerhans cells and intestinal DCs. DCs originate in bone marrow from macrophage and DC precursors (MDP), which give rise to monocytes and common DC precursors (CDP). CDP can differentiate into two major categories: classical DCs (cDCs) and plasmacytoid DC (pDCs). cDCs express CD11c and CD11b markers. Furthermore, cDCs are classified into two major subpopulations: cDC1 and cDC2 [16]. Some cDC1 cells that reside in lymphoid tissues express CD8α, whereas others not in lymphoid tissues express CD103 [17]. cDC1 focuses on binding the internalized antigen to MHC-I and presenting it to $CD8^+$ T cells in a process known as cross-presentation. $CD103^+$ DCs produce large amounts of IL-12 and play a crucial role in the antigen cross-presentation and the initial initiation of $CD8^+$ T cells. The migration of $CD103^+$ DCs from tumor environment to draining lymph nodes is regulated by CCR7, and initially prime naive $CD8^+$ T cells are started by DC in lymph nodes [18]. Among migratory DCs, $CD103^+$ cells are considered to be the main subset of cross-presenting antigens from peripheral tissues, such as skin, lung, and intestine. cDC2 cells are the main subtype of APC. Unlike DC1 cells, cDC2 express CD11b and reside in lymphoid tissues, and present endogenous internalized exogenous antigens to $CD4^+$ T cells, which is the first step of acquired immunity. The other major subset of DCs is pDCs, which specialize in the production of large amounts of type I interferon (IFN) in response to pathogen recognition and participate in antiviral immune responses. However, these cells also secrete IL-12, IL-6, tumor necrosis factor-alpha (TNF-α), and other pro-inflammatory cytokines. As APCs, pDCs also present antigens to T cells but less efficiently than cDCs. DCs can also process lipid antigens and present them on the CD1d molecule to activate NKT cells [19].

11.3.2 Macrophages

Macrophages are versatile innate immunocytes that contribute to diverse processes, express dozens of receptors, produce dozens of enzymes, and secrete hundreds of bioactive products. Thus, these cells play an important role in the body's defense and immune response. Macrophages exhibit a strong ability to intake antigens and express a variety of surface molecules related to antigen uptake, including the Fc receptor, complement receptor, mannose receptor, scavenger receptor, and TLR. Similar to DCs, macrophages also express costimulatory molecules and MHC-I/II molecules and process exogenous antigens to activated T cells. In addition, T cells secrete IFNγ, which positively activates and promotes macrophage function. Thus, macrophages also enhance self-function by presenting antigens. Numerous macrophages are located in the liver and are known as Kupffer cells. These cells suppress T cell activation induced by DCs. TLR2 and TLR4 ligation activates human Kupffer cells by inducing IL-10 synthesis. Moreover, both reactive oxygen species and TLR3 ligation increased the expression of MHC class II and promoted the APC function of these cells. Kupffer cells can switch their immunological roles via two scenarios. These cells can switch from inactivators to activators of NK cells and from tolerance-inducing APCs to immunogenic APCs [20]. Macrophage can be induced to the M1 and M2 phenotypes according to the surrounding microenvironment. Conventional M1 macrophages promote immune responses and mainly participate in cellular immunity, whereas M2 macrophages participate in humoral immunity, which is closely related to immunosuppressive ability.

11.3.3 Other APCs

B lymphocytes play an essential role in humoral immunity. As a professional APC, B cells present specific antigens to promote immunity but induce tolerance when presenting nonspecific antigens. In the presence of DCs or activated macrophages, the role of B cells in presenting nonspecific antigens is negligible. B cells that develop in the bone marrow express MHC class II molecules and this expression is maintained throughout B cell differentiation and maturation. The function of MHC-II in bone marrow-derived B cells differs from that of mature B cells given the reduced expression of CD40, CD80, and CD86 as well as minimal MHC class II-associated invariant chain peptide (CLIP) on their HLA-DR molecules, HLA-DO is lacking, which inhibits DM function and attenuates its peptide-loading activity [21]. Exogenous protein gains access to B cells through fluid-phase pinocytosis or B cell receptor (BCR)-mediated endocytosis. BCR-mediated presentation of specific antigen is far more efficient than presentation in pinocytotic antigens and subsequent T cell activation.

Endothelial cells are recognized as nonprofessional APCs and include vascular endothelial cells (VECs) and lymphatic endothelial cells (LECs). Liver sinusoidal endothelial cells (LSECs) are a typical type of VECs that express various scavenger receptors, C-type lectin receptors, and lipoprotein receptor-related protein-1 for strong endocytic ability. LSECs are not only able to present exogenous antigens on MHC-II but also on MHC-I through cross-presentation, including antigens from virus-infected hepatocytes and apoptotic tumor cells. Amazingly, LSECs cross-present soluble antigens even more efficiently than DCs [22]. Prostaglandin E2 (PGE_2) and IL-10 downregulate the expression of MHC class II, CD80 and CD86, compromising antigen-specific and costimulatory signals [20]. LECs also exhibit a strong endocytic ability and present exogenous antigen to T cells on both MHC-I/II molecules. Moreover, LECs are potent immunoregulators and inhibit DC-mediated antigen presentation.

Tumor cells are regarded as target cells that express MHC class I molecules; process mutated autoantigens, i.e., tumor antigens; and present antigenic information to $CD8^+$ T cells in the form of antigenic peptide/MHC-1 molecular complex. Researchers recently reported that some types of tumors express MHC-II molecules, and upregulation of MHC-II expression prolongs the survival time of tumor patients [23].

11.4 Tumor Antigen Presentation

Tumor antigens originate from endogenous self-antigens, which are poorly immunogenic and subject to changes during tumor progression. In the early stage of cancer development, the immune system generates tumor antigen-specific $CD8^+$ T cells; therefore, tumor cells must clearly use additional approaches to escape immune recognition. Several requirements must be met for antigen presentation to efficiently stimulate anti-tumor T cell responses: (a) the appropriate type of DC effectively recognize and capture tumor antigens; (b) antigens were processed into antigenic peptides and expressed on the surface of DCs; and (c) fully enhance the expression of DC costimulation molecules to ensure the effective activation of T cells [24]. As a tumor grows, tumor cells attempt to become “invisible” to the immune system by modifying the MHC-I antigen loading and presentation pathway. Thus, when cancer progresses, MHC-I expression is downregulated or lost. In general, tumors exhibit broad dysregulation of antigen presentation, especially B cell malignancies. However, malignant cells can affect the antigen presentation function of DCs through various mechanisms, on the one hand, disabling the generation of tumor-associated antigen-specific T cells, and on the other hand, increasing the tolerance of immune cells to tumors [25].

Thus, tumor antigens derived from apoptotic cells are captured by immature DCs, and antigen presentation by these cells likely results in immune tolerance [26]. Immune escape of tumor cells is mainly to block the process of tumor anti-

gen presentation. Antigen presentation has two important processes in antitumor immunity. First, APC activates naive T cells. Second, activated cytotoxic effector T cells recognize target antigens that bind to MHC-I. Second, activated cytotoxic effector T cells recognize target antigens that bind to MHC-I [27]. The dominant paradigm of tumor immunology dictates that the efficient cytotoxic T lymphocytes (CTL) initiation requires the uptake of tumor antigens by DCs in the peripheral tumor area. These cells then migrate to draining lymph nodes and present the antigens to $CD8^+$ T cells in the context of MHC-I [23, 28]. DCs have access to a large amount of tumor antigens via numerous mechanisms, such as phagocytosis/endocytosis of cell-associated or soluble antigens bound to heat shock proteins, gap junction transfer through the capture of exosomes, or "cross-dressing" [29, 30].

Moreover, tumor antigen is cross-presented by professional APCs, such as DCs, via the MHC-I pathway. Thus, understanding and exploiting cross-presentation is becoming a very important topic in cancer immunotherapy because it affects a variety of key issues, including the development of more efficacious vaccines [31]. The selective pressure of $CD8^+$ T cells on tumor cells themselves and immunoediting by malignant cells help to limit T cells' attack of tumor cells [32, 33]. Tumors also inhibit the function of the proteasome, thereby reducing the quantity and quality of antigenic peptides for binding to MHC-I [34]. Disruption of MHC-I function in tumor cells is a common method by which tumors prevent T cell recognition, but we are not aware of dysregulation of MHC-I expression in DCs in the tumor microenvironment [27]. In 2003, Nowak et al. found that induction of apoptosis in tumor cells increased the cross-presentation of tumor antigens and the activation of specific $CD8^+$ T cells, thereby inhibiting tumor growth [35]. Importantly, Sec22b-dependent antigen cross-presentation is important in the treatment of anti-programmed death 1(PD-1). Another study also illustrated that both cross-presented DC subsets, migratory $CD103^+$ DCs, and resident $CD8^+$ DCs are necessary for the effectiveness of anti-PD-1 therapy and radiotherapy for tumors [36]. In addition, tumor antigens are occasionally cross-expressed with MHC-II, which is controlled by the APC-specific regulator of transcription CIITA. In summary, cross-presentation seems to play a critical role both in inducing antitumor $CD8^+$ cytotoxicity and in regulating the outcome of anti-immune checkpoint therapies.

11.4.1 Tumor Antigen Presentation by Dendritic Cells

DCs are professional APCs that can endocytose cell debris or dead tumor cells and transport cancer-associated antigens to the draining lymph node [37]. These cells then present tumor antigens to T lymphocytes and express high levels of costimulatory or coinhibitory molecules that determine immune activation or immunosuppression [38, 39]. Moreover, DCs consistently activate cancer-specific T helper cells and CTL and mediate the early stage of the antitumor response. In general, DCs remain in a dormant immature state and gradually mature after capturing, recognizing, and internalizing specific tumor antigens in peripheral tissues. DCs express a series of pattern-recognition receptors, including TLRs, that allow them to recognize microbial products or inflammatory stimuli and respond quickly. After encountering tumor antigens, DCs are activated via a process that involves enhanced capturing and processing of antigens for the stable presentation of antigen-derived peptides in the context of MHC-I/II and induction of the expression of genes encoding chemokine receptors, cytokines, and costimulatory molecules. Internalized antigen is processed, loaded onto MHC-I/II molecules, and then presented to $CD8^+$ and $CD4^+$ T cells, respectively [40]. Antigen presentation in MHC class I molecules is important for the induction of $CD8^+$ cytotoxic effector lymphocytes, which are essential for clearing tumor cells. Collectively, these changes enable DCs to promote local inflammation and traffic to T cell zones of secondary lymphoid organs, where they prime T cell responses [41]. Different subsets of

DCs are equipped to induce different types of T cell responses. In addition, the location and ability to capture tumor antigens also regulate DCs processing of antigens and subsequent T cell responses. Cross-presentation of antigens is a unique feature of DCs that is very important for antitumor immunity. DCs produce biologically active IL-12 p70, inducing remarkable anticancer immunity by potentiating the activity of NK cells.

The role of pDCs in cancer is thought to be tolerogenic, and high tumor infiltration by pDC is associated with poor prognosis [42]. During the presentation of tumor cell antigens, pDCs, which are unable to internalize cell membrane fragments by phagocytosis, can efficiently acquire membrane patches and associated molecules from cancer cells of different histotypes. The transfer of membrane patches to pDCs occurs in a very short time and requires cell-to-cell contact. Membrane transfer also included intact human leukocyte antigen (HLA) complexes such that tumor-specific $CD8^+$ T cells efficiently recognized the antigens acquire by pDCs [43]. Defects in DC function have been well documented in tumor-bearing patients or mice with advanced disease. These defects manifest in the expansion of immature DCs, which are unable to properly present antigen, and the generation of cells with immune-suppressive activity, including regulatory DCs and myeloid-derived suppressor cells (MDSCs) [44].

In general, mature DCs are considered immune-stimulatory, whereas immature DCs are considered suppressive and tolerogenic. Moreover, increased imDCs, decreased mDC, and DCs with impaired functions are observed in the cancer microenvironment [45]. Tumor cells can secrete IL-10 and IL-6 to impair DC maturation by downregulating both MHC-II and lymph node-homing receptor CCR7 expression and activating signal transducers and activators of transcription 3 (STAT3). Immature and paralyzed tumor-infiltrating DCs (TIDCs) suppress both innate and adaptive immune responses through a variety of mechanisms [46]. TIDCs showed reduced expression of costimulatory molecules and reduced antigen cross-presentation ability [47] and increased expression of related molecules and receptors regulating immunosuppression [48]. TIDCs are characterized by high expression of IL-10 and low IL-12 secretion and induce $FoxP3^+$ Treg differentiation from naive $CD4^+$ T cells [23]. In melanoma, TIDC frequency tends to be increased in the peritumoral area, and these cells exhibit a more mature phenotype. In contrast, more immature TIDCs are found within the tumors [49]. DCs' functional plasticity is complicated in the tumor microenvironment (TME), which makes it difficult to generalize its role in TME. TIDCs as a group exhibited poor response to TLR stimulation in terms of antigen presentation capability. Data showed that the TIDCs coexpress PD-1 and programmed death 1 ligand (PD-L1). Murine DCs expressed low levels of PD-1 in the early stage of tumor growth; however, as the disease progresses, almost all TIDCs eventually have high levels of PD-1, which is induced by the transcription factor STAT3. In vitro, blocking PD-1 signaling in TIDCs enhances the production of immune-stimulatory cytokines, increases the activation of NF-κB in DCs, improves the expression of costimulatory molecules, and improves the ability of these DCs to activate T cells [48, 50]. TIDCs can also inhibit tumor immunity by upregulating the expression of T cell Ig and mucin domain 3 (TIM-3).TIM-3 is an inhibitory marker of Th1-type T cells. Various factors present in both murine and human tumors induce upregulation of TIM-3 in DCs. The immune-activating potential of TIDCs is a balance between multiple inhibitory and activating molecules. Besides PD-L1, DCs also have other mechanisms to block T cell activation. Liu et al. [51] reported that PGE_2 and TGF-β which murine lung tumor cells released transformed immune-activating DCs into immune-suppressive DCs. Tumor-derived PGE2 induces indoleamine 2,3-dioxygenase (IDO), which is expressed in TIDCs and plays an important role in mediating the suppression of adaptive immune responses [52]. TIDCs also suppress adaptive immune responses indirectly by induction of Treg [53].

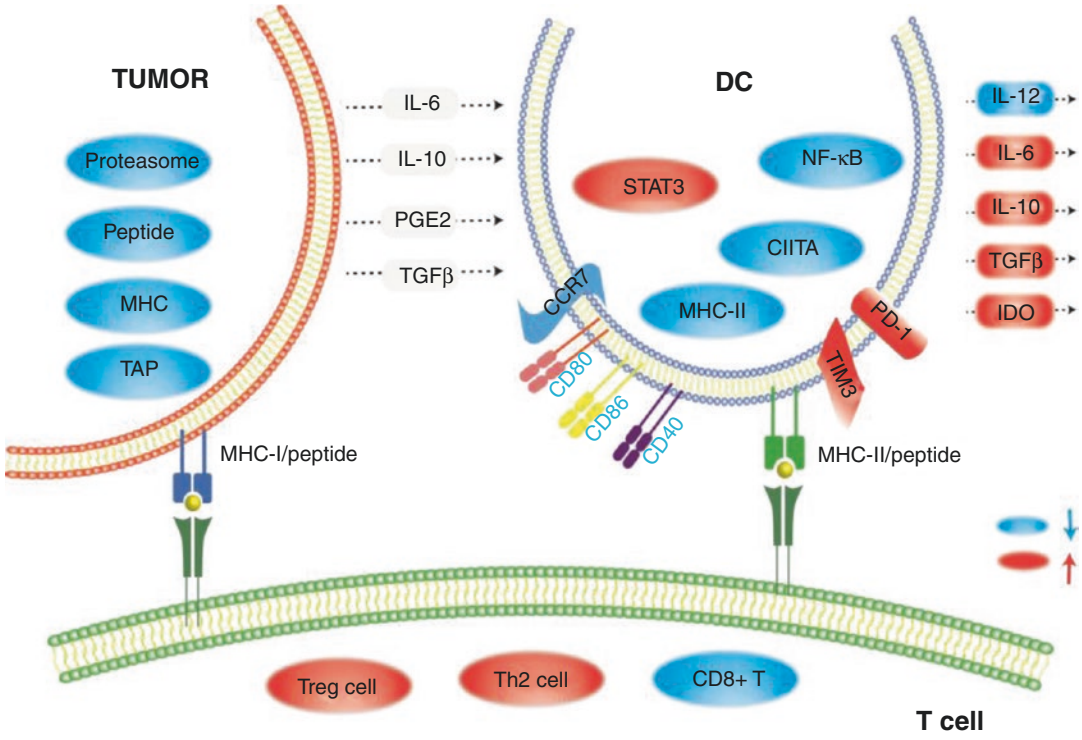

Fig. 11.2 Tumor antigen presentation by DCs. Tumor cells with MHC-I mutations, inhibition proteasome function, and downregulation of TAP lead to reduced expression of MHC-I/peptide. In addition, tumor cells secrete IL-6, IL-10, transforming growth factor β (TGFβ) and prostaglandin E2 (PGE2), thus inhibiting the production of IL-12 and decreasing expression of peptide/MHC-II, costimulatory molecules on DCs. In addition, programmed cell death protein 1 (PD-1), T cell Ig, and mucin domain 3 (TIM-3) are upregulated on the DC surface. Furthermore, activation of transcription factor activators of transcription 3 (STAT3) and attenuated NF-κB signaling suppress DC maturation and promote DC dysfunction. Additional defects in MHC-II expression by downregulation of CIITA are noted. Here, tumor-infiltrating DCs suppress $CD8^+$ T cell activation, skewing $CD4^+$ T cell differentiation toward the Th2 phenotype and increase Treg cells

TIDCs interact with other immune cells, including NK cells and B cells. The impact of factors on tumor antigen presentation by DCs is summarized in Fig. 11.2.

11.4.2 Tumor Antigen Presentation by Macrophages

Numerous types of immune cells are found in advanced tumors, and macrophages are the most abundant. Macrophages are extremely versatile and adopt different activation states or phenotypes in response to signals under different circumstances. Macrophages exhibit both anti- and pro-tumor functions by regulating tumor growth, angiogenesis, invasion, and metastasis [54]. Macrophages are innate immune cells in tissues and their main function is phagocytosis, functioning as the host's first line of defense against pathogens [55]. Macrophages can redirect antigens away from cDCs, reduce the presence of danger signal molecules or damage-associated molecular patterns (DAMPs) by clearance of apoptotic cells and debris and suppress their own activation in response to apoptotic cell phagocytosis [56].

As mentioned above, macrophages are classified into pro-inflammatory M1 and anti-inflammatory M2 cell types. M1 type cells are induced by IFNγ and lipopolysaccharide (LPS); express high levels of MHC molecules, espe-

cially MHC-II; and play crucial roles in pathogen clearance and tumor antigen presentation. M2 type cells are induced by IL-4 and IL-10 and express moderate levels of MHC molecules and IL-12, but these cells produce abundant anti-inflammatory cytokine to promote immunosuppression, tumor infiltration, and metastasis [57]. Unlike DCs, macrophages are generally tissue-resident cells, serving as the first cell to recognize and phagocytose antigens, including tumor cells in the host, and then present them to T cells.

Tumor-associated macrophages (TAM) are a unique group of macrophages, and most TAMs are M2 type. TAMs are important regulators of tumorigenesis that are either tissue-resident cells or derived from peripheral reservoirs, such as the bone marrow and spleen [58]. Depletion of TAMs markedly decreased tumor growth in mice, illuminating the importance of these cells for tumor progression [59]. TAMs lack costimulatory signals, such as CD80/CD86 coreceptors which are the second signals required for T cell activation. In the absence of a costimulatory signal, T cells can be expanded to unresponsive or anergic cells to induce immunotolerance [60]. Furthermore, TAMs and tumor cells secrete immunosuppressive cytokines, such as IL-10, TGFβ1, and PGE2, resulting in downregulation of MHC class II molecules in macrophages not only in the TME but also in the distant spleen and peritoneum, where TAMs exhibit dysfunctional antigen presentation [61].

Recent studies identified a set of macrophages with a unique distribution in secondary lymphoid organs called CD169$^+$ macrophages. These macrophages were identified as lymph node-resident APCs that dominate the early activation of CD8$^+$ T cells. The CD169 molecule is highly expressed by macrophages found in the subcapsular sinus and the medulla of lymph nodes and marginal zone in the spleen [62]. CD169$^+$ macrophages in regional lymph nodes promote CD8$^+$ T cell-mediated antitumor immunity and are associated with a better prognosis for colorectal and endometrial carcinoma patients. The density of CD169$^+$ macrophages exhibits a positive correlation with the number of CD8$^+$ cytotoxic T cells infiltrating tumor tissues [63, 64]. These cells can activate invariant natural killer T (iNKT) cells and CD8$^+$ T cells via two different mechanisms: directly present antigen to CD8$^+$ T cells or indirectly transfer antigens to DCs in the spleen [65]. Asano, K [66] reported that CD169$^+$ macrophages phagocytose dead tumor cells transported via lymphatic flow and subsequently cross-present tumor antigens to CD8$^+$ T cells. Moreover, CD169$^+$ macrophages capture exosomes and mediate the immune response to exosomal antigen [67]. Via this function, CD169$^+$ macrophages control the dissemination of tumor-derived extracellular vesicles and reduce their pro-tumorigenic potential [68]. Therefore, targeting tumor-related macrophages for cancer treatment may represent an attractive approach to prevent tumor progression.

11.4.3 Tumor Antigen Presentation by Other APCs

Most tumor cells are able to present self-antigens to CD8$^+$ T cells through the MHC-I pathway. In fact, tumor cells lose or downregulate their MHC class I molecules and other costimulatory signals to prevent antigen presentation [69]. Studies have demonstrated that high levels of MHC-I activate adaptive responses, the complete lack of MHC-I leads to cytotoxic NK cell-mediated tumor clearance, and low MHC-I leads to tumor progression [70–72]. In addition, tumor cells lack costimulatory signals to present antigens; express high levels of inhibitory ligands, such as PD-L1; and clear tumor-specific T lymphocytes. Interestingly, some types of tumors express MHC-II, and MHC-II expression is associated with tumor regression, increased cytotoxic T cells, and increased overall patient survival [73, 74].

B lymphocytes are considered professional APCs and express a specialized B cell receptor (BCR). B lymphocytes also express MHC-I and II as well as costimulatory molecules that allow them to sense and process antigens from a variety of sources. In cancer, the presence of B cells or tumor-specific antibodies is associated with

tumor progression. In primary tumors, like lung cancer, breast cancer, and colorectal cancer, the accumulation of tumor-specific antibodies is related to poor prognosis and late-stage disease [75–77]. Although B cells have a dual role in tumor immunity through their cellular and humoral responses, there is a defect in the B cells that presents tumor antigens to $CD4^+$ T cells. On one hand, this presentation leads to the inhibition of cytotoxic T lymphocyte activity. On the other hand, it leads to a tumor humoral immune response to B cells. For example, in diffuse large B cell lymphoma, the antigen presentation of B cells is dysregulated because MHC-II expression is reduced by downregulation of CIITA and mutations within the MHC-II locus itself. In addition, in Hodgkin's B cell lymphoma, HLA-DM fails to remove CLIP from the MHC-II peptide and influence the expression of MHC-II/peptide compounds [27].

Endothelial cells, including vascular endothelial cells (VECs) and lymphatic endothelial cells (LECs), exhibit the ability for antigen presentation to regulate immunotolerance in cancer. Treatment with monoclonal antibodies against vascular endothelial growth factors (VEGF) and VEGF-receptors (VEGFR) restores tumor immunity. Liver sinusoidal vascular endothelial cells (LSEC) process tumor antigens from apoptotic cells and cross-present them to $CD8^+$ T cells, inducing tumor immunotolerance [78]. Moreover, VECs express immunosuppressive molecules and inhibitory ligands, such as B7-H3, and PD-L1/PD-L2, to inhibit antitumor immunity [79–81]. LECs are an important component of the structure of primary and secondary lymphoid tissues, where the maturation and activation of immune cells occurs, and these cells play a critical role in tumor escape and metastasis. LECs can cross-present tumor antigens to $CD8^+$ T cells in draining lymph nodes and cause CTL inhibition and deletion. This process is dependent on the secretion of VEGF-C by tumor cells [82]. Other cells, such as neutrophils, mast cells, and eosinophils, also participate in antitumor immunity, but the role of these cells in antigen presentation remains controversial.

11.5 Lipid Metabolism in Tumor APCs

The role of lipid metabolism in the regulation of immune cells has aroused general concerns. Several lines of evidence have demonstrated the importance of tumor immune metabolic reprogramming. Lipids are critical in malignant tumors as they are necessary not only for providing the membrane constituents of proliferating cells but also for energetic, biophysical, and signaling pathways that drive tumorigenesis [83, 84]. Lipid depletion in $CD8^+$ T cells dramatically inhibits cell proliferation and signal transduction, which partly explains the lower number of $CD8^+$ T cells in cancer tissues compared with adjacent tissues [85]. Evidence suggests that alterations in tumor lipid metabolism, including metabolite abundance and accumulation of lipid metabolic products, lead to local immunosuppression in the TME [86]. Unlike normal cells, cancer cells take up fatty acid (FA) from the microenvironment and exhibit a high de novo lipid synthesis rate, suggesting FA accumulation in tumor cells. Many studies have focused on the effects of lipid reprogramming on the tumor immune response, but a few have reported the effects on antigen presentation function.

11.5.1 Lipid Metabolism in DCs

Pathological impairment of DC function is considered a cause of decreased tumor immunity in cancer patients. To avoid the immune response, the maturation or differentiation of DCs is suppressed in several tumors. For example, DCs from hepatocellular carcinoma (HCC) patients exhibit an impaired ability to trigger immune responses, thus promoting immunosuppression [46]. One study confirmed that both NF-κB and STAT3 signaling pathways were simultaneously repressed by cancer sera, suggesting that attenuated NF-κB and STAT3 signaling could be a leading cause of DC dysfunction in cancer [87].

The adverse effect of dietary lipid intake on DC functions has been confirmed by many stud-

ies. Lipid accumulation in DCs was observed in many tumors, such as lung cancer, renal cell carcinoma, colon carcinomas, and thymic lymphomas. Several studies showed that lipid accumulation in DCs in cancer patients might suppress DC function, which subsequently reduces antitumor immunity [88, 89] as well as the expression of costimulatory molecules and DC-related cytokines. Arai, R et al. showed that lung cancer patients had significantly fewer DCs than healthy individuals, especially the number of myeloid DCs (mDcs), and patients with higher-stage cancers had a significantly reduced number of mDCs. In addition, DCs from stage IV lung cancer patients exhibit increased lipid content and reduced T cell proliferation compared with early-stage patients, and further tests revealed higher levels of triglycerides (TAG) in mDCs but not in pDCs [90]. Gardner, Gardner J. K. et al. showed that mesothelioma tumors and their secreted factors promote DC lipid accumulation, reduce DC numbers, in particular cross-presenting $CD8\alpha^{+}CD4^{-}$DCs [91]. TAGs are the main lipid components that accumulate in DCs. Some studies reported no changes in the level of phospholipids and cholesteryl-esters, whereas others observed minimal increases in cholesterol in these DCs. Gao, F et al. reported that lipoprotein lipase (LPL), fatty acid-binding protein (FABP), and the level of triacylglycerol (TAG) in serum increased in mouse thymic lymphomas, contributing to lipid accumulation in DCs. LPL increases the uptake of lipids, and FABP plays roles in fatty acid uptake, transport, and metabolism. The mechanisms of lipid accumulation are unclear. The expression of macrophage scavenger receptor (Msr-1) is increased in DCs with high lipid accumulation, and this protein can increase lipid uptake, specifically TAG, which reduces the ability of DCs to process tumor antigens and stimulate T cell proliferation [88, 92]. In breast cancer, Nadine M. Lerret [92] showed that a single dose of irradiation leads to the downregulation of Msr-1 on DCs within the tumor and reduces lipid uptake of tumor-resident DCs, potentially enabling the DCs to present tumor antigen more efficiently and contribute to tumor clearance. However, in lung cancer patients, increased expression of Msr-1 on the surface of peripheral blood DCs was not observed. Zapata-Gonzalez et al. reported that fatty acids regulate the activity of human-derived DCs mainly via peroxisome proliferator-activated receptor-γ (PPAR-γ) [93]. PPAR-γ primarily acts as a positive transcriptional regulator in human developing DCs by controlling genes involved in lipid metabolism, such as ABCG1, ANGPTL4, CPT1A, and CD36 [94]. PPARγ is highly upregulated during monocyte-derived DC differentiation, and PPARγ-instructed DCs exhibit enhanced phagocytic activity and a modified cytokine-production profile. These cells exhibit increased NKT cell activating capacity. Lipid/fatty acid metabolism-related categories were overrepresented among the genes upregulated by PPARγ ligand. Everts, B. et al. found that during glycolysis, TLR can drive the generation of citrate, which increases the de novo synthesis of fatty acids in DC cells, and the expansion of ER and Golgi promotes the activation of DC, impacting their antigen-presenting ability [95]. This model of glycolysis supports the de novo synthesis of fatty acids by generating nicotinamide adenine dinucleotide 2′-phosphate reduced tetrasodium salt (NADPH) through the pentose phosphate pathway (PPP) and by providing the carbons to supplement intermediates of the tricarboxylic acid (TCA) cycle that are extracted from the mitochondrial TCA cycle in the form of citrate or isocitrate for the synthesis of fatty acids. Notably, the immunogenicity of DCs with high lipid content was diminished when fatty acid synthesis (FAS) in these cells was inhibited. These results support the notion that the de novo synthesis of fatty acid is an integral component of DC activation and is required for the acquisition of an immunogenic phenotype. In pathogen-infected disease, dyslipidemia inhibited TLR-induced production of pro-inflammatory cytokines, including IL-12, IL-6, and TNFα, as well as upregulation of costimulatory molecules by $CD8\alpha^{-}$ DCs. In addition, oxidized low-density lipoprotein (oxLDL) was the key active component responsible for this effect because it directly uncouples TLR-mediated signaling on $CD8\alpha^{-}$ myeloid DCs and inhibits NF-κB nuclear translo-

cation. Previous studies demonstrated that different types of fatty acids have different effects on TLR. Saturated fatty acids activate TLRs, while $n-3$ polyunsaturated fatty acids inhibit TLR activation. TLRs provide critical signals to induce innate immune responses in DCs that are subsequently linked to adaptive immune responses.

Recently, lipid droplets (LDs) in tumor-associated dendritic cells (TADCs) have attracted considerable attention. In addition, the accumulation of lipids in DCs manifests in the formation of large LDs. The presence and size of LDs are defined by the accumulation of fatty acid precursors and their esterification into TAGs and cholesterol esters, which are the major constituents of the hydrophobic core of LDs. In some cancers, TADCs express scavenging receptors, such as Msr-1, which facilitates lipid uptake and accumulation. These findings support the role of these cells in immunogenic immune responses and cross-presentation [88, 96]. Researchers report that tumor-derived factors trigger lipid peroxidation in TADCs, and this process is mediated by X-box binding protein 1 (XBP1). XBP1 activation subsequently induces the lipid biosynthetic program, which results in the accumulation of LDs and blunted antigen presentation, leading to tumor progression [97]. Furthermore, the oxidized lipids in TADCs also affect cross-presentation, demonstrating that the accumulation of oxidized polyunsaturated FAs, cholesterol esters, and TAG impaired cross-presentation without altering the presentation of endogenous antigens. However, the accumulation of non-oxidized lipids does not affect cross-presentation, suggesting that oxidized lipids block cross-presentation by reducing the expression of peptide–MHC class I complexes on the cell surface. In addition, the storage of lipids and the accumulation of modified lipids altered DC function [98].

The above information demonstrates that factors influencing lipid accumulation include advanced age, serum triglyceride levels, and cancer stage. The expression of scavenger receptor B is potentiated during lipid accumulation in mouse bone marrow and spleen-derived DCs. Given that Msr-1 expression is not altered in patients, the receptors mediating DC lipid accumulation may differ between mice and humans. The mechanism of lipid deposition in DCs is related to the PPAR and NF pathways.

11.5.2 Lipid Metabolism in Macrophages

Macrophages undergo changes in their lipid profile in the tumor setting. TAMs undergo changes in lipid metabolism, including enhanced FA biosynthesis, uptake, and storage. TAMs are the predominant M2 phenotype to inhibit CTL antitumor responses in solid cancers [99]. Increased expression of multiple genes involved in lipid metabolism and lipid signaling is noted in distinct populations of macrophages. FAS enzymes are upregulated in M2-polarized macrophages, and the de novo synthesized fatty acids are at least partially used for feedback into fatty acid oxidation (FAO) [100, 101]. In addition, enhanced FAS is required for the augmentation of phagocytosis in monocytes. M1 macrophage inducers LPS and IFN-γ suppress fatty acid intake and oxidation, while M2 macrophages are likely to increase FAO. These processes may be driven by the activation of signal sensors, such as transcriptional activator 6 and PPARγ coactivator-1 beta (PGC-1β), in response to IL-4 treatment. The uptake of lipids, especially TAG, is also critical for FAO and M2 activation [100]. Other studies showed that lipid loading of macrophages is associated with increased tumoricidal and inflammatory capacity. Increasing intracellular lipid levels is associated with an increased cytotoxic activity of murine peritoneal macrophages, particularly in those that were artificially enriched with polyunsaturated FAs in contrast with those enriched in cholesterol [102]. In contrast, one study showed that monoacylglycerol lipase (MGLL) deficiency and increased cofactor of adipose triglyceride lipase abhydrolase domain containing 5 (ABHD5) expression in TAMs contribute to lipid accumulation and promote tumor progression in colorectal cancer [103]. Several studies indicated that TAMs exhibit alterations in

arachidonic acid metabolism. Arachidonic acid metabolism mediates the switch of macrophage phenotypes. For example, PGE2 released by tumor cells can transform TAM from M1 to M2, resulting in immune system evasion [104]. PGE_2, a cyclo-oxygenase (COX)-derived eicosanoid, is increased by M1 stimulation, while IL-4 induces the upregulation of 15-lipoxygenase (15-LOX) in macrophages. IL-10, IL-4, and TGFβ induce adenosine 5′-monophosphate-activated protein kinase (AMPK) activation and drive TAMs to an immunosuppressive M2 phenotype. In particular, increased COX2 expression and PGE_2 production were observed in macrophages infiltrating tumor-bearing lungs compared with the macrophages from naive lungs.

Saturated free fatty acids induce pro-inflammatory activation via TLR4, NF-κB, NLRP3, and JNK pathways in lipid metabolism. The mechanisms of lipid metabolism in TAMs are unclear, but the underlying mechanism involves peroxisome proliferator-activated receptors (PPARs), live X receptors (LXRs), and signal transducer and activator of transcription (STAT) [105, 106]. PPARγ mediates M2 macrophage polarization to promote tumor progression and metastasis. Caspase-1 inactivates medium-chain acyl-CoA dehydrogenase (MCAD) by cleaving PPARγ and induces lipid accumulation in TAMs [107]. MGLL in TAMs functions as a tumor suppressor, and its deficiency is the major contributor to lipid accumulation in TAMs. Moreover, CB2 cannabinoid signaling is an oncogenic factor in tumor cells. Xiang, W. et al. [103] reported that MGLL deficiency via CB2/TLR4 contributed to lipid accumulation, macrophage activation, $CD8^+$ T cell inhibition, and tumor progression in inoculated and genetic cancer models. In contrast, TAMs highly express epidermal fatty acid-binding protein (E-FABP), which promotes the formation of lipid droplets and IFN-β production, thereby inhibiting tumor progression by enhancing the recruitment of tumoricidal effector cells, especially NK cells.

Recent studies on intracellular metabolism in macrophages provide new insights into the functions of these critical controllers of innate and adaptive immunity [108, 109]. Complex changes in mitochondrial metabolism have been characterized in mouse macrophages. M1 type macrophages exhibit decreased respiration and a broken Krebs cycle, leading to accumulation of succinate and citrate, which act as signals to alter immune function. In M2 type macrophages, the Krebs cycle and oxidative phosphorylation are intact, and FAO is utilized. In addition, activated macrophages transform mitochondria from ATP synthesis to reactive oxygen species (ROS) production to promote a pro-inflammatory state. The lipid reprogramming of dendritic cells and macrophages in the tumor microenvironment are presented in Fig. 11.3.

11.5.3 Lipid Metabolism in Other APCs

Obesity may damage B cell function. In human and mouse obesity models, B cell responses are impaired, and essential fatty acid status influences humoral immunity potentially through specialized pro-resolving lipid mediators. This mechanism effectively increased murine Ab levels upon influenza infection [110]. The accumulation of fat influences B lymphopoiesis in bone marrow and further studies showed that adipocytes promote the accumulation of MDSC and subsequently inhibit B lymphopoiesis. Using cytokine array analysis, researchers found that IL-1 produced by MDSCs negatively regulates B lymphopoiesis [111]. Predictably, B cells also affect lipid metabolism. The absence of B cells causes a lack of IgA and impaired Gata4-dependent functions, which is a key player in intestinal gene regulation and function. This shift in intestinal function leads to lipid malabsorption and decreased deposition of body fat [112].

Endothelial cells (ECs) are an important part of new blood vessels in tumor progression. Many metabolic pathways, including FA metabolism, contribute to the altered behavior of tumor endothelial cells. ECs use FAs for DNA synthesis and cellular replication, and ECs express the enzymes required for FA synthesis, including ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FASN). Vascular endo-

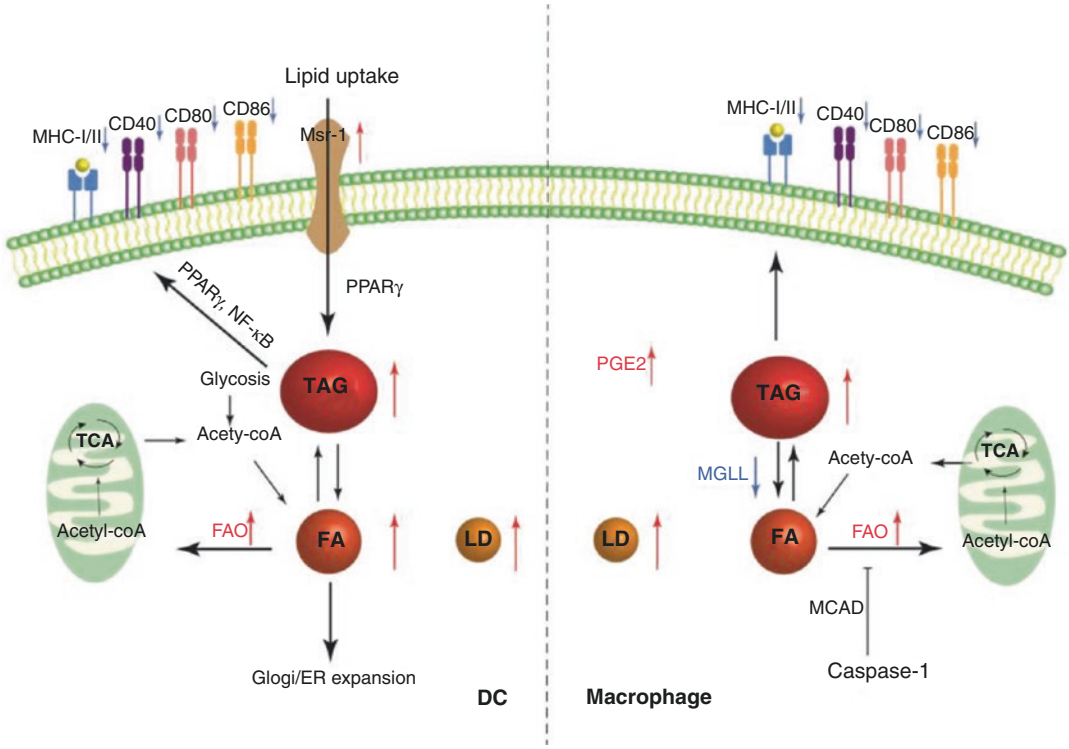

Fig. 11.3 Lipid reprogramming of dendritic cells and macrophages in the tumor microenvironment. (1) Lipid accumulation, primarily in the form of triglycerides (TAGs) and lipid droplets (LD), in DC contributes to its dysfunction in cancer. The expression of macrophage scavenger receptor (Msr-1) in DCs increases lipid uptake, resulting in the expression of costimulatory molecules and reduced MHC class I/II expression. The mechanisms of lipid accumulation involve the PPAR-γ or NF-κB pathways. In general, the metabolic switch from anabolic metabolism to catabolic metabolisms is consistent with DC function modulation from immunogenicity to tolerogenicity. Furthermore, fatty acid oxidation (FAO) renders DC tolerogenic, and increased generation of citrate by the tricarboxylic acid (TCA) cycle promotes fatty acid synthesis (FAS) and the expansion of ER and Golgi networks required for DC activation. (2) Tumor-associated macrophages (TAM) with upregulated FAS enzymes and increased FAO result in immune system evasion. Both monoacylglycerol lipase (MGLL) deficiency and medium-chain acyl-CoA dehydrogenase (MCAD) inactivation by caspase-1 through cleavage of PPARγ contribute to lipid accumulation in TAMs. In addition, PEG2 can transform TAMs from M1 to M2 and lead to the downregulation of MHC molecules

thelium expresses many FA transporter genes, including FAT/CD36 and FABP4, and influences EC proliferation, migration, and sprouting [113]. Carnitine palmitoyltransferase 1a (CPT1a) is a rate-controlling enzyme of FAO that imports fatty acids into the mitochondria, and CPT1a-controlled FAO stimulates EC proliferation as well as lymphatic ECs. Additionally, the transcription factor PROX1 binds to the CPT1a promoter and increases CPT1a gene expression, ultimately stimulating FAO [114].

11.6 Concluding Statements

Immune escape plays a fatal role in tumor progression and is one of the main reasons for dysfunctional tumor antigen presentation. In the TME, the disruption of MHC function as well as high expressions of inhibitory molecules, such as PD-1/PD-L1, IL-10, TGFβ, and PGE2 and downregulation of costimulatory molecules contribute to deficient antigen presentation function. Cancer and immune cell metabolism are instrumental in

tumor initiation, progression, and metastasis. Both MHC-I and cross-presentation processing pathways are involved in the antitumor immune response. Within the cancer microenvironment, there are complex mechanisms that suppress the actions of antitumor immune effectors, and lipid metabolism plays a crucial role in shaping immune cell differentiation and function. Here, we review that lipid metabolic disorders are related to immune suppression in APCs. APCs upregulate FAS and lipid uptake. These features result in lipid accumulation that impairs their function in the TME and ultimately promote tumor progression. As the most powerful APCs, DCs play an important role in tumor antigen presentation. DCs' function is impaired in tumors via the accumulation of lipids, especially TAG, which contributes to an increased number of imDCs and impaired antigen-presenting function and T lymphocyte activation. Furthermore, the lipid loading of DCs caused by increased expression of Msr-1 and PPAR-γ may regulate lipid accumulation via mechanisms involving NF-κB and AMPK. Similar to DCs, macrophage enhanced FA biosynthesis and lipid uptake and storage in the tumor microenvironment. Macrophages are more likely to switch to the M2 phenotype, and these changes may also be mediated by PPARs, LXRs, and STAT.

Above all, lipid metabolism disorders in APCs are associated with suppression of antigen presentation and reduced T cell activity in advancing tumors. The mechanisms of APC dysfunction remain unclear, and more studies are needed to explore these outstanding questions.

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