CD155, an onco-immunologic molecule in human tumors

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CD155 was originally identified as a poliovirus receptor (PVR), with conserved amino acids and domain structure characteristics similar to the immunoglobulin superfamily.1,2 CD155 is also referred to as necl-5, as it belongs to the nectin-like molecule family. These molecules harbor domain structures similar to nectins, which play critical roles in cell adhesion and polarization.3

CD155 heterophilically trans-interacts with nectin-3, colocalizing to epithelial cell–cell junctions.4,5 CD155 overexpression promotes cell migration in a nectin-3-dependent or nectin-3-independent manner.4,6 Moreover, CD155 overexpression stimulates cell proliferation, and enhances growth factor-induced cell proliferation.7 In fact, CD155 overexpression can reduce the expression of nectin-3, and disrupt contact inhibition.8

Regulation of CD155 Expression

DNA damage. DNA damage or DNA-replication inhibitors induce CD155 expression through the activation of ataxia telangiectasia mutated (ATM) and ATM and Rad3-related (ATR) protein kinases. For instance, some chemotherapeutic agents for multiple myeloma patients can upregulate CD155 on human fibroblasts and mouse tumor cells (Fig. 1a)9 Moreover, reactive oxygen species and reactive nitrogen species can also stimulate CD155 expression through DNA damage response (DDR) (Fig. 1a).10,11 Viruses have been extensively demonstrated to induce DDR, leading to genomic instability and the development of human cancers.12,13 Therefore, it is reasonable to ask whether viruses can induce CD155. However, until recently, only HIV-1 Vpr protein was reported to upregulate CD155 involving the activation of ATR kinase and DDR.14 It remains unclear whether CD155 is involved in virus-related human cancers. Interestingly, cytomegalovirus has been observed to downregulate CD155, which is considered to be a mechanism for this virus to escape immune surveillance.15

Ras/FGF. Transformed V12Ras-NIH3T3 cells express higher level of CD155 than wild-type NIH3T3 cells, indicating that oncogenic Ras can upregulate CD155 expression (Fig. 1b).16 This induction involves Raf-MEK-ERK-AP1 signaling, and fibroblast growth factor (FGF) can also upregulate CD155 expression through this signaling.16

Sonic hedgehog signaling. The sonic hedgehog (Shh) signaling pathway plays a critical role in cell differentiation, cell proliferation and tissue polarity. Aberrant Shh-Gli activation is involved in a series of human cancers.17,18 CD155 expression in human Ntera2 cells can be upregulated by treatment with purified shh protein; an intact Gli binding site has been found in CD155 core promoter, which is required for CD155 upregulation (Fig. 1c).19

TLR4 signaling. CD155 expression on dendritic cells (DC) can be upregulated by a series of toll-like receptor (TLR) agonists, including LPS.20,21 This induction involves TLR adapter molecules MYD88 and TRIF, and depends on the...
activation of NF-κB (Fig. 1d). In addition to DC, CD155 expression on neutrophils and macrophages can also be upregulated by LPS. It is unknown whether TLR signaling in the macrophage and neutrophil results in CD155 upregulation. During migration, CD155 is recruited to the leading edge of migrating tumor cells, where it is colocalized with actin and 

overexpression of CD155 in human malignancies

CD155 expression is barely detected in most normal tissues, but upregulated in a series of human malignancies, including colon cancer, lung adenocarcinoma, melanoma, pancreatic cancer and glioblastoma. Clinopathological analysis indicates that CD155 overexpression is correlated with tumor progression and unfavorable prognosis. Moreover, levels of soluble isoforms of CD155 in the sera of cancer patients are significantly higher than those of healthy donors, and are positively correlated with cancer stage. These studies suggest that CD155 may be used as a biomarker for cancer progression and prognosis.

CD155 plays a key role in tumor cell invasion and migration. During migration, CD155 is recruited to the leading edge of migrating tumor cells, where it is colocalized with actin and 

interaction between CD155 and CD226 can downregulate CD226 expression. Similarly, CD112, another ligand for CD226, is also involved in CD226 downregulation. CD226 expression on T and NK cells is increased remarkably in CD155 knockdown mice or mice treated with CD155-neutralizing antibody. This regulation is post-transcriptional based on the fact that CD226 mRNA has not been affected. One mechanism underlying CD226 downregulation may be related to CD155/CD112-induced CD226 internalization.

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Interaction of CD155 with TIGIT in tumor immune evasion

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Fig. 1. Regulation of CD155 expression. (a) Chemotherapeutic agents and reactive oxygen species (ROS)/reactive nitrogen species (RNS) activate ataxia telangiectasia mutated (ATM) and ATM and Rad3-related (ATR) protein kinases, which upregulate CD155 expression. (b) RAS signaling induces CD155 expression via MEK/ERK signaling. (c) Activation of sonic hedgehog induces CD155 expression. (d) Combination of LPS with TLR4 activates NF-κB via adaptor protein MYD88 and TRIF, which stimulates CD155 expression.

Fig. 2. The role of CD155 in tumor development and its underlying molecular mechanisms. Some oncogenic signals induce CD155 overexpression, which regulates tumor cell proliferation, migration and invasion, and tumor angiogenesis.

depends on specific ligands from tumor cells. A study using CD226-deficient mice has shown that CD226 is required for the activation of CD8+ cytotoxic T lymphocytes (CTL) by antigens from tumor cells.

CD155 and CD112 have been identified as the ligands for CD226. Interaction of CD226 with CD155/CD112 triggers NK or T cell-mediated cytotoxicity, accompanied by an increase in cytokine production. Further in vitro studies have shown that tumor cells with higher CD155 expression are more susceptible to CD226-induced killing. In contrast, compared with wild-type mice, CD226-deficient NK or T cells display significantly less cytotoxic activity against CD155-positive tumor cells than wild-type cells, and CD226-deficient mice show increased tumor development and mortality after transplantation of CD155-positive tumor cells. Moreover, CD226 has been revealed to mediate the inhibition of CD155-positive tumor metastasis by NK cells.

Surprisingly, some later studies have shown that CD226 expression in the tumor microenvironment is downregulated. Peripheral blood NK (p-NK) cells and tumor-infiltrating NK (Ti-NK) cells from breast cancer patients express decreased CD226 and some other activating receptors, with weakened cytotoxicity. Factors such as TGF-β1 and PGE2 secreted by stromal cells and/or cancer cells are responsible for the reduction of NK cell CD226 expression and cytotoxicity. These results have also been observed in a cancer MMTV-Neu transgenic mouse model. Moreover, CD226 expression is downregulated on NK cells from myeloma patients with active disease compared with patients in remission and healthy controls.

In addition, interaction between CD155 and CD226 can downregulate CD226 expression. Similarly, CD112, another ligand for CD226, is also involved in CD226 downregulation. CD226 expression on T and NK cells is increased remarkably in CD155 knockdown mice or mice treated with CD155-neutralizing antibody. This regulation is post-transcriptional based on the fact that CD226 mRNA has not been affected. One mechanism underlying CD226 downregulation may be related to CD155/CD112-induced CD226 internalization.

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with high affinity and suppress T cell activation indirectly by modulating DC activity. Studies using TIGIT knockdown mice have revealed that TIGIT inhibits T cell proliferation and activation independent of antigen-presenting cell (APC)-derived CD155. However, the intrinsic inhibitory effect of TIGIT may be still related to CD155. As shown by Lozano and colleagues, T cell-derived CD155 can bind to CD226 to activate T cells under the condition of TIGIT deficiency. Moreover, TIGIT has been demonstrated to directly disrupt CD226 homodimerization, suppressing CD8+ T cell response by interfering with CD155/CD226 interaction.

Contrary to CD226, TIGIT is significantly upregulated on tumor-infiltrating T cells, and its expression parallels with that of other co-inhibitory receptors, most notably PD-1, indicating that TIGIT also acts as a marker of chronically stimulated or exhausted tumor-infiltrating T cells. Moreover, high TIGIT expression on CD8+ T cells is associated with refractory leukemia and leukemia relapse.

One recent study by Inozume and colleagues has shown that CD155 overexpression in melanoma cells inhibits CTL response in the presence of CD226 and this inhibition depends on the interaction between CD155 and TIGIT. It is reasonable to consider that CD155 overexpression in tumor cells may result in increased CD155 combination with co-inhibitory molecules, including TIGIT. However, TIGIT blockade alone or TIGIT knockdown has no obvious effect on tumor growth and metastasis, suggesting that other inhibitory molecules may compensate for TIGIT.

Interaction of CD155 with CD96 in tumor immune evasion

CD96 was originally identified by Wang and colleagues and named as Tactile (T cell activation, increased late expression). Like TIGIT, CD96 also contains an ITIM and is expressed on T cells and NK cells. By using NK92 cells, Fuchs and colleagues have revealed CD96 as another receptor for CD155, and that interaction between CD96 and CD155 mediates cell adhesion. Chan et al. (2014) demonstrate that CD96 is a co-inhibitory receptor on NK cells by generating CD96 knockdown mice. Their study has indicated that CD96 not only competes with CD226 for CD155 binding, but also directly suppresses NK cell function via binding with CD155. CD226 knockdown mice are susceptible to melanoma lung metastasis, but CD96 knockdown mice are resistant to it. CD96 blockade can further suppress melanoma metastasis in TIGIT knockdown mice.

CD155 Ligands-Mediated Signals

**CD155-CD226 ligation.** CD226 ligation is associated with CD226 tyrosine phosphorylation, indicating that CD226 is a signal-transducing molecule. CD226-mediated adhesion and cytotoxicity by NK cells involves PKC, which phosphorylates CD226 at Ser352. CD226 Ser352 phosphorylation facilitates the association of CD226 with LFA-1 (CD11a/CD18), inducing CD226 tyrosine phosphorylation via fyn protein tyrosine kinase.

**CD155-TIGIT ligation.** Ligation of CD155 with TIGIT results in TIGIT phosphorylation at Tyr225, recruiting SHIP1 via adaptor molecule Grb2; SHIP1 further blocks phosphatidylinositol 3-kinase (PI3K) and ERK signaling, and inhibits NK cell-mediated cytotoxicity. Phosphorylated TIGIT can also recruit SHIP1 via adaptor molecule β-arrestin 2, suppressing NF-κB activity and IFN-γ production in NK cells. These findings indicate that SHIP1 is a key molecule in CD155-TIGIT signaling (Fig. 3). Indeed, SHIP1 silencing opposes TIGIT/CD155-mediated inhibitory signaling and restores NK cell cytotoxicity.

**CD155-CD96 ligation.** CD96 has been demonstrated to suppress NK cell function via binding with CD155; however, CD96-mediated signaling remains unknown.

**CD155-nectin-3 ligation.** Similar to interaction between nectins, interaction of CD155 with nectin-3 also induces the activation of Cdc42 and Rac, involving molecules including c-Src, Rap1, FRG and Vav2.
As an immunoregulatory molecule, CD155 can combine with costimulatory molecule CD226, and coinhibitory molecules TIGIT and CD96, having a dual function in oncoimmunity. Accordingly, the balance between CD155/CD226 and CD155/TIGIT or CD155/CD96 maintains normal NK and T cell function. However, this balance may be disrupted in the tumor microenvironment. On one hand, tumor cells usually overexpress CD155; on the other hand, tumor-infiltrating immune cells may express decreased CD226 and increased TIGIT. Therefore, CD155/TIGIT or CD155/CD96-mediated inhibitory signaling may be dominant in the tumor microenvironment (Fig. 4).

Some other findings also lead us to deliberately consider the role of CD155 in human tumors, such as the overexpression of CD155 on human tumor cells, involvement of some oncogenic signaling in the regulation of CD155 expression, attribution of CD155 to tumor growth and metastasis, and correlation of CD155 expression with tumor progression and prognosis. Thus, more investigations should be undertaken to determine the effect of anti-CD155 treatment for tumors. It has been demonstrated that chemotherapeutic agents can induce CD155 expression on tumor cells. Due to the possibility that CD155 overexpression may counteract the efficiency of chemotherapeutic agents, combination of anti-CD155 therapy with chemotherapy could be considered under this condition.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1. Mendelsohn CL, Wimmer E, Racaniello VR. Cellulor receptor for poliovirus: molecular cloning, nucleotide sequence, and expression of a new member of the immunoglobulin superfamily. Cell 1989; 56: 855–65.
2. He Y, Bowman VC, Mueller S et al. Interaction of the poliovirus receptor with poliovirus. Proc Nat Acad Sci USA 2000; 97: 79–84.
3. Takai Y, Irie K, Shingai T, Sakisaka T, Ikeda W. Nectins and nectin-like molecules: roles in cell adhesion, migration, and polarization. Cancer Sci 2003; 94: 655–67.
4. Ikeda W, Kagunaka S, Itoh S et al. Tag4/Nectin-like molecule-5 heterophilically trans-interacts with cell adhesion molecule Nectin-3 and enhances cell migration. J Biol Chem 2003; 278: 28167–72.
5. Mueller S, Wimmer E. Recruitment of nectin-3 to cell-cell junctions through trans-heterophilic interaction with CD155, a vitronectin and poliovirus receptor that localizes to alpha(v)beta3 integrin-containing membrane microdomains. J Biol Chem 2003; 278: 31251–60.
6. Ikeda W, Kagunaka S, Takekuni K et al. Nectin-like molecule-5/Tag4 enhances cell migration in an integrin-dependent, Nectin-3-independent manner. J Biol Chem 2004; 279: 18015–25.
7. Kagunaka S, Ikeda W, Shingai T et al. Enhancement of serum- and platelet-derived growth factor-induced cell proliferation by Nectin-1/Tag4/poliovirus receptor/CD155 through the Ras-Raf-MEK-ERK signaling. J Biol Chem 2004; 279: 36419–25.
8. Minami Y, Ikeda W, Kajita M, Fujito T, Monden M, Takai Y. Involvement of up-regulated Necl-5/Tage4/PVR/CD155 in the loss of contact inhibition in transformed NIH3T3 cells. Biochem Biophys Res 2007; 352: 856–60.
9. Soriani A, Zingoni A, Cerboni C et al. ATM-ATR-dependent up-regulation of DNAM-1 and NKG2D ligands on multiple myeloma cells by therapeutic agents results in enhanced NK-cell susceptibility and is associated with a senescent phenotype. Blood 2009; 113: 3503–11.
10. Ardolino M, Zingoni A, Cerboni C et al. DNAM-1 ligand expression on Ag-stimulated T lymphocytes is mediated by ROS-dependent activation of DNA-damage response: relevance for NK-T cell interaction. Blood 2011; 117: 4778–86.
11. Fionda C, Abruzzese MP, Zingoni A et al. Nitric oxide donors increase PVR/CD155 DNAM-1 ligand expression in multiple myeloma cells: role of DNA damage response activation. BMC Cancer 2015; 15: 17.
12. Cerboni C, Fionda C, Soriani A et al. The DNA damage response: a common pathway in the regulation of NKG2D and DNAM-1 ligand expression in normal, infected, and cancer cells. Front Immunol 2014; 4: 508.
13. Hollingsworth R, Grand RJ. Modulation of DNA damage and repair pathways by human tumour viruses. Viruses 2015; 7: 2542–91.
14. Vassena L, Giuliani E, MatsuI S, Cohen EA, Doria M. The human immunodeficiency virus type 1 Vpr protein upregulates PVR via activation of the ATR-mediated DNA damage response pathway. J Gen Virol 2013; 94: 2646–9.
15. Tomasenc P, Wang EC, Davison AJ et al. Downregulation of natural killer cell-activating ligand CD155 by human cytomegalovirus UL141. Nat Immunol 2005; 6: 181–8.
16. Hirota I, Irie K, Okamoto R, Ikeda W, Takai Y. Transcriptional activation of the mouse Nect-1/Tag4/PVR/CD155 gene by fibroblast growth factor or oncogenic Ras through the Raf-MEK-ERK-AP-1 pathway. Oncogene 2005; 24: 2229–35.
17. Rimkus TK, Carpenter RL, Qasem S, Chan M, Lo HW. Targeting the sonic hedgehog signaling pathway: review of smoothed and GLI inhibitors. Cancers 2016; 8: 22.
lymphoblastic leukemias: evidence for the involvement of the poliovirus receptor (CD155) and nectin-2 (CD112). Blood 2005; 105: 2066–73.

38 Castriconi R, Dondero A, Corrias MV et al. Natural killer cell-mediated killing of freshly isolated neuroblastoma cells: critical role of DNAX accessory molecule-1-poliovirus receptor interaction. Cancer Res 2004; 64: 9180–4.

39 Iguchi-Manaka A, Kai H, Yamashita Y et al. Accelerated tumor growth in mice deficient in DNAM-1 receptor. J Exp Med 2008; 205: 2959–64.

40 Chan CJ, Andrews DM, McLaughlin NM et al. DNAM-1/CD155 interactions promote cytokine and NK cell-mediated suppression of poorly immunogenic melanoma metastases. J Immunol 2010; 184: 902–11.

41 Mamessier E, Sylvain A, Thibult ML et al. Human breast cancer cells enhance self tolerance by promoting evasion from NK cell antitumor immunity. J Clin Invest 2011; 121: 3609–22.

42 Mamessier E, Sylvain A, Bertucci F et al. Human breast tumor cells induce self-tolerance mechanisms to avoid NKG2D-mediated and DNAM-mediated NK cell recognition. Cancer Res 2011; 71: 6621–32.

43 El-Sherbiny YM, Meade JL, Holmes TD et al. The requirement for DNAM-1, NKG2D, and NKp46 in the natural killer cell-mediated killing of myeloma cells. Cancer Res 2007; 67: 8444–9.

44 Carlsten M, Norell H, Bryceson YT et al. Primary human tumor cells expressing CD155 impair tumor targeting by down-regulating DNAM-1 on NK cells. J Immunol 2009; 183: 4921–30.

45 Sanchez-Correa B, Gayoso I, Bergua JM et al. Decreased expression of DNAM-1 on NK cells from acute myeloid leukemia patients. Immunol Cell Biol 2012; 90: 109–15.

46 Seth S, Quo Q, Danisch S et al. Intranodal interaction with dendritic cells dynamically regulates surface expression of the co-stimulatory receptor CD226 protein on murine T cells. J Biol Chem 2011; 286: 39153–63.

47 Yu X, Harden K, Gonzalez LC et al. The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. Nat Immunol 2009; 10: 48–57.

48Stanietzky N, Simic H, Arapovic J et al. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. Proc Nat Acad Sci USA 2009; 106: 17858–63.

49 Joller N, Hafler JP, Brynedal B et al. Cutting edge: TIGIT has T cell-intrinsic inhibitory functions. J Immunol 2011; 186: 1338–42.

50 Lozano E, Dominguez-Villar M, Kuchroo V, Hafler DA. The TIGIT/CD226 axis regulates human T cell function. J Immunol 2012; 188: 3869–75.

51 Johnston RJ, Comp-Agrar L, Hackney J et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8+ T cell effector function. Cancer Cell 2014; 26: 923–37.

52 Kong Y, Zhu L, Schell TD et al. T-Cell Immunoglobulin and ITIM domain (TIGIT) associates with CD8+ T-cell exhaustion and poor clinical outcome in AML patients. Clin Cancer Res 2016; 22: 3057–66.

53 Bläke SJ, Stannard K, Liu J et al. Suppression of metastases using a new lymphocyte checkpoint target for cancer immunotherapy. Cancer Discov 2016; 6: 446–59.

54 Wang PL, O’Farrell S, Clayberger C, Kremsky AM. Identification and molecular cloning of tactile. A novel human T cell activation antigen that is a member of the Ig gene superfamily. J Immunol 1992; 148: 2600–8.

55 Fuchs A, Celli M, Giuriato E, Shaw AS, Colonna M. Cutting edge: CD96 (tactile) promotes NK cell-target cell adhesion by interacting with the poliovirus receptor (CD155). J Immunol 2004; 172: 3994–8.

56 Shibuya A, Lanier LL, Phillips JH. Protein kinase C is involved in the regulation of both signaling and adhesion mediated by DNAX accessory molecule-1 receptor. J Immunol 1998; 161: 1671–6.

57 Shibuya K, Lanier LL, Philips JH et al. Physical and functional association of LFA-1 with DNAM-1 adhesion molecule. Immunity 1999; II: 615–23.

58 Liu S, Zhang H, Li M et al. Recruitment of Grb2 and SHIP1 by the ITT-like motif of TIGIT suppresses granule polarization and cytotoxicity of NK cells. Cell Death Diff 2013; 20: 456–64.

59 Li M, Xia P, Du Y et al. T-cell immunoglobulin and ITIM domain (TIGIT) receptor/poliovirus receptor (PVR) ligand engagement suppresses interferon-gamma production of natural killer cells via beta-arrestin 2-mediated negative signaling. J Biol Chem 2014; 289: 17647–57.

60 Sato T, Irie K, Okamoto R, Ooshio T, Fujita N, Takai Y. Common signaling pathway is used by the trans-interaction of Necl-5/Tage4/PVR/CD155 and nectin, and of nectin and nectin during the formation of cell-cell adhesion. Cancer Sci 2005; 96: 578–89.