Review

Distinct Pattern of Human Vδ1 γδ T Cells Recognizing MICA

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γδ T cells represent one unique recognition pattern, the limited recognition, which distinguishes from the specific recognition for αβ T cells and pattern recognition for macrophages. Vδ1 γδ T cell is the major subset of human γδ T cells, which predominates in mucosal tissue including the intestinal epithelia. Presently, a few antigens that human Vδ1TCR can recognize have been identified. Among them, MHC class I chain-related molecules A (MICA) have been studied most intensively. Besides Vδ1TCR, MICA is also the ligand of NKG2D, a C-type lectin-like activating immunoreceptor. In human, only Vδ1 cells can simultaneously express both types of receptors of MICA while NK cells, αβ T cells and other subsets of γδ T cells likewise express NKG2D. Although the precise mechanisms are still enigmatic, this distinct pattern of Vδ1 cells recognizing MICA predicts unique biological significance of Vδ1 cells in immune defense. Recent years, some progresses have been made in this issue. In this review we summarize the related reports and put forward some novel views based on our group's studies. *Cellular & Molecular Immunology*. 2005;2(4):253-258.

Key Words: Vδ1TCR, MICA, NKG2D, γδ T cell

Introduction

This year, studies in molecule mechanisms of γδ T cells recognizing their ligands made some symbolistic breakthrough (1-3). However, as the first defense line of the human immune system, interacting pattern of Vδ1 γδ T cells preferentially localized in mucosal tissues such as intestine and spleen with their ligands – MHC class I chain-related molecules A (MICA) is still mysterious. So far as we have known, their interactions have the following three traits: i. Both types of receptors at Vδ1 cells surface, Vδ1TCR and NKG2D, can simultaneously recognize and bind to MICA; ii. There are close associations between the tissue distribution of Vδ1 cells and physiologically expression of MICA molecules; iii. MICA molecules affect Vδ1 cells' lineage development. Obviously, more definite knowledge about this problem is quite important to the development of basic immunology principle and the illustration of the crucial value of γδ T cells in innate and adaptive immunity. That also helps to develop new clinical diagnosis and therapy strategies based on γδ T cells or MICA.

Molecule mechanisms of Vδ1 cells binding to MICA

As the most gene-dense and extraordinary polymorphism region of the human genome, major histocompatibility complexes (MHC) and their protein products have been playing a top essential role in the endless battles of human immune system against pathogenic trespasser. MICA gene also locates within this region and has 30% homology with classical MHC I (4, 5), and both protein products resemble in chemical structure. However, unlike their counterparts, MICA molecules do not bind to β_2 microglobulin (β_2m) and cannot bind to and present antigen peptides (6, 7). In addition, many reports proved the expressing characteristic of MICA-"stress", including transformation (6, 8, 9), virus infection (9), allograft (10), heat (6), etc. So far, the concept of "stress" is still very obscure. Recently, Gasser et al.'s report maybe attributes the "stress" to DNA damage (11). Under physiological condition, only endothelial cells and fibroblasts express MICA (12). MICA can be recognized and bound by NK cells, αβ T cells and γδ T cells through the killer receptor – NKG2D (13). Specially, only Vδ1 subset of γδ T cells can bind to MICA through TCR (8).

At present, the crystal structures of MICA and NKG2D monomer as well as their complex were analyzed, which can

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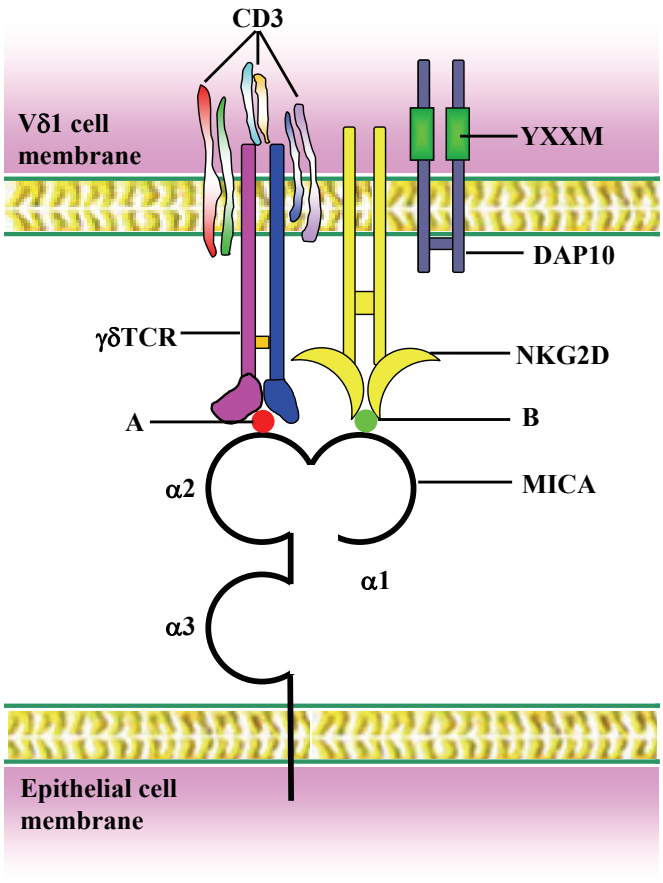

Figure 1. Human Vδ1TCR and NKG2D simultaneously bind to MICA and transduce activation signal through different pathways. "A" and "B" respectively represents imaginable region of Vδ1TCR and NKG2D binding to MICA.

make people better understand their function domains and reaction mechanisms. MICA molecule, comprising 383 amino acid residues, with an apparent molecular mass of 43 kD, includes three external domains (α1-3), a transmembrane domain and a cytoplasmic domain (4, 14). The extracellular part of MICA consists of two structural domains: the α1α2-platform domain and the C-type immunoglobulin-like α3 domain. NKG2D receptor belongs to C-type lectin groups. However, unlike its counterparts – NKG2A, NKG2C, NKG2E, which are assembled as heterodimers with CD94 and recognize a non-classical MHC class I molecule known as HLA-E (in humans) or Qa1 (in mice) (15), NKG2D is present as a homodimer and recognizes MICA, MICB and UL binding proteins (ULBPs) (16). Signals triggered by the human NKG2D receptor are transmitted through the DAP10 dimer, which seems crucial for activation patterns of different effector cells (17). The cocrystallization of human MICA-NKG2D reveals a NKG2D homodimer bound to a MICA monomer in an interaction that is analogous to that seen in T cell receptor – MHC class I protein complex. Similar surfaces on each NKG2D monomer interact with different surfaces on either α1 or α2 domain of MICA. The binding interactions are large in area and highly complementary. The central section of the α2-domain helix, disordered in the structure of MICA alone, is ordered in the complex and forms part of the NKG2D interface (18).

Vδ1TCR is another known receptor that has the ability to recognize MICA (8) (Figure 1). In humans, there are two major subsets of γδ T cells – Vγ9Vδ2 T cells and Vδ1 T cells, respectively expressing distinct TCRs and recognizing different types of antigens. The former recognize nonpeptide phosphate, amine, and aminobisphosphonate compounds (1, 19). However, due to their extremely limited diversity, Vδ1 T cells are proposed to respond not to a diversity of microbial antigens, but to unique "stress antigens" that are markers of cell infection or transformation. Such being the case, all known antigens of Vδ1 T cells, including MICA, accord with this characteristic.

The molecule basis of "limited" diversity recognition is gradually being illustrated. Earlier functional studies suggested that recognition pattern of γδTCRs may be more similar to that of antibodies than that of αβTCRs (20, 21). Indeed there was some evidence from molecule basis supporting the viewpoint, such as framework structure of Vδ more closely resembles that of VH than that of Vα, Vβ or VL (22) and the CDR3 length distribution of TCRδ chains is similar to that of immunoglobulin heavy chains (23). However, surging evidence suggests that recognition mechanism of γδTCRs is unique, probably representing a kind of unknown pattern of immune molecule interaction. According to recent works by two groups (2, 3), it could be concreted that the patterns of Vδ1 TCR recognizes MICA as follows: i. δ chain alone can recognize and bind to MICA *in vitro*, which indicates that δ chain plays a more important role in interacting with MICA than γ chain does; ii. Vδ1TCR directly recognizes MICA, neither needs antigen presentation nor has MHC restriction; iii. Vδ1TCR displays the limited diversity recognition. The molecule basis is the exit of "putative binding box" motif within CDR3 region, which derives from germ line-encoding residues; iv. Sequence diversity around these residues origins from VDJ gene junction and modulates TCR ligand-binding affinities; v. Vδ gene fragment that encodes CDR1 and CDR2 correlates mainly with tissue origin (Figure 2).

Activation patterns of Vδ1 cells by MICA

Earlier studies demonstrated that Vδ1 cells can be activated by antigens directly, which do not need MHC molecule presentation (24). Although CD28 expression is variable and γδ T cells seem not comply with the "αβ T cell paradigm of double signal recognition", Hayday predicted that γδ T cell activation should require other stimulating signals besides the signal provided by TCR (25). Upon that, NKG2D becomes one of the most powerful candidates for γδ T cell costimulators. Actually, several research groups shed light on this problem and published some valuable reports. Thomas Spies group suggests: NKG2D-MICA alone cannot activate

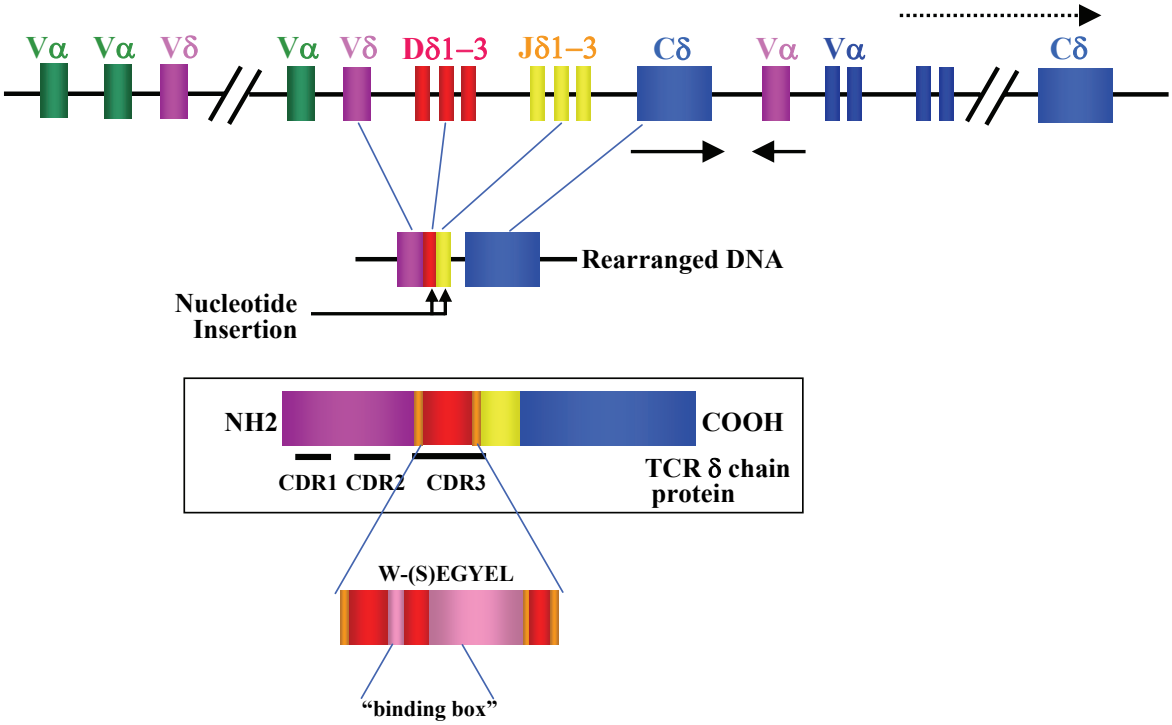

Figure 2. TCRδ gene rearrangement and "putative binding box" motif location.

γδ T cells, but can increase their proliferation and cytotoxicity effects; blocking NKG2D ligation with McAb or sMICA cannot fully inhibit, but can partly impair the differentiation and effector function of γδ T cells (including Vγ9Vδ2 and Vδ1 T cells) (13, 26, 27). That is consistent with our results that immobilized MICA can expand human Vδ1 T cells *in vitro* that display MICA-dependent cytotoxicity to human epithelial carcinomas (28). Strikingly, Rincon-Orozco's study provides distinct evidence that Vγ9Vδ2 T cells may also be directly activated by NKG2D (29).

Whether NKG2D acts as direct stimulator or costimulator remains mysterious to date. Probably it is more reasonable to regard it as a unique stimulating pathway, which is different from direct activation for NK cells or indispensable activation for αβ T cells.

As for Vδ1 cells, although earlier studies indicated that MICA delivers both the TCR-dependent signal and the NKG2D-dependent costimulating signal (27), more details of interaction patterns between Vδ1-MICA and NKG2D-MICA cannot be obtained. Bewilderingly, normal intestinal epithelial cells express MICA, but Vδ1 T cells in this region cannot always be in activation or effection. In fact, Vδ1 T cells are at rest state generally. To explain this contradiction, we propose three hypotheses: i. "Threshold" hypothesis: Vδ1 cells would be tolerant to low-level expression of MICA molecules but would be activated when expression of stress antigens exceeded a threshold; ii. "Anergy" or "memory" hypothesis: during the early development, because encountering MICA, Vδ1 cells became anergy or memory cells, then would be re-activated when infection or transformation occured; iii. "Polarization" hypothesis: the physiological location of MICA within epithelial cells governs whether MICA can contact and activate Vδ1 cells. The intestinal epithelium is composed of a sheet of polarized epithelial cells (30) and the plasma membranes of these cells are separated by tight junctions into apical and basolateral domains with distinct functional characteristics (31). The latter define the prime contact surface with the large number of the intraepithelial T and NK lymphocytes (IELs) shielding the entire gut surface against microbial or tumor invasion attempts (31). The full-length MICA protein is located on the basolateral membrane, whereas the cytoplasmic tail-deleted MICA protein is aberrantly transported to the apical surface (32).

Biological effects of activated Vδ1 cells by MICA

It is unclear whether γδ T cells en masse have a prevalent effector function. Most characteristics of activated γδ T cells resemble those of conventional αβ T cells, including cytolytic effect, release of perforin and granulysin, expression of Fas/FasL, and production of IFN-γ (33, 34). Similarly, the differential productions of IL-2 and IFN-γ, or IL-4, IL-5, IL-6, and IL-10, respectively, define Th1 and Th2 γδ T cells, just as the categories of αβ T cells (35-38). Although γδ T cells are predominantly Th1 (39), they have the intrinsic capacity to produce Th2 cytokines such as IL-4 (36, 40). In addition, a few specific effector functions of γδ T cells have

been described, including the productions of keratinocyte growth factor (KGF) (41), connective tissue growth factor (CTGF) (42) and fibroblast growth factor-9 (FGF-9) (43). Inconceivably, Brandes et al. provided powerful evidence that Vγ9Vδ2 T cells also display principal characteristics of professional antigen-presenting cells such as dendritic cells (44).

Vδ1 T cells, due to their speciality in anatomical distribution, are the "first line of defense" (45). Firstly, Vδ1 cells play important roles in defence against epithelial cancers, especially those localized in the gut, lung and skin (46-48). Besides exhibiting a selective lytic activity against a variety of tumors, Vδ1 T cells can inhibit tumor cell growth by producing and releasing a number of cytokines, including tumor necrosis factor (TNF)-α, and IFN-γ. Secondly, Vδ1 cell population represents an important immune barrier against pathogens which attempt to enter the body through the mucosal surfaces. Nevertheless dissimilarly with αβ T cells, Vδ1 cells do not respond to diverse microbial antigens, but to unique ''stress antigens'' (see above). Thirdly, Vδ1 cells can repair damage mucosal tissue through production of repair cytokines, including KGF, FGF-9, CTGF, etc. Moreover, Vδ1 cells must play a role in inflammatory bowel disease because several reports indicated an accumulation and clonal expansion of γδ T cells in the inflamed mucosa of patients with Crohn's disease (49, 50). Lastly, Vδ1 cells can exert immunoregulatory activity through the release of cytokines and chemokines (51).

MICA regulates development of Vδ1 cells

Probably in all species, γδ T cells are developed earliest among all the T cells (52, 53). TCRγδ gene rearrangements were detected in human at the 8th week of fetal development (53). Although there is no consensus as to the exact developmental stage in which αβ or γδ lineage diverges, γδ T cell and αβ T cell lineages (bearing the pre-TCR) are thought to be derived from common double negative ($CD4^-CD8^-$, DN) precursors (54). Although the mechanism behind this lineage diverge remains undefined, it is undoubted that TCR plays a critical role in both αβ and γδ T cell developments either at or subsequent to the point of lineage commitment. The pre-TCR and the γδTCR are the two TCR isoforms that are expressed on the surface of DN thymocytes when αβ/γδ lineage commitment occurs (55-58). DN precursors, undergoing TCRγ and TCRδ gene rearrangements and expressing mature γδTCRs are capable of differentiating along the γδ lineage pathway (59, 60). This year, Silva-Santos et al. reported that double positive ($CD4^+CD8^+$, DP) cells regulate the differentiation of early thymocyte progenitors and γδ T cells, by a mechanism dependent on the transcription factor RORγt, and the lymphotoxin (LT)β receptor (LTβR) (61).

However, when and where do the Vδ1 T cells diverge, how do they shift into tissues, and what are the effector factors of Vδ1 cell differentiation? The precise answers for all these questions are nil. Recently, through a transgenic mice (Tg) model, unpublished data from Park et al. demonstrated that MICA could positively regulate the development of γδ IELs in the neonatal stage of the T3b-driven MICA Tg mice and in the early phase of bone marrow-chimeric irradiated MICA-Tg/RAG-2-deficient mice (62). Later data further approved that the strength of the TCR signal was critical determinant in the lineage fate decisions. Hayes SM found that increasing the γδTCR single strength favors γδ T cells lineage development, whereas weakening the γδTCR single strength favors αβ T cells development (63). Haks found that in the presence of a ligand, a transgenic γδTCR mediates almost exclusive adoption of the γδ lineage, while in the absence of ligand, the same γδTCR promotes αβ lineage development (64). Besides TCR single strength, there are some other signaling cascades that probably influence lineage commitment, including IL-7 receptor (IL-7R) (65), Notch (66), RORγt (61), etc. In addition, Pennington et al. proposed the view that γδ T cells were positively rather than negatively selected on cognate self antigen and that gut γδ IELs might develop extrathymically (67). According to above data, we can get insight into the prospect of MICA regulating Vδ1 cell development.

Epilogue

The pattern of human Vδ1 cells recognizing MICA is unique. We attempt to unveil the mysteries from three different levels: molecule level, cell level and tissue level. Seemingly, the molecule mechanisms are very well-known because of the illustrations of the cocrystal structure of human NKG2D-MICA (18) and murine TCRγδ-T22 (2). The hypothesis of conformational recognition based on germline encoding recognition can also logically explain the characteristics of γδ T cells recognizing antigens–"limited" recognition.

Regretfully，the immunobiology of human Vδ1 cells cannot be precisely defined yet. The major obstacle is the extreme difficulty to obtain enough purified native human Vδ1 cells, therefore most data about this question origin from mice model. Our group has got ahead in human Vδ1 cells' studies. We successfully expanded human Vδ1 cells *in vitro* by immobilized MICA (28). Based on this, lots of original data were obtained, which are helpful to final illumination of this problem.

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