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ESSENTIALS The innate immune system comprises evolutionarily ancient mech- anisms that mediate first-line responses against microbial patho- gens, and are also important in priming and execution of adaptive immune responses, and in defence against tumours. These re- sponses, which recognize microbial non-self, damaged self, and absent self, are characterized by rapidity of action and involve various different cell types, cell-associated receptors, and soluble factors. Previously believed to lack plasticity or memory, certain in- nate immune responses have recently been shown to be capable of ‘learning’ or ‘training’. Cellular components of the innate immune system—these are mainly derived from myeloid precursors in the bone marrow and include monocytes, dendritic cells, and granulocytes (neutrophils, eosinophils, and basophils). It has recently been discovered that, at least in mice, most tissue macrophages are derived from a sep- arate progenitor population before birth. Two small populations of lymphoid cells—natural killer and natural killer T cells—are also in- cluded because they lack the clonally rearranged receptors of B and T lymphocytes. Receptors—the innate immune system uses a relatively small rep- ertoire of germline-encoded largely non-rearranging receptors. (1) Pattern recognition receptors include Toll-like receptors and mannose receptors and recognize invariant molecular signatures, usually microbial in origin, known as pathogen-associated molecular patterns. (2) Natural killer family of receptors—these largely have spe- cificity for self or altered self molecules (e.g. recognizing conserved features of human leucocyte antigen class 1 molecules; can be either stimulatory or inhibitory). Soluble mediators—these include (1) complement; (2) defensins— typically small microbicidal proteins, with other actions to stimulate both innate and adaptive immune responses; and (3) cytokines— frequently act over relatively short distances by binding to cell- surface receptors and initiating signalling via intracellular second messengers; play major roles in stimulating immune cell differenti- ation and proliferation. Clinical features of dysregulation of the innate immune system— (1) hypofunction—can result in uncontrolled infections (e.g. in chronic granulomatous disease); (2) excess activity—can result in autoinflammatory disease (e.g. periodic fever syndromes); (3) dysfunction—may contribute to common conditions of multi- factorial aetiology (e.g. Crohn’s disease). Introduction The innate immune system is an evolutionary ancient defence system, with elements present in invertebrates, that mediates defence against microbial

pathogens. It is also important in both the priming and the execution of adaptive immune responses. Although it is increasingly appreciated that the innate and adaptive responses are tightly inter- woven, innate immune responses are characterized by rapidity of action and with limited capacity for ‘learning’ or memory. The innate immune system frequently relies upon recognition of conserved molecular fea- tures of microbial pathogens—pathogen-associated molecular pat- terns (PAMPs). The innate immune system also recognizes damaged self and absent self, and hence plays an important role in rooting out malignant cells. It is useful to think of the components of the innate system separately. Most cells of the innate immune system are derived from myeloid precursors in the bone marrow. These include mono- cytes and their derivatives—macrophages and dendritic cells, blood granulocytes (neutrophils, basophils, and eosinophils), and tissue mast cells. Natural killer (NK) and natural killer T (NKT) cells, which are derived from the lymphoid cell lineage, are also included within the in- nate immune system as they lack the clonotypic receptors of lymphoid T and B cells characteristic of the adaptive immune system. An increasing number of receptor recognition systems for non- self, damaged self, and missing self are being identified. The para- digm family of innate immune receptors are the Toll-like receptors (TLRs). These are present in Drosophila melanogaster (fruit flies), where for example the absence of Toll predisposes to overwhelming fungal infection. Important soluble factors include innate immune system cytokines, defensins, and pentraxins. Dysregulation of innate immune responses is increasingly rec- ognized as causing inflammatory human disease. Hypofunction of the innate immune system can result in uncontrolled infections, as seen in chronic granulomatous disease. Excess innate immune ac- tivity can result in autoinflammatory disease; examples of this type of disease include the periodic fever syndromes. Innate immune 4.1 The innate immune system Paul Bowness

 dysfunction also contributes to common conditions of multifac- torial aetiology such as Crohn’s disease. Cells of the innate immune system Cells of the innate system are predominantly of the myeloid lineage, and arise from either fetal progenitors or in the bone marrow (see Table 4.1.1 and Fig. 4.1.1). Myeloid cell lineage Mononuclear phagocytes: Macrophages monocytes
and dendritic cells Macrophages and monocytes are related cell types, the former found in tissues and the latter in the blood. Macrophages (‘big eaters’) are able to phagocytose (engulf) large particles including whole bacteria and apoptotic or necrotic dying cells. Phagocytosis is initiated following either recognition of antibody/complement coating (opsonization), or recognition of PAMPs by PRR such as the mannose receptors. Phagocytosed microbes are usually killed by mechanisms including production of reactive oxygen species. Organisms that are able to survive within macrophages, such as the mycobacterial species responsible for tuberculosis and lep- rosy, can cause major disease. Different types of macrophages are found in different anatomical locations. Recent studies in mice have shown that most tissue macrophages are embryonic- ally seeded into tissues, from yolk sac or fetal liver, where they are capable of self-renewal. The same is probably true for hu- mans, since for example skin macrophages (Langerhans cells) are found in normal numbers in patients with GATA2 mutations who lack blood monocytes, and are likely therefore to be of distinct (embryonic) origin. Table 4.1.1 Cell types of the innate immune system Myeloid lineage Origin Site-circulating Site-tissue resident Monocyte/macrophage family Largely derived from fetal erythromyeloid progenitors Tissue macrophages including Kuppfer cells (liver), alveolar macrophages (lung) Microglia (CNS) Langerhans cells (skin epidermis) Common myeloid progenitors in the bone marrow Monocytes (blood) Dendritic cells Osteoclasts (bone) Intestinal

macrophages Myelocytic family Common myeloid progenitors in the bone marrow Neutrophils Eosinophils Basophils Mast cells Lymphoid lineage Common lymphoid progenitors in bone marrow Natural killer (NK) cells Natural killer T cells (NKT) Dendritic cell Monocyte Lymphocytic lineage (circulating and tissue- resident) Myelocytic lineage Circulating Tissue-resident NK cell NKT cell CD56+, absent CD3 CD56+, CD3+ Basophil neutrophil eosinophil macrophage Cytoplasmic granules a b c Fig. 4.1.1 Cell types of the innate immune system.

4.1 The innate immune system 309 Macrophages are also able to secrete and respond to cytokines (see following paragraphs), and secrete proteases and growth fac- tors important in tissue remodelling and repair. Uptake of modi- fied low-density lipoprotein (LDL) by macrophages in arterial vessel walls gives rise to foam cell formation and is thought to be critical in the pathogenesis of atherosclerosis. Excessive systemic macrophage activation can result in the life-threatening haemophagocytic syn- drome seen in children with viral infection and systemic juvenile idiopathic arthritis. The macrophage population within the spinal cord, known as microglial cells, have recently been demonstrated to play a key role in modulation of pain sensation in male but not female mice (where the adaptive immune system plays a major role), both implicating the innate immune system in nociception and pointing to important sex differences. Monocytes are derived from haematopoietic stem cell pre- cursors in the bone marrow and make up 3 to 9% of circulating blood leucocytes in adults. Although lacking cytoplasmic gran- ules, monocytes have lysosomes containing acid phosphatase and express the CD14 and CD68 markers. Monocytes them- selves usually leave the blood within 48 h to further mature and reside in tissues as monocyte-derived tissue-resident cells (MCs) with phenotypic and functional properties very similar to macro- phages or dendritic cells (although these monocyte-derived cells are ontogenically different). For example, recent evidence sug- gests that most ‘macrophage-like’ cells in the intestine are such monocyte-derived cells. Recently monocytes have been shown to mediate the phenomena of both innate immune ‘priming’ and postsepsis immunoparalysis. The former denotes a form of innate immune memory whereby previous exposure to microbial products results in enhanced im- munity, and the latter reduced responsiveness. Immune priming can be induced with the fungal product β glucan. Immunoparalysis can follow exposure to bacterial lipopolysaccharide (LPS). This endotoxin-induced tolerization is mediated by epigenetic mech- anisms and manifested by altered metabolic pathways. Thus, these novel examples show how programming of the innate immune system results in its ability to ‘learn’ from environmental challenges. It is likely that further examples of epigenetic modification of innate immune responses will be shown in future to result in innate im- mune memory. Dendritic cells are now recognized as vital players in the im- mune system. Although immature dendritic cells are largely tolerogenic, mature dendritic cells are the most potent known stimulators of immune responses. Dendritic cells are characterized by their ability to produce long cellular extensions known as den- drites (see Fig. 4.1.1). Dendrites are important both for sampling their environment for antigens and danger signals and for con- tacting other cell types. Immature dendritic cells patrol the tissues and transduce danger signals through recognition of PAMPs by PAMP receptors. These serve to drive both maturation of dendritic cells as well as their migration to adjacent lymphoid tissues, such as draining lymph nodes, where priming of adaptive immune re- sponses occurs. A programme of cellular and molecular changes occurs, outlined in Table 4.1.2, which facilitate this migration and immune stimulation. Thus, for example, expression of the CCR7 receptor facilitates homing to lymph nodes or spleen. Mature den- dritic cells show reduced antigen uptake but increased expression of HLA class II molecules, carrying antigen already taken up in the periphery for presentation to T cells. The HLA/antigen com- plex provides

‘signal 1’ and the costimulatory molecules CD80 and CD86 (formerly known as B7.1 and B7.2) give ‘signal 2’ to initiate T-cell adaptive immune responses. It has recently become clear that several different types of den- dritic cells exist, with differing functional properties, as shown in Table 4.1.2. The two principal types of dendritic cells are classical (formerly known as myeloid) and plasmacytoid dendritic cells. Classical dendritic cells are derived from common myeloid pro- genitors in the bone marrow and are now themselves recognized to include various subpopulations, their subsequent phenotype and behaviour exhibit plasticity depending on tissue environmental factors. Plasmacytoid dendritic cells (pDCs) are now thought to originate from pre-pDC which derive from common dendritic cell precursors under the stimulus of FLT3 ligand. Plasmacytoid dendritic cells produce both α- and β-type 1 interferons, which have potent antiviral properties. Their likely role in defence against viral infections is supported by their expression of the Toll-like re- ceptor TLR9 (see following paragraphs). Excessive α-interferon production by plasmacytoid dendritic cells has been implicated in the pathogenesis of skin psoriasis and juvenile systemic lupus erythematosus. Polymorphonuclear phagocytic cells or granulocytes Neutrophils, eosinophils, and basophils comprise the polymorpho- nuclear cells, all of which, together with monocytes, are capable of phagocytosis. Neutrophils are the most abundant white cells in the blood, and also the principle component of pus. They can rapidly leave the circulation to migrate to areas of inflammation. They are drawn down concentration gradients of cytokines such as interleukin (IL)-8 and γ-interferon (see next) in a process known as chemotaxis. Neutrophil granules contain abundant toxic defensins, cathepsins, and enzymes such as elastase. Deficiency of the NADPH oxidase en- zyme (EC 1.6.3.1) in individuals (usually young males) with chronic granulomatous disease results in inability of phagocytes to generate Table 4.1.2 Human dendritic cell subtypes Cell type Example Function Phenotypic markers Classical DC Immature Lung CD103+ DC Antigen surveillance and capture by endocytosis and phagocytosis CD11c, CD1a Mature Lymph node DC Stimulation of adaptive immune response Type 3 (lambda) interferon production CD11c, CCR7, HLA class 2, CD40, CD80/86 Plasmacytoid pDC Type 1 interferon production CD123 hi, lack CD11c

 superoxide and its bactericidal derivatives peroxynitrite, hydroxyl radicals, and hydrogen peroxide. As a result, bacterial and fungal infections are not cleared and large inflammatory granulomas may form. By contrast, familial Mediterranean fever (OMIM 240100), another genetic disorder (of the pyrin gene) primarily affecting neutrophils, results in excessive inflammatory activity causing peri- tonitis, arthritis, and amyloidosis. Eosinophils are short-lived gran- ulocytes whose granules stain red on staining with eosin. IL-5 is a key mediator of eosinophil activation. Eosinophils are important in combating parasitic infections but are also implicated in asthma and allergy. Basophils are the least common form of granulocyte. Basophils are capable of releasing histamine and cytokines including IL-4 (see next). Mast cells Mast cells, also known as mastocytes, are tissue-resident granulo- cytic cells that may originate from a distinct lineage. They are found in the skin, lungs, and gastrointestinal tract and express the high- affinity receptor for IgE (FcεRI). Mast cells play an important role in allergy, anaphylaxis, and immunity to parasites. Mast cells coated with antigen-specific IgE release granules containing histamine, cytokines, and eicosanoids upon antigen binding. The ‘weal and flare’ reaction is an example of such a response. Lymphoid cells of the innate immune system NK cells Natural killer or NK cells are a small but important blood lympho- cyte population (c.2%), distinct from T cells and B cells. They do not express the T-cell receptor for antigen (or CD3), nor the surface immunoglobulin B-cell receptor, and in contrast to adaptive im- mune responses mediated by T cells, have the ability to kill target cells without prior sensitization. This is known as ‘natural’ killing. They therefore

play a key early defence role against many infectious pathogens. NK cells are also currently being used in clinical trials as adoptive cellular immunotherapeutics against numerous cancers. NK cells can be activated by NK receptors (see next), by the binding of antibody–antigen complexes to their Fc receptors, and by inter- ferons and cytokines. Human NK cells are classified into two populations according to the intensity of CD56 (neural cell adhesion marker, NCAM) sur- face expression, as well as possession of CD16, the FcγIII receptor. CD56dim CD16bright make up approximately 90% of circulating NK cells and CD56bright CD16negative/dim comprises the remaining 10%. By contrast, CD56bright NK cells predominate in lymph nodes and sites of inflammation. CD56bright NK cells produce abundant cyto- kines (e.g. γ-interferon) and have immunoregulatory function, while CD56dim play a key role in natural and antibody-mediated cell cytotoxicity. They are capable of rapidly killing infected or ma- lignant cells, sharing with cytotoxic (CD8) T cells the ability to induce apoptosis, and the cytolytic granules containing perforin and granzymes. The cytotoxic activity of NK cells is controlled by a balance of stimulatory and inhibitory receptors. Stimulatory re- ceptors include the natural cytotoxicity receptors, some of which recognize microbial products, and some of the NK family of re- ceptors (NKRs) including NKG2D, described later. Almost all NK cells also express inhibitory receptors for self HLA (usually HLA class 1 with or without self peptide), which serve to limit killing of self cells under normal circumstances. Consequently, NK cells have the ability to recognize absence of self or ‘missing self’. NK cells have a major role in the early innate immune response to viruses, and can also kill antibody-coated cells through their FcγR3 receptors. Innate Lymphoid Cells Innate lymphoid cells (ILC) are a recently described family of tissue resident innate lymphocytes. ILC are related to NK cells, lack classical T or B cell lineage markers, and play important roles in lymphoid or- ganogenesis, tissue homeostasis and local tissue immune responses. NKT cells NKT cells are a minor population of lymphocytes (0.2% of periph- eral blood lymphocytes) that coexpress both NK markers including CD56 and the T-cell receptor for antigen (TCR). They recognize foreign or self glycolipids presented by the nonpolymorphic major histocompatibility complex (MHC) class 1-like molecule CD1. NKT cells can recognize relatively conserved glycolipids derived from bacteria and parasites, although the best-character- ized ligand, α-galactosylceramide, is derived from a sponge. These glycolipids are bound and ‘presented’ by CD1 to the NKT cell TCR. Two types of human NKT cells are currently distinguished. Type 1 or iNKT express an invariant T-cell receptor (using the TCR α- chain AV24AJ18) and recognize α-galactosylceramide presented by CD1d. Type 2 NKT express variable TCRs and are CD1-re- stricted but do not respond to α-galactosylceramide, presumably recognizing distinct glycolipids. Upon activation NKT cells pro- duce IL-4, γ-interferon and granulocyte colony stimulating factor (G-CSF; see next). The function of NKT cells is currently under intense investigation, with recent evidence in a murine model for a role in causing asthma. They may also play a role in immunity to tumours, and it is possibly relevant that the glycolipids lysosomal glycosphingolipid iGb3 and ganglioside GD3 are overexpressed by melanoma cells. Receptors of the innate immune system Unlike the adaptive immune system, the innate immune system uses a relatively small repertoire of germline-encoded largely non-rearranging receptors. Charles Janeway first proposed that conserved molecular patterns in microbes would be recognized by pattern recognition receptors (PRRs). These PAMPs would be both essential for the pathogen and distinct to host molecules. Recognition of such PAMPs is increasingly seen as a major func- tion of the innate immune system. It is now recognized that innate immune receptor recognition systems can also have specificity for damaged self (e.g. necrotic cells) and missing self. The term DAMPS is used interchangeably to signify both damage- or danger- associated molecular patterns. Recognition of PAMPs or DAMPS by the innate immune system—the immunological ‘danger’ signals proposed by Matzinger—provides a key trigger in

initiating both in- nate and adaptive immune responses. ‘Missing self’ is detected by loss of the inhibitory signals provided by receptors for self molecules including those for self HLA molecules. The TLRs principally recog- nize PAMPs; another very different grouping of receptors, the NKRs frequently recognize self and altered self.

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derived) Fibronectin (host-derived) Hyluronan (host-derived) ssRNA Flagellin Spaetzle Toll Drosophila Fig. 4.1.2 Toll-like receptors and their ligands.

312 SECTION 4 Immunological mechanisms acid-inducible gene I (RIG-I, and other RIG-1-like helicases) and melanoma differentiation-associated gene 5 (MDA5) which are important in responses to pathogens. The NLR family is large and increasing and includes the NOD, NALP, NAIP, and CIITA subfam- ilies. NOD2 variants are associated with Crohn's disease. Scavenger receptors (class A–H), sialic-acid-binding Ig-like lectins (Siglecs), and C-type lectins (e.g. DC-SIGN and mannose receptor) also have roles in recognition of pathogen determinants as well as some host molecules. Soluble factors Complement The complement proteins comprise a vital arm of the innate im- mune response described in detail in Chapter 4.2. The classical, lectin, and alternative pathways comprise cascades that ultimately activate the membrane attack complex resulting in lysis of targeted cells. Covalent attachment of activated C3 to microorganisms is a key signal to the innate immune system to take up and destroy for- eign material. The complement pathway is particularly important in immune responses to polysaccharide antigens. Defensins These are small microbicidal proteins of usually 29 to 40 amino acids. α-Defensins are largely stored in the granules of neutrophils and, to a lesser degree, macrophages. Once released they exert direct antimicrobial (including anti-HIV) activity, and can also induce mast cell degranulation and attract both naive T cells and imma- ture dendritic cells. β-Defensins are chemotactic for immature den- dritic cells and memory T cells bearing CCR6. Other peptides with antiviral, antibacterial, or antifungal activity include cathelicidin, histatins, cathepsin G, azurocidin, chymase, eosinophil-derived neurotoxin, and lactoferrin. Mannose-binding lectin (MBL) MBL is a member of the collectin subfamily of C-type lectins. MBL and the related surfactant proteins A and D have an antimicrobial role in pulmonary defence against bacterial infections. MBL initi- ates the lectin pathway of complement activation following binding to mannose, N-acetylglucosamine, fucose, or glucose residues on microorganisms. Pentraxins The pentraxins are a family of proteins with a ring structure made up of five monomers. They include C-reactive protein, a liver- derived acute-phase protein, induced by inflammatory cytokines such as IL-1 and IL-6, which protects against endotoxin-mediated mortality in animals. Cytokines Cytokines are a group of proteins important in host defence that are secreted by cells of the innate and adaptive immune systems. The first to be described was interferon, a compound produced by vir- ally infected tissue that 'interfered' with subsequent viral infection of uninfected tissue. Several overlapping terminologies are used to describe groups of cytokines, based upon their function. Thus, monokines are made by monocytes, and lymphokines by lympho- cytes; chemokines are cytokines with chemotactic activities; and interleukins are cytokines made by one leucocyte and acting on other leucocytes. Cytokines commonly have autocrine actions on the cells that secrete them, and paracrine actions on nearby cells. Cytokines are synthesized de novo in response to specific stimuli, frequently act over relatively short distances, and bring about their effects by binding to cell-surface receptors and initiating signalling via intracel- lular second messengers. Cytokines frequently exhibit redundancy and pleiotropy (i.e. one cytokine can act on different cell types). Cytokine receptors fall into several categories: haematopoietin re- ceptors such as the IL-2 receptor; tumour necrosis factor (TNF) family receptors; interferon and chemokine receptors (see next). Many cytokines play major roles in stimulating immune cell dif- ferentiation and proliferation. The functions of some of the major cytokines are briefly summarized in Table 4.1.4. Cytokines are in- creasingly being targeted in human disease therapy, as their roles are elucidated. Thus, tumour necrosis factor alpha (TNFα), also de- scribed as cachexin, is now known to play a central role in the joint pathology, malaise, and systemic features of rheumatoid arthritis

as well as other inflammatory arthropathies including psoriatic arth- ritis, ankylosing spondylitis, and Crohn’s disease. Treatment with monoclonal anti-TNF antibodies or recombinant TNF receptors is highly effective in most patients. IL-1 has been shown to be im- portant in Muckle–Wells syndrome and treatment with interleukin receptor antagonists is effective. Table 4.1.3 Natural killer (NK) and related innate immune receptors Receptor Type Cellular expression Ligand KIR Ig NK and T cells HLA class 1, specific alleles (e.g. KIR3DL1 recognizes
HLA-B27 and related HLA-B alleles) LILR Ig Monocytes, DC, B HLA class 1, general NKG2D Lectin activatory All NK/some T MICA/B NKG2A/CD94 Lectin NK/T HLA-E with HLA-derived peptide Natural cytotoxicity receptors (NCR) NKp30, 46 Ig NK Malignant cells NKp44 Ig Activated NK Malignant cells NKp80 Ig NK AICL on monocytes Ig denotes immunoglobulin family.

4.1 The innate immune system 313 Chemokines These are small (c.8–10 kDa) glycoproteins, which are usually proinflammatory and result in cellular attraction along concentra- tion gradient. Four major groups are recognized, C, CC, CxC, and CxxxC, based on the relative separation of their two N-terminal cysteines. CC and CxC are the major groups, C and CxxxC having only one member each, lymphotactin and fractalkine, respectively. Most CxC chemokines are chemoattractants for neutrophils me- diated by an ELR motif adjacent to the cysteines (e.g. IL-8, which induces migration from the bloodstream into tissues). By contrast, CC chemokines attract lymphocytes, monocytes, basophils, and/or eosinophils. Examples of CC chemokines are MCP-1, RANTES, and MIP-1α (CCL3). Monocyte chemoattractant protein MCP-1 (CCL2) is a potent monocyte chemoattractant that induces monocyte migra- tion from the bloodstream into tissues and subsequent maturation into macrophages. Chemokine receptors have seven transmembrane helices and signal through intracellular G proteins. CC chemokines bind to CC chemokine receptors, and CxC chemokines bind to CxC chemokine receptors, of which at least seven are described. The chemokine receptors CCR5 and CxCR4 are also coreceptors for HIV infection of macrophages and CD4 T cells. Interferons The interferons are a group of cytokines with potent antimicrobial and antiproliferative effects that are produced in response to prod- ucts of bacterial or viral infection, such as double-stranded RNAs, cytokines, or mitogens. They have multiple effects, characteristic- ally mediated through JAK-Stat pathways, that include upregulation of HLA class 1 and 2 expression, and generally have potent anti- viral activity. Type 1 interferons include α-interferons produced by lymphocytes (of which at least 13 are recognized), β-interferons produced by fibroblasts, and others cell type. All type 1 interferons bind to a unique cell-surface receptor, the interferon-α receptor. Only a single type 2 interferon is recognized, γ-interferon. This is Table 4.1.4 Production and action of selected cytokines Cytokine Cell source Target cell Action GM-CSF Th cells Myeloid progenitor cells Growth and differentiation Monocytes Inflammation Il-1α Monocytes T, B NK, other Stimulation IL-1β Macrophages Fever, inflammation Dendritic cells B lymphocytes IL-2 Th1 CD4 T T, B, NK Activation, proliferation IL-4 Th2 CD4 T T, B, macrophages Activation, proliferation, class switching IL-6 Monocytes B, plasma cells Differentiation, antibody secretion Macrophages, etc. Il-8 Macrophages Neutrophils Chemotaxis Endothelial cells IL-12 Macrophages NK cells Activation IL-17 T cells Many Inflammation Host defense Gut homeostasis IFN-α Leucocytes Many Inhibition of viral replication Increased HLA class 1 expression IFN-β Fibroblasts, pDCs Many Inhibition of viral replication Increased HLA class 1 expression IFN-γ Leucocytes Many Inhibition of viral replication Increased HLA class 1 expression Macrophage activation T-cell proliferation B-cell class switching MIP-1α (CCL3) Macrophages Monocytes, T cells Chemotaxis MIP-1β (CCL4) Lymphocytes Monocytes, T cells Chemotaxis TNFα Macrophages Macrophages Cytokine production including IL-1 NK, lymphocytes Tumour killing TGFβ Monocytes, T lymphocytes Monocytes, T cells

Cell differentiation and proliferation GM-CSF. granulocyte macrophage colony stimulating factor; IFN, interferon; IL, interleukin; TGF, tissue growth factor.

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Revision #1
Created 2026-01-22 16:44:21 UTC by Omar Ayman
Updated 2026-01-22 16:44:21 UTC by Omar Ayman