Immunological Accessory Molecules

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Immunological accessory molecules are proteins expressed on the surface of immune cells that can modulate in a positive or negative manner the ability of the cell to develop or to perform one or more of its functions. Thus, accessory molecules are critical to the success or failure of controlling the immune response to foreign antigens such as infectious agents or organ transplants, the aberrant response to self-antigens as in the case of autoimmune disease or the response to tumours.

Introduction

Accessory molecules are cell surface proteins that promote or suppress the response of immune cells. Accessory molecules are so named to distinguish them from primary signalling proteins that recognize foreign antigen and initiate immune responses. Primary signalling molecules include the T-cell antigen receptor (TCR), the B cell antigen receptor (integral membrane antibody) and in some cases certain pattern-recognition receptors. Accessory molecules include cell surface molecules involved in immune cell activation and differentiation, in inhibition of immune cell activity and in cell homing and adhesion. Accessory molecules also include cell surface receptors that bind soluble proteins such as cytokines or the receptors that bind chemokines which are found in both soluble and cell surface-associated forms. Additional accessory molecules are tetraspanins, pattern-recognition receptors (including Toll-like receptors, TLR) and the Fc receptors (FcR) that capture the heavy chain Fc portion of antibodies and display the antibody on the cell surface. Indeed, it is difficult to identify a protein expressed on an immune cell surface that when properly engaged does not modulate in some manner the function of that cell. The number of surface molecules identified has increased at a rapid rate in recent years. As an example, a T cell can express well over 200 different surface proteins during its lifetime and each seems to contribute to function. Brief introductions to each class of molecule will be presented here and their distribution and activities will be defined (**Table 1**).

Nomenclature

The nomenclature used for various classes of accessory molecules is evolving. Many were named originally according to action (e.g. ICAM for intercellular adhesion molecule or LFA for leucocyte function-associated antigen) or according to the protein that they recognize as ligand (e.g. the cytokine receptor, interleukin 2 receptor). This is gradually being supplemented and in some cases replaced by organized numerical designations. The first numerical stratification was the cluster of differentiation (CD) system, which assigns a number to each verified immune cell surface molecule. CD numbers consolidated several names for the same protein under a single rubric. Some proteins consist of only one polypeptide chain and can be described by one CD number (e.g. ICAM-1 is CD54). Others are formed by two or more chains and are defined by a CD number for each chain (e.g. LFA-1 is CD11a–CD18). The number of CD proteins identified exceeds 340, and continues to climb so the present work will discuss only representative examples. A more recent numerical stratification was applied to chemokines and their receptors. As an example, a chemokine originally known as MIP-1α is now referred to as CCL3 and its receptors are CCR1 and CCR5. In most cases the change to numerical identification has proven helpful and simplifying. Occasionally it causes more confusion. Sometimes, especially when more than one polypeptide chain forms a receptor and that protein is shared with other receptors, the colloquial name remains more convenient (e.g. LFA-1 instead of CD11a–CD18).

Adhesion Molecules

Overview

Adhesion molecules are plasma membrane proteins that mediate transient interaction of immune cells with the extracellular matrix (ECM) or with other cells. Immune cells migrate in two ways, actively along the ECM using one type of adhesion molecule and passively through the

Table 1 Families of accessory molecules based on function

Family	Function	Examples
Adhesion molecules	Engage counter receptors on other cells or stick to ECM. Stabilize cell–cell interactions. Promote migration and homing. Receive signals	CD4, CD8, CD11a–CD18, CD54, Selectins, CD29, α4β7
Fc receptors	Bind Ig heavy chain, promote phagocytosis. initiate ADCC, induce cytokine secretion	FcγRI, FcγRII, FcγRIII, FcαR, FcεRI, FcεRII
Tetraspanins	Assist cell signalling at the cell surface level	CD81
Cytokine receptors	Bind cytokines, induce positive or negative actions, promote proliferation, differentiation and effector function	IL-1R1, IL-2Rαβγ, IL-4R, IL-6R, GM-CSFR
Chemokine receptors	Bind chemokines, guide homing and migration, receive signals	CCR, CXCR, CX3CR, XCR
Costimulatory molecules: positive regulators	Bind counter receptors, receive signals to enhance proliferation, differentiation and effector function, enhance mediator secretion, prevent apoptosis	CD28–CD86, CD40–CD154, CD54–CD11aCD18
Costimulatory molecules: negative regulators	Bind counter receptors, receive signals to suppress cell proliferation, differentiation and effector function, induce apoptosis	CTLA-4, TNFR1–TNF, CD95–CD95L, KIR
Pattern recognition receptors	Bind microbial products, stimulate cells to perform antimicrobial activity	TLR, mannose-binding protein

circulatory system, which they leave actively (extravasation) using different types of adhesion molecules to interact with endothelial cells. In addition, adhesion molecules allow immune cells to interact transiently with several other cell types. In this context, adhesion molecules serve as both an anchoring mechanism and as a sensory array allowing the cell to receive signals from the cell with which it interacts.

Classification

Adhesion molecules most relevant to the immune response are typically described as falling into four classes: mucins, selectins, integrins and cell adhesion molecules (CAMs). Mucins are serine-/threonine-rich proteins that are heavily glycosylated; examples include CD34, PSGL-1 and MAdCAM-1. Selectins are transmembrane proteins with extracellular lectin domains that bind to specific carbohydrates, especially sialylated versions as are found on mucins. Integrins are heterodimers expressed by leucocytes that consist of α and β chains and are categorized by the β subunit.

Examples of the β1 (CD29) integrins are the very late activation (VLA)-1, -2, -3, -4, -5 and -6 proteins that differ in their α chains and can bind fibronectin, collagen or laminin which constitute the ECM. β2 integrins include LFA-1, Mac-1 and p150/95. These share the β chain (CD18) but have distinct α chains (CD11a, CD11b and CD11c) and have as their counter receptors the intercellular adhesion molecules (ICAMs) expressed on cell surfaces. CAMs are members of the immunoglobulin (Ig) superfamily that contain a variable number of extracellular Ig domains and include ICAM-1, -2, -3 and VCAM. MAdCAM-1 is an example of an adhesion molecule that contains both Ig- and mucin-like domains and is important in the migration of leucocytes through the mucosal endothelium.

Cell migration

Cells of the immune system are the most mobile of all cells, and circulate continually through the blood, lymphatic system and tissues. In collaboration with chemokine receptors (described later), adhesion molecules mediate the routing of

various immune cells to specific sites in the body. Factors that regulate expression of adhesion molecules can therefore control where and when immune cells travel. Extravasation from the vascular system begins with a process called rolling in which the cells are induced to move more slowly than other blood components by the stickiness of selectins interacting with their counter receptors the mucins. Members of each group are expressed on the leucocyte surface as well as the endothelial cell surface. An activating event, usually due to chemokines, causes intracellular leucocyte signalling proteins to increase the affinity of surface integrins. The interaction of integrins on the leucocyte (e.g. LFA-1), with CAMs on the endothelial cell (e.g. ICAM-1) assists the leucocyte to flatten and also aids in passage of the leucocyte between endothelial cell tight junctions. Inflammation provides signals that increase leucocyte extravasation at inflamed sites but this transendothelial migration also occurs during normal immune surveillance at a less intensive frequency. Once free of the vascular system, leucocytes migrate towards sites of injury or to sites targeted for surveillance using the ECM as a highway. Movement within the tissues is generally controlled by integrins such as those involving the β1 subunit. These bind to ECM components fibronectin, collagen or laminin depending on the α subunit that contributes to forming the integrin heterodimer. As mentioned, some adhesion molecules participate in selective targeting of leucocyte migration. For example, naive T cells expressing CD62L (L-selectin) target to lymph nodes and those expressing integrin α4β7 target to the gut. **See also**: Immunological Adhesion and Homing Molecules; Integrin Superfamily

Intercellular adhesion and signalling

Adhesion molecules anchor the close contact with other cells that lymphocytes require for transfer of information leading to cell activation, differentiation or function. Examples include interaction of T cells with antigen-presenting cells (APC) to receive signals to activate and differentiate and interaction of cytotoxic T cells with target cells to deliver cytotoxic signals. Interaction between the TCR on the T cell and the antigen–MHC complex on the APC is stabilized and strengthened by several adhesive counter receptor pairs. The CD4 and CD8 molecules bind MHC class II and I, respectively, and are the basis for the MHC restriction of CD4- and CD8-bearing T cells. LFA-1 (CD11a–CD18) binding to ICAM-1 (CD54), and CD2 binding to CD58, also stabilize the complex. These interactions are not static. Stimulation of T cells through the TCR triggers an increase in the binding affinity of LFA-1 for ICAM-1. The dynamic nature of this system allows, for example, a resting T cell to remain relatively noninteractive until it receives sufficient signals from its environment to enable activation of its adhesion systems. Finally, in recent years it has become apparent that proteins previously thought to function in adhesion also receive essential signals and transmit them into the cell on which they reside. For example, LFA-1, ICAM-1 and CD2 all reside on

T cells and when engaged by counter receptors, are capable of transmitting classical second signals (discussed later) into the T cell. **See also**: CD Antigens; Major Histocompatibility Complex: Interaction with Peptides; T-cell Receptors; T Lymphocytes: Cytotoxic; T Lymphocytes: Helpers

Fc Receptors

Overview

Fc receptors (FcR) are transmembrane glycoproteins that allow immunoglobulins (Ig, antibodies) to bind to cells. FcRs are widely expressed by haematopoietic cells. The FcR interacts with the Fc (constant) domain formed by the heavy chains of the antibody molecule. This allows the antigen-binding domains (Fab) of the antibody to stand away from the cell and receive antigen. Thus, FcRs do not bind antigen directly but do bind antigen–antibody complexes enabling cells to respond to the presence of antigen. Since antibodies have different specificities, a cell that expresses FcRs can respond to a wide variety of antigens based on the diverse antibodies the FcRs can capture. When properly engaged, FcRs generate intracellular signals that modulate the biological activity of the cell. Some FcRs activate whereas others inhibit cellular responses. **See also**: Antibody Classes; Antigen–Antibody Binding

Function

FcRs can be viewed as a link between humoral and cell-mediated immunity. Binding of antigen to antibodies resting in an FcR can result in such diverse actions as (1) triggering a cell to secrete cytokines or other molecules such as reactive oxygen intermediates involved in inflammatory reactions, (2) promoting a cell to phagocytose microbes, (3) initiating a cytolytic killing function (antibody-dependent cell-mediated cytotoxicity, ADCC) or (4) when on an APC, can facilitate antigen processing and presentation to T cells. In these ways, FcRs can direct the uptake and elimination of foreign microbes such as viruses, bacteria and parasites, and participate in the destruction of virus-infected cells. **See also**: Antibody-dependent Cell-mediated Cytotoxicity (ADCC)

FcR types

The distinct classes of antibody are characterized by different heavy chains (e.g. IgG = γ, IgA = α and IgE = ε), and different FcRs exist for binding to each (e.g. FcγR, FcαR and FcεR, respectively). Subclasses exist within each FcR group and these subclasses serve different functions or are differentially expressed on particular cell types. IgG FcR have four classes, FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16) and FcγRIV. Two classes of IgE receptors exist, FcεRI (high affinity) and FcεRII (CD23, low affinity).

FcγR1 (CD64) is expressed mainly by macrophages and dendritic cells, and promotes phagocytosis of immune complexes, which are antigens or microbes bound by antibody molecules. FcγRII (CD32) is present on monocytes, granulocytes and B cells. CD32 is involved in phagocytosis and ADCC, degranulation of neutrophils resulting in tissue destruction, and inhibition of the immune response. FcγRIII (CD16) is expressed on macrophages, natural killer (NK) cells and neutrophils. CD16 is also involved in phagocytosis and ADCC. Similarly, FcαR is present on neutrophils and macrophages and allows phagocytosis of IgA-coated antigens. FcεRI and FcεRII are thought to have evolved as part of the defence against parasites but they are better known for involvement in allergic reactions. Mast cells and basophils express FcεRI. When complexes of IgE and allergen are bound to these cells via FcεRI, degranulation is initiated resulting in the release of histamine, serotonin and leucotrienes. These molecules contribute to the swelling (oedema) and redness (erythema) associated with allergies. FcεRII (CD23) is primarily involved in the regulation of IgE production by B cells. CD23 is expressed on B cells, monocytes and dendritic cells. **See also**: Antigen–Antibody Complexes; Dendritic Cells (T-lymphocyte Stimulating); Histamine Biosynthesis and Function; Natural Killer (NK) Cells; Neutrophils

Two other classes of FcRs exist which are not involved in effector functions of cells but are responsible for the movement of antibodies across cell membranes. The poly IgR transports polymeric antibodies (polymeric IgA and to some extent pentameric IgM) across epithelial surfaces (e.g. into the gut lumen). In humans FcRn (neonatal) transports IgGs from mother to fetus during gestation. **See also**: Fc Receptors

Tetraspanins

Overview

Tetraspanins comprise a large superfamily of membrane proteins that pass four times across the cell membrane. Tetraspanins range in mass from 25 to 50 kDa, and leucocytes are capable of expressing ∼20 tetraspanins. Tetraspanins chiefly assist cell surface signalling.

Structure

Tetraspanins possess four transmembrane domains and each domain contains conserved polar and nonpolar amino acid residues. Transmembrane domains 1 and 2 flank a small extracellular loop (SEL) whereas transmembrane domains 3 and 4 flank a large extracellular loop (LEL). A conserved CCG motif along with other cysteine residues contribute to disulfide bonds present in the LEL. The structural domains appear to be associated with specific functions. The LEL mediates specific protein–protein interactions with laterally associated proteins in the membrane and the cytoplasmic domains provide linkage to cytoskeletal and signalling molecules.

Function

The major role of tetraspanins is to organize other proteins into microdomains (tetraspanin-enriched microdomains, TEMs) at the cell surface. In B cells, the tetraspanin CD81 seems to reorganize the membrane and stabilize signalling complexes in response to costimulation. CD81 has been shown to associate directly with the signalling complex comprised of CD19, CD21 and Leu-13 that lowers the threshold for cell activation through the B-cell receptor (BCR). In T cells there is evidence that several tetraspanins function directly as costimulatory molecules. For example, in murine T cells co-stimulation through CD3 plus CD81 was comparable to co-stimulation through CD3 plus CD28 as measured by proliferation and upregulation of CD25 and CD69. In the human Jurkat T-cell line IL-2 production was induced after co-stimulation with immobilized anti-CD81 and anti-CD3.

Cytokine Receptors

Overview

Interactions between cytokines and their specific receptors are important mechanisms of immunoregulation. Cytokines are low molecular weight proteins that influence leucocyte haematopoiesis, proliferation, differentiation, survival, effector function and homing. Cytokine receptors bind to cytokines produced by the same cell (autocrine), by nearby cells (paracrine), or by distant cells (endocrine) leading to stimulatory or inhibitory effects depending upon the cytokine and the cell type on which the receptor is expressed. A particular cytokine can have diverse functions (pleiotropy) when the same receptor is expressed on different cells, and different cytokine receptors can share similar functions (redundancy) on the same cell. Receptors are named for their cognate cytokines, which are named according to function (e.g. GM-CSF for granulocyte macrophage colony stimulating factor) or are given more general designations as 'interleukins' (e.g. IL-2). **See also**: Cytokines; Cytokine Receptors; Interleukins

Classification

Cytokines and their receptors can be classified by structural attributes or functional activities. Most cytokine receptors are homodimers, heterodimers or trimers of membrane-spanning proteins given α, β and γ designations and some receptors share subunits. Based upon structural similarities, cytokine receptors are grouped into five categories: Ig superfamily, Type I, Type II, tumour necrosis factor (TNF) receptor family and chemokine receptor family (discussed later).

The Ig superfamily group includes receptors for IL-1α, IL-1β, M-CSF, SCF and IL-18, which contain extracellular Ig-like domains. Type I cytokine receptors share structural similarities, including four conserved cysteines, and a WSXWS motif in the extracellular domain. They include receptors for leucocyte growth factors IL-2, -4, -7, -9, -15 and -21, which share CD132, the common cytokine receptor gamma chain (γ_c). A common receptor beta chain (β_c) is shared by the receptors for IL-3, IL-5 and GM-CSF. Receptors for IL-6, IL-11, oncostatin M and leukaemia inhibitory factor (LIF) share the signal transducing protein gp130. Common receptor chains alter the binding affinity of the receptors for the cytokines. For example, the IL-2 receptor has three affinities for IL-2. The low affinity receptor is IL-2Rα, the intermediate affinity receptor contains the IL-2Rβ and -2Rγ subunits, and the high affinity receptor contains IL-2Rα, -2Rβ and -2Rγ. The Type II cytokine receptors also contain four conserved cysteines in the extracellular domains and are receptors for the interferon (IFN) and the IL-10 families. IFNα, -β and -ω are somewhat confusingly called Type I IFNs, whereas IFNγ is a Type II IFN but all use Type II cytokine receptors. The IL-10 family includes IL-10, -19, -20, -22, -24, -26, -28 and -29 and each uses a different receptor. The TNF receptors bind TNFα, -β (lymphotoxin) and BLyS (B-lymphocyte stimulator) as well as apoptosis-related proteins (e.g. Fas) and some costimulatory molecules. TNF receptors include TNF-RI and -RII and are characterized by cysteine-rich domains in extracellular regions. The chemokine receptor family is described in a separate section in this article.

Function

Cytokines have diverse roles in the immune response. Some are proinflammatory (e.g. IL-1, -6 and TNFα), some induce cell proliferation (e.g. IL-2 with T and B cells), and others induce differentiation. IL-2, IFNγ and TNFβ generate cell-mediated (T_H1) responses, while IL-4, -5, -6, -9, -10 and -13 produce primarily humoral (T_H2) responses. IL-3, -5, GM-CSF, G-CSF, EPO and SCF control haematopoietic differentiation to produce new cell types. Suppressive cytokines such as TGFβ and IL-10 are associated with regulatory T-cell function and inhibit immune responses. **See also**: Haematopoiesis; Myeloid Cell Differentiation; Tumour Necrosis Factors

Signalling

In general, cytokine binding occurs through the receptor α subunit and signal transduction is facilitated by the β or γ subunit. Cytokine receptor signalling cascades often utilize the Jak-STAT and Ras/MAP kinase pathways. Most cytokines are secreted, but some can also be membrane-bound (e.g. IL-1α, TNFα and TGFβ). Most cytokine receptors are membrane-bound, but some can become soluble receptors due to alternative mRNA splicing or proteolytic cleavage of the membrane-bound forms.

These retain cytokine-binding activity and they can be detected in blood and urine. The precise role of soluble cytokine receptors is not known, although they may inhibit cytokine signalling. Immune disorders can be related to cytokine receptors. X-linked severe combined immunodeficiency (XSCID) is caused by mutations in the common cytokine receptor γ_c gene and results in drastically reduced numbers of T cells and NK cells. **See also**: Signal Transduction Pathways in Development: the JAK/STAT Pathway

Chemokine Receptors

Overview

Chemokine receptors in combination with certain adhesion molecules form the guidance system by which leucocytes are targeted to specific areas of the body. As such they participate in cell migration and adhesion to specific sites and migration within specific areas such as the thymus and lymph nodes. In addition, engagement of chemokine receptors activates signalling pathways resulting in changes in gene expression and cell phenotype.

Classification

Chemokines, named because they are chemotactic cytokines, range in mass from 6 to 14 kDa. Greater than 50 chemokines have been partitioned into four classifications based on position of conserved cysteines near the *N*-terminus. CC chemokines have two adjacent cysteines. CXC and CX3C chemokines have two cysteines separated by one or three nonconserved amino acids, respectively. C chemokines have only one cysteine near the *N*-terminus. Chemokines function in soluble form and also are found decorating the surface of destination cells as a guide to chemotaxis by immune cells. Chemokine receptors (R) have been classified according to the chemokine class to which they bind, and thus are the CCR, CXCR, CX3CR and XCR receptors (**Table 2**). Chemokine receptors are seven transmembrane domain proteins and members of the G-protein coupled receptor (GPCR) family. Nineteen chemokine receptors have been identified, and range between 340 and 370 amino acids. In each, the *N*-terminus is extracellular and the *C*-terminus is intracellular. Each chemokine binds a unique receptor or set of receptors and each receptor binds one chemokine or a unique set of chemokines.

Function

Chemokine receptor engagement modulates signal transduction pathways and can initiate either an agonistic or antagonistic response. Chemokines induce cell adhesion and migration when chemokines on the surface of endothelial cells interact with receptors of migrating leucocytes to activate and upregulate integrins. High concentrations of CXCL12 repel some T cells to focus an inflammatory

Table 2 Chemokine receptors

Receptor	Synonyms	Ligand
CCR		
CCR1	CKR1, CC CKR1, CMKBR1	CCL3,5,7,8,13,14,15,16,23
CCR2	CKR2, CC CKR2, CMKBR2	CCL2,7,8,12,13
CCR3	CKR3, CC CKR3, Eot R, CMKBR3	CCL5,7,8,11,13,14,15,24,26
CCR4	CKR4, CC CKR4, CMKBR4, K5-5	CCL17,22
CCR5	CKR5, CC CKR5, ChemR13, CMKBR5	CCL3,4,5,8,11,13,14,20
CCR6	GPR-CY4, CKR-L3, STRL22, CRY-6, DCR2, CMKBR6	CCL20
CCR7	BLR-2, CMKBR7	CCL19,21
CCR8	TER1, CKR-L1, GPR-CY6, ChemR1, CMKBR8	CCL1,4,16
CCR9	GPR9-6	CCL25
CCR10	GPR2	CCL27,28
CCR11	PPR1	CCL2,8,13,19,21,25
CXCR		
CXCR1	IL-8RA, IL-8R-I, IL-8R	CXCL2,3,5,6,7,8
CXCR2	IL-8RB, IL-8R-II, IL-8R	CXCL1,2,3,5,6,7,8
CXCR3	IP10/MigR, GPR9	CXCL9,10,11
CXCR4	HUMSTSR fusin, LESTR, HM89	CXCL12
CXCR5	BLR-I, MDRI5	CXCL13
CXCR6	Bonzo, STRL33, TYMSTR	CXCL16
XCR		
XCR1	GPR5	XCL1,2
CX3CR		
CX3CR1	GPR13, V28, CMKBRL1	CX3CL1
Duffy	DARC	CXCL1,7,8, CCL1,5
D6	CCR9, 10, JAB61	CCL2,4,5,8,13,14,15

response in an area. Some chemokines induce a cytotoxic cell response: e.g. CXCL8 interacting with its receptor on neutrophils induces release of defensins, and other specific CC, CXC and CX3C chemokines can promote NK cell degranulation. CCL2 and CCL3 promote T-cell proliferation. CCL1 protects T cells from apoptosis while CXCL12 may induce CD4 + T-cell apoptosis via the Fas pathway. It is important to note that chemokines do not exert the same effect on all cell types. For example, CCL3 causes different effects in T as compared with B cells.

Chemokine receptors have roles in biological processes. Pro-thymocytes use CCL25 produced by thymic dendritic cells to move into the thymus and begin development. Chemokines produced within the thymus and dynamically expressed patterns of chemokine receptors on the surface of developing T cells direct T cells to specific sites within the thymus for successive stages of the developmental process. Chemokines and their receptors are essential in maintaining cell homoeostasis, organ development and secondary lymphoid tissue development and organization. CCR7 on naïve T cells allows migration into lymph nodes and also helps direct naïve cells to specific sites within lymph nodes. Dendritic cells use CCR7 to migrate through the lymphatic vessels to become APCs for naïve T cells in the lymph nodes. Activated T cells expressing CXCR5 can enter lymph node follicles and participate in T cell–B cell interactions to generate germinal centres.

During leucocyte migration chemokines on vascular endothelial cells bind to receptors on the leucocyte inducing activation of β2 integrins prior to extravasation of the cell into tissue. In microbial infections, monocytes produce CXCL8, CXCL2, CCL3 and CCL4 to recruit leucocytes to the infected site. Chronic inflammatory diseases are also mediated by chemokine–chemokine receptor interactions. Autoimmune rheumatoid arthritis involves chronic inflammation of the joints where leucocyte infiltration is directed by chemokines. CXCL8, CXCL5, CXCL1, CCL2, CCL3 and CXC12 are produced in the synovial tissues and attract neutrophils, monocytes and CD4 memory T cells to the synovial spaces. Chemokine receptors are sometimes co-opted by tumours and viruses. During some breast cancer metastases tumour cells express CXCR4 and CCR7 while their ligands are expressed in organs to which the tumour cells metastasize suggesting a role for chemokines during metastasis. Chemokine receptors are used by viruses as entry sites into the host cell. Human immunodeficiency virus 1 (HIV-1) uses CCR5 and CXCR4 to enter macrophages, dendritic cells and T cells.

Thus, chemokine receptors are accessory molecules to activation, proliferation, migration and adhesion of immune cells. Their function is redirected in virus infection and in some tumour metastases. These receptors represent a relatively new and potentially fruitful set of targets for developing therapeutic approaches.

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Costimulatory Molecules: Positive Signal Transducers

Overview

Costimulatory molecules are those accessory proteins that transmit signals to a cell to enhance the response of that cell in a positive manner. Although this concept may apply to many cell surface proteins, the term most generally refers to proteins expressed on T cells with counter receptors on the cells that present antigen to them, and this system provides the most instructive example. T cells leave the thymus in immature form with the ability to cycle between the blood and the lymphatic system and with no ability to enter other tissue types. Absent interaction with their cognate antigen these cells will die. Interaction with their specific antigen, properly presented in the context of MHC on the surface of an APC induces naïve T cells to activate, expand in number by proliferation and differentiate into effector cells capable of carrying out functions in response to the foreign antigen. After time, the population of effector cells contracts leaving memory cells capable of more rapid and vigorous response should the same antigen be encountered again. To activate a naïve T cell, two signals are required. First (Signal 1) is the cognate antigen, properly presented by MHC. A second or costimulatory signal (Signal 2) is delivered by any of a number of counter receptor pairs. This signal is a fail-safe signal and if it is not received by the naïve T cell, the cell is induced to die or become anergic in the presence of only Signal 1. Responses by memory cells to the same antigen can be induced by the first signal alone, but second signals have strong modulatory effects on these cells as well. Signalling into the T cell is likely to be accompanied by counter signalling into the APC when the costimulatory counter receptor proteins engage. This activity has additional effects on the immune response. **See also**: Antigen Presentation to Lymphocytes

Costimulatory proteins

The best-studied T-cell costimulatory protein is CD28, which interacts with its counter receptors CD80 and CD86 on the APC. The combination of Signals 1 and 2 induces signalling events not induced by Signals 1 or 2 delivered alone and the outcome for the cell is rescue from the cell death induced by Signal 1, followed by clonal expansion and change in cell phenotype. Costimulatory proteins can be partitioned into two classes, those present on resting naïve T cells and those that are induced by the initial Signal 1–Signal 2 combination. Examples of the first group are CD28, LFA-1 and ICAM-1. All three are expressed on both naïve and memory T cells and are available to receive second signals from APCs. Examples of proteins from the second group that are induced during T-cell activation include ICOS, 4-1BB, OX40 and LIGHT. It is most likely that this class of proteins potentiates the activation–differentiation process should they be engaged by their counter receptors. Proteins are traditionally assigned to

costimulatory status when they are observed (a) to be resident on a T cell and (b) to induce proliferation when stimulated in conjunction with stimulation through the TCR (Signal 1). Examples of these proteins include (but are not limited to): CD2, CD5, CD9, CD27, CD28, CD44, CD46, CD81, LFA-1, ICAM-1, VLA-4, ICOS, 4-1BB, OX40, LIGHT and SLAM.

Classification

Costimulatory molecules for T cells fall into several categories. The CD28 family includes ICOS and two inhibitory proteins described later, CTLA-4 and PD-1. The integrin family is represented by LFA-1 and VLA-4. The Ig superfamily includes the ICAMs and the TNF receptor family includes 4-1BB, OX40 and LIGHT. Additional categories are numerous as the group of proteins capable of delivering costimulatory signals is quite large.

Additional cell types

Other cell types utilize costimulation to modulate function. B cells experience modulation of function and differentiation when antigen receptor (BCR) signalling is augmented by costimulation (e.g. by the tetraspanin CD81 complex mentioned earlier). B cells proliferate, increase antibody production and undergo Ig heavy chain class switching in response to costimulation. As mentioned, counter receptor engagement on APCs increases their ability to function. Macrophages and dendritic cells, serving as APCs can receive signals that enhance antimicrobial and antiviral activities.

Implications

Costimulatory signals synergize with signals delivered through the antigen receptor and induce T-cell activation, proliferation and acquisition of effector functions while protecting the cell from apoptosis induced by the antigen signal alone. An increasing number of proteins qualify for some form of costimulatory status. Basic questions revolve around the circumstances under which each comes into play, where in the body each has its primary function and exactly how many outcomes are available when each acts alone or acts in concert with one or more additional costimulators.

Inhibitory Molecules: Negative Signal Transducers

Overview

Inhibitory molecules are transmembrane proteins that receive signals which instruct the cell on which they are resident to downregulate specific functions and reduce the participation of the cell in the immune response. Thus, these proteins function in a negative manner. Such negative

functions are essential in inactivating an immune response once the crisis has been averted. These negative functions sometimes also prevent inappropriate activation of the immune response to self-antigens.

Lymphocyte inhibition

In the context established with the previous section, some T-cell surface proteins receive negative signals that inactivate the cells. Examples are CTLA-4 expressed mostly on T-cells, and PD-1 expressed on T cells, B cells and monocytes. When engaged by their counter receptors, both send signals into the cell to blunt activation and proliferation, effectively serving as immune attenuators. Receptors for IL-10 and TGFβ also serve as immune attenuators. When they receive signals in the form of these cytokines sent by regulatory T cells, these receptors exert negative effects on the activated cells on which they reside.

Induction of cell death

Members of the TNF–TNFR families transmit signals leading to cell death by apoptosis. Examples of these include CD95 (Fas) and its counter receptor CD95L (Fas ligand), TRAIL and its counter receptors DR4 and DR5, and TNF and its counter receptor TNFRI. The proteins resident on the target cell (CD95, DR4, DR5 and TNFRI) signal the cell to initiate apoptosis when they are engaged by their counter receptors. Each such protein contains a 'death domain' in its cytoplasmic region. These types of proteins are used to induce death in lymphocytes after they have effected resolution of an infection. Such activated cells must be eliminated before they continue to cause damage to healthy tissue. These mechanisms are also used by cytotoxic cells to eliminate other unwanted cells such as tumour cells.

Prevention of killing

Another class of inhibitory molecules, the MHC-class I inhibitory receptors, also called inhibitory NK receptors (iNKR) are primarily expressed on NK cells and represent sensory detectors for expression of MHC class I molecules (human leucocyte antigen (HLA) in humans) on the surface of potential target cells. NK cells are responsible for killing tumour cells and virus-infected cells. MHC I is expressed on most cells and as long as iNKRs sense sufficient MHC, the cell remains safe from NK attack because engagement of iNKRs sends an inhibitory signal into the NK cell. If virus infection or tumours cause decrease in MHC I expression, the NK cell uses iNKRs to sense this and attacks the cell. Some T cells express iNKRs and this may represent a mechanism to suppress certain kinds of T-cell response. In humans, iNKRs are members of the KIR family (killer Ig-like receptor); in mice they are members of the Ly49 family. It should be noted that these families also include activating receptors that respond to specific ligands and directly activate the NK cell to kill.

Pattern-recognition Receptors

Overview

Some accessory molecules recognize and respond directly to invading microorganisms. Bacteria, fungi, protozoa and viruses possess structural and genomic components that are essential for their survival but are not produced by mammalian hosts. These microbial components are known as pathogen-associated molecular patterns (PAMPs). PAMPs are detected by pattern-recognition receptors (PRRs) on host leucocytes and other cell types. Some PRRs are localized to the cell surface, while others are found in intracellular compartments or are secreted molecules. Cell surface PRRs include scavenger receptors, the macrophage mannose receptor, the β-glucan receptor and the CD14 LPS receptor. A newly identified class of PRRs is the TLR family (TLR, **Table 3**). TLRs are Type I integral membrane glycoproteins that share some sequence homology with members of the IL-1 R family. The TLR cytoplasmic domain contains a Toll/IL-1R (TIR) domain with three conserved sequence boxes. However, the TLR extracellular region contains between 19 and 25 copies of leucine-rich repeat (LRR) motifs not found in the IL-1Rs. Each of the 12 TLRs identified in mammals recognizes a unique set of microbial components. **See also**: Innate Immune Mechanisms: Nonself Recognition

Binding partners

The cellular localization of TLRs is related to their specialized functions. Cell-surface TLRs recognize structural components of bacteria, fungi and protozoan parasites while intracellular TLRs detect viral and bacterial nucleic acids that have been trafficked to endosomes. Gram-positive bacteria, Gram-negative bacteria and mycobacteria possess distinct structural components, but are each recognized by TLRs. Bacterial PAMPs that are detected by TLRs include lipopolysaccharide (LPS), peptidoglycan, lipoteichoic acid, lipoproteins, lipoglycans, flagellin, porins and unmethylated CpG motifs known as CpG-DNA. Zymosan and mannan molecules are fungal cell-wall moieties recognized by certain TLRs. Antiviral immunity is enhanced by TLRs that recognize viral single-stranded RNA, double-stranded RNA, CpG-DNA and some viral envelope proteins. Different protozoan parasite species contain TLR ligands including glycosylphosphatidylinositol-mucin (GPI-mucin), glycoinositolphospholipids, haemozoin and profilin-like molecules. In addition, host proteins such as heat-shock protein 60, 70 and fibrinogen can be detected by TLR4, perhaps as indicators of cellular damage. Although human TLR11 is nonfunctional, murine TLR11 recognizes components of uropathogenic bacteria and profilin-like molecules. The functions of TLRs 10 and 12 are still being studied.

Table 3 Toll-like receptors

TLR	Cellular compartment	Example ligands	Microbes recognized
TLR1	Cell membrane	Triacyl lipopeptides	Bacteria
TLR2	Cell membrane	Peptidoglycan, lipoteichoic acid, porins, lipopeptides, lipoglycans, zymosan	Bacteria, fungi, measles virus, *Trypanosoma* sp.
TLR3	Endosomal membrane	Double-stranded RNA	Viruses
TLR4	Cell membrane	Lipopolysaccharide, glycans, envelope proteins, glycoinositolphospholipids	Bacteria, fungi, respiratory syncytial virus, *Trypanosoma* sp.
TLR5	Cell membrane	Flagellin	Bacteria
TLR6	Cell membrane	Lipoteichoic acid, lipopeptides, zymosan	Bacteria, fungi
TLR7	Endosomal membrane	Single-stranded RNA	Viruses
TLR8	Endosomal membrane	Single-stranded RNA	Viruses
TLR9	Endosomal membrane	CpG DNA, haemozoin	Bacteria and viruses, *Plasmodium*
TLR10	Cell membrane	Not known	Not known

Location and signalling

TLRs are found on all leucocyte subsets (macrophages, dendritic cells, granulocytes, T cells and B cells). Conventional T cells can express TLR1, 2, 3, 4, 5, 8 and 9. Ligand binding to some TLRs increases T-cell proliferation in a manner similar to a costimulatory signal. Regulatory T-cells (T_{reg}) express TLR2, 5 and 8, which influence T_{reg} suppressive activity. Other cell types such as fibroblasts and epithelial cells also express some TLRs. TLR expression can be upregulated or downregulated depending upon the cytokine environment or activation state of the cell. Upon ligand binding, the TLRs dimerize and conformational changes occur. Next, the adaptor proteins MyD88, TIRAP, TRIF or TRAM selectively bind to TLR TIR domains and signal transduction cascades occur through several proteins including IRAK-1, IRAK-4, TRAF6, TAK1, TAB1, TAB2, TAB3, NF-κB and MAP kinases. Depending upon the signalling pathway utilized, the transcription factors AP-1, NF-κB, IRF-3, IRF-5 or IRF-7 are activated. Transcription factor activation leads to the expression of proinflammatory cytokines, type I interferons and chemokines and the upregulation of MHC class II and costimulatory molecules.

Function and implications

TLRs are important regulators of both innate and adaptive immunity. TLRs are found on all leucocyte subsets, and TLR triggering leads to the production of cytokines and induction of costimulatory molecules that propagate adaptive immune responses. Most TLR signals preferentially induce cell-mediated T helper 1 (T_H1) responses, however, TLR2 signals can favour antibody-mediated T_H2 responses. TLRs have been shown to be essential components of antimicrobial defence mechanisms. For example, mutations in the human TLR2 gene are associated with diminished response to bacterial lipoproteins and greater susceptibility to Staphylococcal septic shock, while mutations in human TLR4 are associated with a reduced response to LPS and a greater susceptibility to Gram-negative bacterial infections. TLRs are important accessory molecules tasked to directly detect pathogens and direct the immune responses against those pathogens.

Concluding Remarks

Immunological accessory molecules are crucial in all facets of the immune response. Signals delivered into the cells on which they are resident play significant roles in cell activation, differentiation, proliferation, function and entry into or avoidance of cell death by apoptosis. These molecules are increasingly numerous, occupy diverse classes of proteins and serve a great complexity of functions in the immune response. Questions that will be addressed in coming years will certainly deal with the varied and overlapping nature of their functions. Important consideration will accrue to questions of how and when they function

individually (if they ever do) and how and when they function in combination.

Further Reading

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