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Research of CD305 and its Implication in Maternal-Fetal Immune Tolerance

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Abstract

Immune responses are controlled by the opposing actions of activating and inhibitory signals. Inhibitory receptors are expressed to prevent excessive immune responses. Paternal alloantigen coming from trophoblasts could stimulate maternal lymphocytes during pregnancy. The mechanisms of maternal-fetal immune tolerance in the successful pregnancy are remained to be elucidated. CD305 belongs to the inhibitory receptors family, which are involved in controlling the balance of the immune system to prevent improper activation. Upon interaction with their ligands, CD305 could attenuate the signals provided by activating receptors, thereby increasing the threshold for activation. CD305 and its interaction with CD306 plays an important role not only in the differentiation of hemopoietic progenitors, monocyte-derived DCs, neutrophils and megakaryocytes, but also in the activation control of NK, T and B cells in various phases of the immune response. In this review, we summarize recent research progress about CD305 in the differential regulation and immune inhibitory functions in many kinds of leukocytes. Together with our new research results about CD305 in the regulation of decidual immune cells, we further discuss its significance and implication in maternal-fetal immune tolerance.

Keywords: *CD305; CD306; LAIR; Maternal-Fetal Interface; Immune Tolerance*

Introduction

Leukocyte receptor complex (LRC) comprises a large cluster of cell surface receptors including the killer immunoglobulin-like receptors (KIR) and the leukocyte Ig-like receptors (LILRs), osteoclast-associated receptor (OSCAR) and glycoprotein VI (GPVI). These receptors share ancient homology in the structure and function. CD305, as a new member in the LRC, has been reported as 9.1C3 [1-3], P40 [4] and leukocyte-associated Ig-like receptor-1 (LAIR-1) [5] in the past two decades. CD305 was named in the 8th international HLDA conference in 2004 [6], and its 84% homologous molecule which has been reported as LAIR-2, also got the number CD306. As an immunoglobulin superfamily (IgSF) type I TM protein receptor of 287 amino acids, CD305 contains a single extracellular C2-type Ig-like domain with two ITIMs (VTYAQLx24 ITYAAV) in its cytoplasmic tail. Due to its functional and structural characteristics, both in gene and protein, CD305 has been paid more attention recently in the research of differential regulation and immune inhibitory functions.

The location and Ligands of CD305

The encoded gene of CD305, just like other two important immunoglobulin superfamily receptors: KIRs and LILRs, is also located in the LRC in human chromosome 19q13.4. Gene blast analysis shows that an inverse duplication event has taken place as a late evolutionary event, centered about the CD305 genes in the LRC [7]. Therefore, CD305 is genetically and functionally related to many of the immunoreceptors present in the LRC. CD305 is expressed on CD34+ hemopoietic progenitors [2,8] and almost all immune cells, including NK cells, B and T lymphocytes, thymocytes, monocytes [4,5,9], DCs [10], eosinophils [8], basophils and mast cells [11].

CD305 binds both transmembrane and extracellular matrix collagens [12, 13]. As the functional ligands, collagens can inhibit the activation of primary immune cells and cell lines *in vitro* [12, 14]. Although some transmembrane receptors, such as integrins, discoid in

domain receptors (DDR) and Glycoprotein VI (GPVI) have been confirmed to recognize the typical collagen triple helix and have the potential to signal [15], both human and mouse CD305 bind collagen specifically whereas other cell surface proteins gave no binding, except for the related inhibitory leukocyte immunoglobulin-like receptor subfamily B member 4 (Lilrb4, CD85K, Gp49B) [16].

Immune cells present in the bloodstream do not encounter matrix collagens under physiologic conditions. But their exposure to the collagen-rich sub endothelium will result in abrogation or inhibition of immune cell function through the inhibitory signal transduced by CD305 into the cell [12]. Its high affinity for collagen also implicates a possible role for CD305 as an adhesion molecule for immune cells. CD305 could inhibit GPVI activation in cell lines that both express these receptors [17]. The inhibitory and activating collagen receptors CD305 and GPVI are simultaneously expressed on a subset of megakaryoblasts and promegakaryocytes, which might reveal a role for CD305 in the regulation of collagen-activation through GPVI and in the differentiation of megakaryoblasts [18].

The interaction of CD305 with collagen has been explored by a combination of X-ray crystallography, NMR titrations and mutagenesis. The crystal structure of the collagen-binding domain of CD305 was closely resembles the KIR2DL2, LILRA5 and GPVI D1 domains. The available crystal structures will facilitate the development of compounds targeted at specifically modulating immune responses via the CD305/collagens interaction or thrombosis through GPVI [19]. Moreover, the existence of mRNA coding for CD305 isoform lacking the transmembrane domain [5], suggests that soluble CD305 (sCD305) can block the interaction of the transmembrane receptor with collagens. This will contribute to the exploration of specific means for intervention in collagen-induced signalling in immunological disorder diseases.

The function and signalling pathway of CD305

The differential and immunological activities of leukocytes are controlled by numerous interactions between membrane receptors and their ligands. The differential regulation and immune inhibitory functions of CD305 have been extensively described in many kinds of leukocytes.

The differentiation and proliferation of hemopoietic progenitors could be influenced by collagens in the bone marrow [2,20]. CD305 could inhibit the differentiation of monocyte-derived DCs in the presence of GM-CSF *in vitro* [10] and GM-CSF-dependent proliferation and protein kinase B activation in primary leukaemia cells [21]. Sustained engagement of CD305 also induced apoptosis in leukaemia cell lines [22].

The expression of CD305 is also related to neutrophil differentiation. CD305 is expressed on the immature neutrophils, but very low on the surface of peripheral blood neutrophils [8]. Our recent study shows that CD305 is expressed on the early stage of human primary megakaryocytes and the cross-linking of CD305 could negatively regulates cytokine-mediated differentiation of megakaryocytes derived from cord blood $CD34^+$ cells [23].

CD305 could inhibit the cytotoxic activity of NK cells using specific monoclonal antibodies [4,5,9] and abrogate the cytotoxic activity of T cells induced by CD3 cross-linking or antigen stimulation [5,9,24,25].

CD305 signalling leads to down regulation of calcium mobilization in primary human B cells induced by B cell receptor cross-linking and in U937 cells mediated by FcR-induced degranulation of RBL-2H3 [26-28]. What's more, similar to CD85j (LIR-1, ILT2) and CD152 (CTLA-4), the cross-linking of CD305 could resulted in the down-regulation of IL-10, IL-8, TNF-a release and the inhibition of IgG and IgE production [29].

Therefore, CD305 could act at the end of the immune response, when the factors causing it to have disappeared. However, tumor cells, which have been known to upregulate ECM and TM collagens, could downregulate immune responses through CD305 [30]. These researches suggest that extracellular matrix (ECM) collagens can regulate the activities of immune cells *in vivo*, and set thresholds of activation on immune cells that have migrated into or are resident in tissues. Therefore, it is meaningful to illuminate the immune regulation role of CD305/collagens in the collagens-rich tissues or collagen-producing cells.

Upon receptor aggregation, CD305 operating like a classical ITIM-encoding receptor, ITIMs are phosphorylated by Src kinases, which recruit SHP-1 and SHP-2 but not SHIP. Both ITIMs are required for optimal phosphatase recruitment and full inhibitory function, although mutants with only one functional ITIM are still capable to inhibit cellular responses of the NK-like YT.2C2 cells and basophilic cells [27,31].

Coimmunoprecipitation studies demonstrated that the exclusive phosphotyrosine-containing protein associated with SHP-1 in Jurkat T cells under physiological conditions is CD305, suggesting that it is an important negative regulating pathway in T cells and other immune cells [31,32]. In DT40 cells deficient in SHP-1 and SHP-2, CD305 appears to recruit Csk, which negatively regulates Src kinase activity [33-35]. This interaction required the SH2 domain of Csk and phosphorylation of the N-terminal ITIM of CD305 [33]. Csk has also been shown to be recruited to another inhibitory LRC member, LILRB2, and the non-LRC encoded receptor, signal-regulatory protein (SIRP) [36,37]. These data suggest there are some common signalling pathways among different inhibitory receptors in conditions where PTPs are limiting. Interestingly, Programmed cell death (PCD) elicited via CD305 was not blocked by different caspase inhibitors, at variance with apoptosis induced via CD95/Fas, which was prevented by the caspase-1 and caspase-8 specific inhibitors. As blocking of NF-KB activation has been shown to rescue sensitivity to anti-cancer drugs in solid tumors, CD305 may represent a possible target for pharmacological approaches aimed to potentiate anti-leukemic therapy [22].

In summary, CD305, as an ITIM-bearing receptor, plays an important role not only in the differentiation of hemopoietic progenitors, monocyte-derived DCs, neutrophils and megakaryocytes, but also in the activation control of NK, T and B cells in various phases of the immune response, such as anti-virus response [38]. The extensive function of CD305 and its unique signalling pathway need to be illuminated through more researches.

The application and implication of CD305

CD305 belongs to the immune inhibitory receptors family, which are involved in controlling the balance of the immune system to prevent improper activation or overactivation, which may result in tissue damage or autoimmune diseases. Upon interaction with their ligands, these receptors attenuate the signals provided by activating receptors, thereby increasing the threshold for activation. Therefore, CD305 has great significance in immune tolerance.

Resting and activated NK cells derived from the chronic active Epstein-Barr virus (CAEBV) patient showed a marked and significant loss of CD305 expression. It would be worthwhile for clinicians with cases of CAEBV to assess NK cells for defects in CD305 expression [39]. CD306, a soluble receptor, also binds collagens and could act as a negative regulator of CD305 signalling by masking available collagen-binding sites for CD305 [20,40]. Proteolytically shed sCD305 could conceivably perform a similar function to CD306. sCD305 can be detected in the supernatant of stimulated lymphocytes and in the sera of transplantation and HFRS patients [41]; CD306 is present in the synovial fluid of patients suffering from rheumatoid arthritis (RA) [20,41]. Both sCD305 and CD306 could be detected in the plasma and urine of healthy control subjects and patients with RA. Urinary levels of both proteins were significantly increased in RA patients, and CD306 levels in urine were significantly correlated with markers of inflammation [42].

Recent research in SLE patients with low CD305 expression on B cells has shown that CD305/collagen engagement delivered a lower inhibiting signal on Ig production, which indicates defective CD305 expression and function in SLE B lymphocytes, possible contributing to an altered control of B lymphocytes behaviour [43]. Furthermore, molecules that may contribute to immune dysregulation in SLE include High Mobility Group Box 1 (HMGB1), the first component of the complement system (C1q) and CD305 [44,45].

Although the exact function of sCD05 and CD306 in those patients remains to be investigated, they could be used as a predictor of immune response and related diseases. The clinical implication about the changes of sCD305 and CD306 in urine or serum samples is worthy to be paid more attention.

A global gene expression microarray analysis of surplus chorionic villus sampling (CVS) tissues identified CD306 as down-regulated in the first trimester of pregnancies destined for preeclampsia [46]. In situ hybridization (ISH) and immunohistochemistry (IHC) staining

for CD306 detected specific, highly localized expression at the leading edge of EVT anchoring cell columns in first trimester placentas [47]. The precise restriction of this protein only to the sites of EVT invasion strongly suggests that it functions to regulate this invasion through the binding to the extracellular material into which these trophoblasts invade. The decreased CD306 expression noted in first trimester placentas that ultimately developed preeclampsia further suggests that alterations in CD306 may play an etiologic role in preeclampsia [47]. An inspiring finding was that the CD305 mRNA was high in trophoblast cells, being in the top 25 of all transcripts in both VT and EVT. But there is no surface expression at the protein level on trophoblast cells [48]. Because we have shown that CD305 serves as a negative regulator of megakaryocytopoiesis [23], the hypothesis is that the abnormal translation and expression of CD305 on the invading trophoblasts could result in the inactivation and inhibition of trophoblasts' proliferation and invasion through the binding of collagen in some diseases potentially associated with abnormal EVT invasion, and CD306 could prevent these processes. Activated CD4+T cells were the main producers of CD306 in RA patients [42]; could the dicidual immune cells (DIC) be another source of CD306 or the main source of sCD305?

CD305 is a special inhibitory receptor due to its extensive expression on almost all cells of the immune system and its collagen ligands, which are also extensively expressed in many kinds of tissues. CD306 is a more potent antagonist of CD305 function *in vivo* [42]. The absence of CD306 in lower primates, and the restriction of this gene to the great apes, suggests that the emergence of CD306 may have occurred shortly before or nearly parallel with this rapid coevolution of lineage III KIR receptors with MHC-C. Although CD305-deficient mice show certain phenotypic characteristics distinct from wild type mice, including increased numbers of splenic B, regulatory T, and dendritic cells, they are healthy and fertile, which suggest that any adverse effects of CD305 absence may be balanced *in vivo* by other inhibitory receptors in mice [49]. Therefore, the rapid evolution within the leukocyte receptor sub cluster containing CD306 and the KIR genes suggests that these molecules and their effects on placentation may have played an important role in the evolution of higher primates [47]. The interplay of CD305 with sCD305 and CD306 need to be elucidated: What is the role of this interplay in the placentation? What is the exact regulating mechanism of CD305 on the differentiation and function of DIC and what is the feed-back control of CD305 mediated effects on cell proliferation and differentiation in deciduas? Further identification of CD305 and CD306 abnormalities in the maternal-fetal interface may help determine their functions in EVT invasion and the primary etiology of RSA, preeclampsia, fetal growth restriction and preterm birth as well. Collagens produced at the maternal-fetal interface have been proved to allow the LAIR-1-mediated inhibition of dNK for the successful implantation and decidualization [50]. Together with the new research report in human cervical cancer [51] and ovarian cancer [52], CD305 may provide diagnostic biomarkers and/or therapeutic targets for these diseases.

KIRs are associated with preeclampsia [53], and LILRB1 are associated with HLA-G for normal placentation [54]. Therefore, the illustration of the interplay of CD305 and CD306 and their cooperation with other immune receptors, especially those encoded in the LRC, just like KIRs and LILRs would be helpful for mapping the whole clear pictures about the maternal-fetal immune tolerance. The literature reviewed here represents major researches in the understanding of CD305 and CD306. With the recent identification and characterization of CD305 and CD306 in differentiation and immune regulation, the next exploring researches about their roles in maternal-fetal interface are possible and clear.

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