Arch Immunol Ther Exp, 2005, 53, 245–253
PL ISSN 0004-069X

WWW.AITE–ONLINE.ORG
Review

Received: 2004.06.23
Accepted: 2004.12.17
Published: 2005.06.15

Innate immunity: cells, receptors, and signaling pathways

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Source of support: Ministry of Science and Informatics, grant no. 6P05A 038 20.

Summary

Essential differences between the innate and acquired branches of immunity are described. These differences concern the detection system (receptors and pathogen structures) and the cells engaged in both systems as well as the effectory mechanisms. In contrast to those of the acquired system, receptors of the innate system, which developed during evolution, recognize unchanged structures on large groups of pathogens (e.g. lipopolysaccharide in Gram-negative bacteria). Two lineages, natural killer (NK) and dendritic cells (DCs), play important roles in the innate system. Phenotypic and functional differentiation is observed among NKs and DCs, so each of their sublineages plays a different role in the innate system. Every lineage of cells of the innate immune system express different stimulatory and sometimes also inhibitory receptors on their surfaces (e.g. NK cells). Among the stimulatory are Toll-like receptors (TLRs), mannose and scavenger receptors, and the stimulatory receptors of NK cells. All TLRs show similarity in structure and in the kind of molecules involved in intracellular signaling. The immune reactions of the innate system involve cytokine-dependent resistance of cells against infection with pathogen, production of cytokines (tumor necrosis factor, interferons, interleukins, chemokines) and MHC-independent killing. Although these reactions protect the host from invasion by microorganisms, they can also be responsible for significant tissue damage or may stimulate the development of autoimmunity. Therefore innate immunity must be under rigorous control. The possible regulatory mechanisms of innate immunity are discussed.

Key words: **innate immunity • receptors • intracellular signaling • immune reactions • regulation**

Full-text PDF: http://www.aite-online/pdf/vol_53/no_3/7448.pdf

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CHARACTERISTICS OF INNATE IMMUNITY

Innate immunity is one of the branches of a host's defense which protects the organism from infection by a pathogen. Innate immunity is activated very quickly after infection in the organism and precedes the development of acquired immunity. Charles Janeway, professor of immunobiology of the Yale University School of Medicine, who died on April 2003, was called "the father of innate immunity". He was the first to predict that recognition pattern receptors mediate the ability to recognize invasion by microorganisms. This thesis was presented during the Cold Spring Harbor Symposium in 1989[34]. The first cytokine, interferon (IFN), discovered by Isaacs and Lindenmann[33] in 1957, contributed to the development of knowledge on innate immunity. Their discovery initiated the discovery of other cytokines. The two branches of immunity, the innate and the acquired, are quite different in many respects, such as the systems of recognition, the cells involved, and the mechanisms of their action. The differences are presented in Table 1. Innate immunity is first of all an ancient system, present in most organisms. Receptors of the innate immune system were developed during the evolutionary process. The presence of similar structures in plants, invertebrates, and in vertebrates, including mice and humans, confirmed this idea. In contrast, the receptors of the acquired system developed only in vertebrates as a result of the rearrangement of genes. There are also differences in the pathogen structures recognized by both systems. The receptors of the innate immune system recognize conserved structures present in a large group of pathogens, for example lipopolysaccharide (LPS) in all Gram-negative bacteria, while the receptors of the acquired system recognize single epitopes expressed on a single pathogen. The cells engaged in both systems are also different. The innate system includes natural killers (NKs), dendritic cells (DCs), macrophages, γ/δT lymphocytes, neutrophils, and B-1 cells. In the acquired system, antigen-presenting cells (APCs) – including DCs and macrophages – $TCD4^+$, $TCD8^+$, and B lymphocytes are engaged. The effectory reactions of the innate system are nonspecific. They are connected with the cytokine-dependent antiviral, antibacterial states of cells, with pathogen phagocytosis, and with the production of cytokines, especially IFNs, tumor necrosis factors (TNFs), interleukins (ILs), and chemokines. It involves the killing of infected or transformed cells that is dependent on NK cells, macrophages, DCs, and the complement system but independent of MHC.

IMPORTANCE OF NK AND DCS IN THE INNATE SYSTEM

DCs, which are, together with NK cells, considered as playing a role in the development of innate immunity, should be specially considered[19, 60]. DCs, together with macrophages, and the cytokines released by them link the innate and acquired immune systems[2, 15, 45, 50, 58, 68]. In addition, functional diversity is observed in both DC and NK cells, so different subpopulations might play different roles in innate immunity[14, 19, 24, 46]. Myeloid-origin DCs, called CD1 or APC type I, with the phenotype CD11c, CD1c, are responsible for antigen ingestion, activation of T lymphocytes, and the stimulation of the mixed lymphocyte reaction (MLR). The other, the plasmocytoid subpopulation (PDC), also called DC2, APC2, or natural IFN-producing cells, with the phenotype $CD123^+$, BDCA2, BDCA4, produces an immense amount of IFN type 1, 1000 times more than other cells. PDCs modulate antigen presentation, possibly by the IFN effect[6].

The natural killers are believed to limit viremia and tumor burden by killing infected or transformed cells and by producing cytokines, especially IFN-γ[46, 60]. It would be interesting to know if these two functions

Table 1. Differences between innate and acquired immunity

Differences concern	Innate immunity	Acquired immunity
Detection system:		
receptors	▪ acquired during evolution	▪ acquired during rearrangement of genes
pathogen structures	▪ PAMPs; ▪ unchanged structures; ▪ present on large groups of pathogens	▪ particular domains present on one pathogen
Effectory functions	▪ non-specific cytokine-dependent immunity of cells, against viruses, bacteria, and tumors; ▪ cytotoxicity of NK cells, macrophages, DCs and complement; ▪ production of cytokines (IFNs, TNFs) lymphokines, chemokines; ▪ phagocytosis, oxygen burst; ▪ production of natural IgM antibodies with unknown specificity	▪ production of specific antibodies; ▪ cytotoxicity dependent on MHC; ▪ cytotoxicity dependent on complement and antibodies; ▪ production of cytokines
Cells engaged	▪ macrophages,DCs, NK, γδT cells, B-1α, neutrophils	▪ APC, B lymphocytes, $TCD4^+$, $TCD8^+$ lymphocytes

are connected with all NK cells or with special NK cell populations. According to Deniz et al.[21], a freshly isolated NK1 subset produced IFN-γ, but hardly any IL-4, IL-5, and IL-13. In contrast, an IFN-γ-non-secreting NK2 subset produced IL-4, IL-5, and IL-13. They found that both subsets showed similar cytotoxicity to K562 cells. Ferlazzo and Munz[24] reviewed results obtained by different authors. They showed differences between two other subpopulations of NK cells: $CD56^{dim}/CD16^{+}$ and $CD56^{bright}/CD16^{-}$. These subpopulations differed in body distribution, killing ability, receptor expression, and also in intensity of cytokine production, but not in the profile of the cytokines produced. Higher production of both types of cytokines was observed in $CD56^{bright}$ NK cells. Characteristics of these two subsets are shown in Table 2. According to these authors, cytotoxicity seems to be connected with only one subpopulation, i.e. $CD56^{dim}$ cells. The function and localization of both subsets, $CD56^{bright}$ and $CD56^{dim}$, is different. Most whole peripheral blood NK cells (95%) are composed of $CD56^{dim}$ cells. Most $CD56^{bright}$ cells (75%) are situated in the lymph nodes. NK and dendritic cell contact results in NK cell activation and DC maturation. According to Ferlazzo and Munz[24], the possible sites of such cell contact are inflamed tissues and secondary lymphoid organs, as presented in Fig. 1. Upon infection, NK cells are recruited from peripheral blood to the inflamed tissues. Cytolytic perforin-containing $CD56^{dim}$ NK cells, present in peripheral blood, could interact with DCs before their maturation and migrate to the secondary lymphoid tissues. In the secondary lymphoid tissues, e.g. lymph nodes, DCs can interact with immunomodulatory $CD56^{bright}$ NK cells, where the maturation process of DCs takes place.

Table 2. Characteristics of subsets of NK cells according to Ferlazzo and Munz[24]

NK cell subpopulations	$CD56^{bright}$	$CD56^{dim}$
Perforin	–	+
CCR7	+	–
CD62L	+	–
Inhibitory receptors		
KIR2DL1	–	+/–
KIR2DL2/3	–	+/–
KIR3DL1	–	+/–
KIR3DL2	–	+/–
P75/AIRM1	+	+
NKG2A	+	+/–
Activating receptors		
CD16	–	+
NKp30	+	+
NKp46	+	+
NKG2D	+	+
2B4	+	+
NTBA	+	+

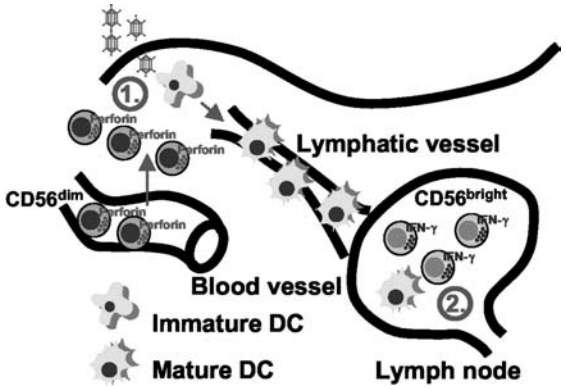

Figure 1. Inflamed tissues and secondary lymphoid organs are possible sites of DC/NK interaction. The figure was recopied after the kind agreement of authors[24]. Explanation: 1, 2 – two possible sites of DC/NK interaction.

RECEPTORS OF THE INNATE SYSTEM AND INTRACELLULAR SIGNALING

Recently, considerable progress has been observed in the knowledge of receptors of the innate immune system. Several types of innate immunity receptors have been identified and are presented in Table 3. The most important receptors belong to the family known as Toll-like receptors (TLRs). The *toll* gene was first discovered in the early 1980s by the German researchers Nusslein-Volhard and Wieschaus in the genome of *Drosophila melanogaster.* This gene was responsible for dorsal-ventral development of the fly[4]. The gene was named in German "toll", which means "crazy", or "cool". Almost 10 years later, this gene was found to be responsible for antifungal resistance of the *Drosophila*[42]. Similar genes and gene products were recognized in other invertebrates, i.e. *Coenorhabdis elegant* and *Anopheles gambiae*[10, 20, 56], and in plants[32, 36] and mammals. It is interesting that the product of the gene *N* of the plant was found responsible for tobacco mosaic virus resistance. The gene *N* is similar, if not identical, to *toll*[67]. The products of genes similar to *toll* were named Toll-like-receptors. Similar structures were found in mice and humans. The intracellular domain of the IL-1 receptor was found to be identical to that of TLRs. TLRs are now considered the main receptors recognizing pathogen-associated molecular patterns (PAMPs). Medzhitov et al.[48] mentioned the cloning of the first TLR-4. Ten TLRs are now recognized in humans and they have been cloned[3], and their structures, ligands, and the pathways of intracellular signaling are known. All the receptors have domain structures with leucine repetitions, and all have the same intracellular domains and similar pathways of intracellular signaling[38]. The signaling pathway presented in Fig. 2 includes the following molecules: adaptor molecule,

Table 3. Receptors of innate immunity

Type of receptor	Expressed on cells	Ligands	Function	References
Toll-like receptors	monocytes, macrophages, DCs, epithelial cells, mast cells, neutrophils	lipoproteins, peptidoglicans, zymosan, LPS, flagellin, CpG DNA, viral dsRNA, viral envelope structure	antibacterial, antiviral, antitumor	3, 17, 20, 30, 31, 38, 39, 65, 66
Mannose receptors	macrophages, DCs, hepatic endothelial cells, kidney mesangial, tracheal smooth muscle, retinal pigment epithelial cells	carbohydrates present on the envelope structures of viruses containing DNA and RNA, cell walls of microorganisms chondroitin-4 sulfate, pituitary hormones	phagocytosis, IFN-α production, modification of acquired immunity, clearance of apoptotic cells	5, 7, 16, 26, 40, 44, 49, 57, 64
Scavenger receptors	macrophages, DCs, some endothelial cells, smooth muscle cells	LTA, lipid A of LPS, LDL, CpG DNA	uptake and clearance effete components, phagocytosis of bacteria	9, 53
NK activating receptors (CD16, NKG2D, NKp30, NKp46, 2B4, NTBA)	NK cells, macrophages	not identified	antitumor and antiviral activity, killing of tumor and virus--infected cells	1, 12, 13, 18, 22, 24, 25, 61

which is myeloid differentiation factor 88 (MyD88), IL-1 receptor-associated kinase (IRAK), TNF receptor-associated factor (TRAF)6, mitogen-activated protein (MAP) kinases, and nuclear factor (NF)-κB. Further study, however, revealed that the signaling pathway may sometimes not include all the same elements. Skerrett et al.[62] found that that MyD88 is essential for pulmonary host defense against *Pseudomonas,* but not against *Staphylococcus*. There were also doubts about the participation of MyD88 in the antiviral signaling pathway.

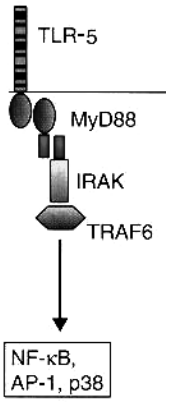

Figure 2. Schematic of mammalian TLR signaling pathway.

Ligands for different TLRs are presented in Table 4. Some pathogen structures are recognized by a homodimer of one receptor, some by a heterodimer consisting of two different TLRs. TLRs were at first considered receptors recognizing only bacteria; later it was found that TLRs could recognize viruses and also play a role in anti-tumor immunity[30, 31, 38, 54, 65, 66]. Four TLRs are engaged in antiviral immunity: 3, 4, 7, and 9. Usually, antiviral immunity is suggested from IFN production. For example, the plasmocytoid DCs which produce large amounts IFN-α express two or only one TLR receptor: TLR-7 and TLR-9 or only TLR-9[39]. The cells produce IFN type 1 after infection with virus, induction with viral double-stranded (ds)RNA, or with synthetic poly I:C. At first, TLRs were known as receptors recognizing only the exogenous PAMP structures of pathogens. Activation of TLRs results in the activation of NF-κB by dissocia-

Table 4. Ligands of Toll-like receptors (TLRs)

TLRs	Ligands
TLR-2	peptidoglycan, lipopeptides, products of Gram--positive bacteria, *Saccharomyces cerevisiae*, zymosan, *L. interrogans* and *P. gingivalis,* LPS, lipoarabinomannan and phosphatidyloinositol dimannoside *M. tuerculosis*
TLR-3	viral replicative form dsRNA, synthetic dsRNA-ply I:C
TLR-4	LPS of Gram-negative bacteria, taxol, HSP 60, fibronectin, F protein of respiratory syncytial virus, envelope structures of different viruses
TLR-5	bacterial flagellin
TLR-7	chemical compounds with antiviral (imidazoquinolines) and anticancer (imiquimod, R-848) activity
TLR-9	bacterial DNA, CpG DNA, structures of HSV-1 virus
Heterodimer TLR:	
TLR-1/TLR-2	bacterial lipopeptide
TLR-6/TLR-2	mycoplasmal lipopeptide
TLR-?/TLR-2	peptidoglican

tion and phosphorylation of an inhibitor, IκB, and its subsequent degradation. Then, released from its inhibitor, NF-κB moves from the cytoplasmic region to the nucleus, where it binds to the promoters of genes of several cytokines, chemokines, and adhesion molecules and activates the production of all the molecules. The activation of cytokine and chemokine production by NF-κB was thought to participate in antiviral immunity; however, there was no clear view of the pathway of activation leading to the production of IFN-α/β. It was earlier shown that the IFN-regulating factors IRF-3 and IRF-7 are engaged in massive IFN type 1 production. However, the receptors and the pathway that leads to IFN production were at most only partially known. At present we only know that the TLRs and the mannose receptors (MRs) are engaged in these processes. It appeared interesting to see if the intracellular signaling is similar to that of other pathogens. When mice with a knocked-out gene for the adaptor protein MyD88 were obtained and the production of IFN was compared with that of control mice, it was obvious that not MyD88, but another adaptor protein was engaged in the pathway. The first adaptor molecule proposed instead of MyD88 was TIRAP. However, the mice with the gene for this molecule knocked out also produced IFN. In the end, Sato et al.[59] found that the TRIF molecule is an adaptor for IFN production. The adaptor molecule leads to the activation of both transcription factors, NF-κB and IRF-3. The scheme of the pathways leading to IFN-β production was elaborated by Pitha[54]. The unexpected similarities in the cellular pathway responses to the bacterial product LPS and viral dsRNA are amazing. Viral dsRNA reacts with TLR-3. Association of TRIF with the non-canonic kinase TBK1 results in the formation of a complex. The complex also contains IRF-3. Phosphorylated IRF-3 is translocated to the nucleus and stimulates the expression of IFN type 1 and chemokine genes. A similar pathway, based on the activation not of TLR-3, but of TLR-4, also led to IFN-β production by LPS stimulation. In contrast, Krug et al.[39] recently demonstrated that infection of myeloid DCs with herpes simplex virus (HSV) induces IFN type 1 by activating TLR-9/MyD88. This means that the signaling pathway for IFN-α/β is not definitely clarified. The other problem was if the activation of NF-κB is able to establish an antiviral state independently of IFN-α/β. Bose et al.[11] found that it is in fact possible. Moreover, they found that TNF-α and IL-1β elicited an antiviral response which was NF-κB-dependent.

The next group of receptors of the innate immune system which were found are MRs, which belong to the lectin family. They are present on murine and human macrophages, DCs, and also on murine endothelial cells in liver. They are absent from freshly isolated blood monocytes, which are able to express them after 3 or more days of culture *in vitro*[37]. Milone and Fitzgerald-Bocarsly[49] showed that antibodies against MR, as well as monosaccharides (i.e. N acetyl glucosamine) and polysaccharide mannan, could block MR and inhibit IFN-α synthesis by DCs stimulated with enveloped viruses (HSV-1, HIV). As the mannose receptor was the first structure found to play a role in antiviral innate immunity by producing IFN, it was interesting for us to see if the receptor is important in the cytokine-dependent antiviral immunity detected by the vesicular stomatitis virus infection of leukocytes. We found that blockade of MRs with monosaccharides in murine resident peritoneal cells resulted in a reduction in the immunity; however, the MR blockade on leukocytes freshly isolated from human blood did not affect innate immunity (our unpublished data). The obtained results were understandable, as fresh human monocytes do not express MR. Other receptors, e.g. TLRs or receptors present on NK cells, might participate in maintaining the immunity in the human leukocytes.

Another group, known as scavenger receptors (SRs), present on myeloid DCs, macrophages, and endothelial cells, are also considered receptors of the innate immune system[53]. SRs, similarly to Toll, are present in invertebrates (*Drosophila*) and vertebrates (humans and mice). They play important roles in the uptake and clearance of effete components. They bind and internalize microorganisms such as Gram-positive and -negative bacteria. Till now there has been no information regarding their engagement in antiviral innate immunity. Some SR receptors, e.g. SRCLI and SRCLII, are present in human tissues: placenta, lungs, and also on smooth muscle cells in artheriosclerotic plaque in blood vessels. Most scavenger receptors have a collagenous domain responsible for binding to bacterial structures, an α-helical structure, and a cysteine-rich domain. The tail in the cytoplasmic domain is supposed to interact with PKC kinase. Mice with knocked-out genes for SR are more sensitive to bacterial infection. Lipoteichoic acid (LTA), lipid A, and polyanionic ligands such as LDL and CpG DNA are known as ligands for SRs.

Apart from receptors on macrophages, monocytes, DCs, and neutrophils, there are also receptors on NK cells which stimulate the innate antiviral and antitumor immunity. Table. 3 presents the stimulatory and inhibitory receptors present on both NK subpopulations. Both the stimulatory and inhibitory receptors belong to the Ig-like and lectin-like family[27]. They differ especially in the structure of the transmembrane

domain. The inhibitory receptors contain a tyrosine-based inhibitory motif (ITIM), while the stimulatory receptors contain a tyrosine-based activatory motif (ITAM). Inhibitory receptors examine cell on the basis HLA content. Among the stimulatory receptors the most important seem to be NKG2D, NKp46, NKp30 in human NKs, and Ly49 in murine NKs. NK function is regulated by the interaction of the inhibitory and stimulatory receptors and their ligands. However, little is known about the ligands.

ENDOGENOUS MOLECULES COULD CONTRIBUTE TO TLR ACTIVATION

There was accumulating evidence that TLRs, apart from recognizing of exogenous PAMPs, are also able to detect endogenous molecules. During the Immunology Congress held in Stockholm in 2000, Matzinger[47] presented the "Danger Model", according to which TLR receptors could recognize not only non-self pathogen structures, but also altered self structures. Johnson et al.[35] published a review concerning the activation of mammalian TLRs by endogenous agonists such as macromolecular degradation products (heparan sulfate, hyaluronan, fibronectin extra domain A), necrotic cell contents (chromatin, heat-shock proteins), and inflammatory gene products. These endogenous, as well as exogenous, PAMPs may activate TLRs. The possible activation of innate immunity by endogenous agonists was very useful in explaining our results. During our studies on the innate immunity of embryonal tissues of human placenta, amniotic membranes, endothelium of the umbilical cord vein, and also human and murine leukocytes, we found that contact of the cells or tissues with viruses is not necessary to induce the innate antiviral immunity[23, 51, 52, 69, 70]. The immunity is present in embryonal tissues as well as in freshly isolated leukocytes. Infection with viruses only indicates the degree of the immunity. When the cells or tissues were preincubated some days *in vitro* before infection, the immunity was gradually reduced. The results indicated that during incubation a natural agent(s) present in freshly isolated cells e*x vivo* was lost *in vitro*. Contact of the virus with leukocytes or embryonal tissues was, however, necessary for IFN inducton. This innate antiviral immunity, which is present in human embryonal tissues and in leukocytes, is dependent on endogenous cytokines, which are produced spontaneously by cells in minimal amounts. The minimal amounts of the different cytokines are sufficient to maintain the innate immunity of the cells. When the cytokines were eliminated with specific antibodies against IFN-α, IFN-β, IFN-γ, and TNF-α, the immunity was reduced[51, 52]. Moreover, there was no correlation between the state of innate immunity and the titer of IFN and TNF produced by the cells. As innate immunity includes not only the cytokine-dependent antiviral immunity, but also the killing of infected cells independent of MHC and the production of different cytokines and chemokines, the contact of pathogen with cells may be necessary to develop these reactions of innate immunity.

POSSIBLE REGULATORY MECHANISMS OF THE INNATE SYSTEM

Different receptors play roles in the stimulation of innate immunity by producing different cytokines by cells of the immune system, stimulating the killing of infected or transformed cells, or stimulating phagocytosis or apoptosis[27]. Although inflammatory and immune reactions protect the host from invasion by microorganisms and eliminate debris at the site of tissue injury, they can also be responsible for significant tissue damage or may even stimulate the development of autoimmunity. Therefore innate immunity must be under strict control. The possible regulatory mechanisms might involve the regulation of different levels of the development of innate immunity:

- on the level of contact of different cells,
- by soluble receptors,
- by restricting the level of ligands for the TNFR family,
- on the level of intracellular cytokine signaling by molecules known as SOCS,
- by inhibitory receptors present on the same cell,
- by Tyro-3 family receptors,
- by adenosine release.

One regulatory mechanism is observed on the level of cell contact and is thought to regulate both innate and adoptive immunity. Zitvogel[71] reviewed the problem of the regulation of innate as well as acquired immunity resulting from the contact and cross-talk of dendritic and NK cell populations. This cross-talk between the NK and DC cells finally results in the maturation of DCs and activation of NK cells. The activation process includes the production of IFN-γ by the NK cells and stimulation of their proliferation. The kinetics of NK proliferation decides the fate of immature DCs. The regulation process is presented in Fig. 3. If there are many more activated NK cells than immature DCs, the latter are killed and, consequently, innate and acquired immunity are reduced. If the number of immature DCs is higher than that of activated NK cells, maturation of the DCs takes place and acquired immunity is promoted. Perhaps a similar type of regulation occurs between the cells of another lineages.

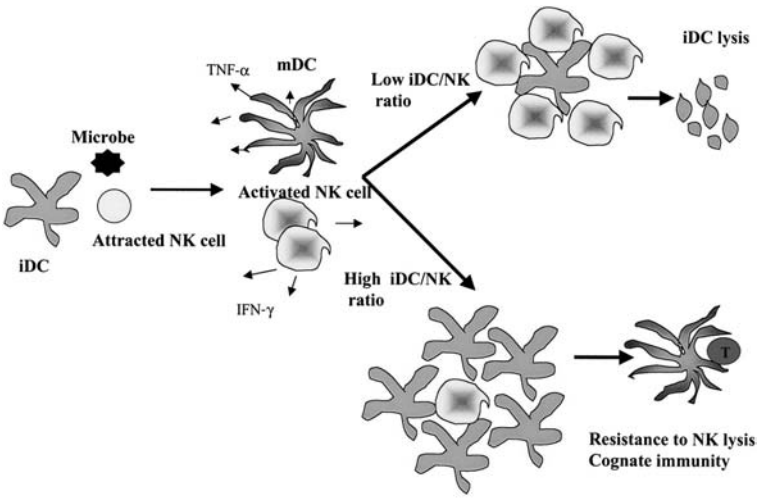

Figure 3. Bidirectional cross-talk between DCs and NK cells. After encounter with a pathogen, immature DCs (iDC) secrete TNF-α with or without IL-12, undergo maturation, and induce resting NK cell activation. The interaction between iDCs and activated NK cells results in either DC maturation or cell death. The mechanisms that determine the outcome between death and maturation depend on a dynamics between DCs and NK cell density and on the DC maturation stage. At high iDC/NK cell ratio, DCs become activated and resistant to NK cell lysis, enabling amplification of NK cell activation and elicitation of cognate immune responses. When NK cells are overwhelming, iDC-mediated NK cell lysis turns off local immune responses. The figure was recopied after kind permission of author[71].

Another example of a regulatory mechanism mentioned above might concern the presence of both inhibitory and stimulatory receptors on NK cells, which prevents over-stimulation of the cells. Another possible control might be connected with the presence of Tyro-3 family receptors. The receptors are present on immune cells (monocytes and macrophages) and on cells of the reproductive and nervous systems. Lemke and Lu[43] presented an interesting review article on a regulatory activity of the three receptors with protein tyrosine kinase function as central regulators of the activation state of macrophages. In the absence of these receptors, macrophages become constitutively activated. This, in turn, results in a hyperactivated immune system and the development of autoimmunity in mice.

Cytokines of the TNF family are very important mediators of innate immunity. As the receptors for most cytokines are expressed constitutively on cells, activation regulation involves the precise control of ligand production[8].

Cytokines are the central mediators of the innate system of immunity. Fujimoto and Naka[28] reviewed suppressor of cytokine signaling (SOCS) family of molecules which regulate innate immunity on the level of cytokine signaling. SOCS molecules were discovered in 1997 and considerable progress in knowledge about them is observed. The molecules play essential roles in the negative regulation of a wide range of cytokines, such as IFNs, ILs, and TNFs. The authors suggest that SOCS might be involved in the regulation of TLR ligands in innate immunity.

Another possibility of control may be connected with soluble forms of receptors. The presence of the soluble forms of TLR-2 in human plasma and breast milk was first demonstrated by LeBouder et al.[41]. They showed that the sTLR2 released constitutively from monocytes is able to modulate cell activation. Its level increased upon cell activation. If other soluble forms of TLRs are discovered, sTLRs will create a powerful mechanism of regulating cell activation.

The role of adenosine as an endogenous regulator of innate immunity was recently reviewed by Hasko and Cronstein[29]. This purine nucleoside limits damage from exuberant immune response. It is constitutively released to the extracellular space in small amounts, but in metabolically stressful conditions, e.g. at injured and inflamed sites, it is produced in higher concentration. The nucleoside interacts with specific G protein-coupled receptors on inflammatory and immune cells to regulate their function. Adenosine--acting A2A receptors inhibited stimulated neutrophils, adhesion to and killing of endothelial and other cells, bactericidal activity, apoptosis, expression and shedding of adhesion molecules, secretion of cytokines and growth factors, as well as the synthesis of leukotriene B4. It has been documented that the stimulation of adenosine receptor decreases the TLR-induced release of cytokines. Adenosine suppression of exuberant innate immunity might perhaps be the most important control mechanism. The controlling effects of other mechanisms, for example that concerned with the regulation process among NF-κB members, could also be considered[63].

In view of inherited disorders in NF-κB-mediated immunity, first discovered by Puel et al.[55], a precise study of receptors, their signaling, and their regulatory system seems very important. Recently, in volume 198 of the Immunological Review, wholly devoted to the innate immunity of invertebrates, this type of immunity was called the "primitive immune system". In light of current knowledge, the system does not appear at all primitive, just insufficiently explored.

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