Editorial Commentary

Stem Cell INVESTIGATION

CD157 and CD200 at the crossroads of endothelial remodeling and immune regulation

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The endothelial cells that coat the inner wall of blood vessels are essential for the maintenance of the vascular network, metabolic homeostasis and stem cell populations in tissue or tumor microenvironments (1-3). Angiogenesis is defined as neovascular formation through the sprouting and proliferation of endothelial cells from preexisting blood vessels. VEGF (VEGFA) and FGFs that transduce signals through VEGFR2 and FGFRs, respectively, are representative proangiogenic factors (4,5). In contrast, hematopoietic stem cells (HSCs) generated from hemangiogenic endothelial cells in the aorta-gonad-mesonephros (AGM) region of the developing embryo ultimately reside in the perivascular niche of postnatal bone marrow (6). HSC-derived myeloid progenitor cells give rise to macrophages, myeloid-derived suppressor cells (MDSCs) and endothelial progenitor cells (EPCs, also called myeloid angiogenic cells or MACs) that regulate angiogenesis and immunity (7). M2-like macrophages and MDSCs produce VEGF and FGF2 to promote angiogenesis (8), whereas EPCs integrate into the endothelial network of blood vessels to support vascular regeneration (9). Endothelial and immune cells work together in a variety of processes during fetal development, tissue repair and tumor formation.

Recently, Wakabayashi *et al.* found upregulation of the expression of *Abcg2*, *Abcb1a*, *Cd34*, *Cd157 (Bst1)*, *Cd200 (Ox2)*, *Cxcl12*, *Dusp2*, *Igfbp3*, *Il6*, *Mycn*, *Sema3g* and *Tnfrsf10b* in the stem cell-enriched "side population" of liver endothelial cells in comparison with the main population of liver endothelial cells (10). The authors focused on the surface markers CD157 and CD200 and found that CD157/CD200 double-positive liver endothelial cells formed more CD31 (PECAM1)-positive colonies than CD200 single-positive or CD157/CD200 double-negative liver endothelial cells in vitro. The expression levels of *Atf3*, *Fosl2*, *Myc* and *Sox7* were significantly upregulated in the CD157/CD200 double-positive cells compared with the CD200 single-positive or CD157/CD200 double-negative cells; however, the functions of these transcription factors in CD157/CD200 double-positive endothelial cells remain unclear. CD157/CD200 double-positive endothelial cells derived from other organs or tissues, including the brain, heart, limb muscle, lungs, retina and skin, possess enhanced endothelial colony-forming potential. Wakabayashi *et al.* transplanted endothelial cells into the splenic parenchyma of adult mice after inducing endothelial damages with genotoxic pyrrolizidine alkaloid and subsequent whole-body irradiation and found that CD157/CD200 double-positive endothelial cells were incorporated into the damaged liver vasculature; gave rise to CD157/CD200 double-positive, CD200 single-positive and CD157/CD200 double-negative endothelial cells; and reconstituted the portal vein, sinusoids and central vein in the repaired liver.

CD200 and CD200R1 are dual markers of mammary stem cells with mammosphere-forming potential and mammary gland-repopulating capacity, and the expression levels of *Cd157*, *Cdh3*, *Fzd7*, *Lgr4*, *Lgr6* and *Wnt10a* are upregulated in the CD200/CD200R1 double-high population of mammary epithelial cells (11). CD200 is a marker of the limbal stem cells that maintain the corneal tissue, and *ABCB5*, *CDH3*, *PAX6* and *WNT7A* expression levels are upregulated in the CD200-positive population of corneal epithelial cells (12). In contrast, CD157 is a marker

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of Paneth cells in intestinal crypts that support the self-renewal and proliferation of intestinal stem cells (13), as well as fibroblastic reticular cells at the interface of germinal centers and the T cell zone that support the affinity maturation of plasma cells (14). These facts indicate that CD157 and CD200 are surface markers of stem or niche cells in several tissue microenvironments.

CD157, a glycosylphosphatidylinositol (GPI)-anchored protein, functions as a component of integrin adhesion receptor complexes that activate SRC, ERK and AKT signaling cascades and as an ectoenzyme catalyzing nicotinamide adenine dinucleotide into cyclic ADP-ribose, which increases the intracellular Ca^{2+} concentration through mobilization from the intracellular pool (15). CD157 expression is found on neutrophils and upregulated by the chemokine CCL2 (MCP1) in circulating monocytes, and these expression patterns regulates the transendothelial migration of neutrophils and monocytes, respectively (16,17). CD157 is involved in the integrin-mediated migration of UE7T-13 cells derived from bone barrow mesenchymal stem cells (MSCs) (18). Because CD157 overexpression induces epithelial-to-mesenchymal transition (EMT) and enhances the motility and invasiveness of tumor cells, the upregulation of CD157 expression is associated with a poor prognosis in patients with epithelial ovarian cancer or biphasic malignant pleural mesothelioma (19,20). In addition, CD157 is expressed by hematological malignancies, such as the M4 and M5 subtypes of acute myeloid leukemia (AML) and B-cell precursor acute lymphoblastic leukemia (BCP-ALL) (21,22).

The *CD157* gene and paralogous *CD33* gene are clustered in a head-to-tail manner at human chromosome 4p15.32 (15). The single-nucleotide polymorphism rs11724635 of the human *CD157* gene is associated with the risk of Parkinson's disease in Asian, European and United States populations [odds ratio per minor allele dose =0.87 ($P=2.43\times10^{-9}$)], with a population-attributable risk of 7.82% (95% CI: 5.30–9.47) (23). Parkinson's disease is a neurodegenerative disease that is characterized by motor symptoms, such as bradykinesia and resting tremor (24,25), and nonmotor symptoms, including anxiety, cognitive dysfunction, depression, hyposmia and sleep disorder (26,27). *Cd157* knockout mice manifested anxiety- and depression-like symptoms (28); however, the causal link between the *CD157* SNP and Parkinson's disease remains unclear.

CD200 is a transmembrane protein with two extracellular immunoglobulin-like domains and a short cytoplasmic tail that is expressed on a variety of cells, such as B and T lymphocytes, endothelial cells, neurons and pancreatic islet cells (29,30), and whose expression is upregulated by IL4 (31). CD200 transduces signals through CD200R (CD200R1), a transmembrane protein with two extracellular immunoglobulin-like domains and a cytoplasmic NPxY motif (32,33). CD200R is expressed on myeloid-lineage immune cells (MDSCs, macrophages, monocytes, dendritic cells, basophils and eosinophils) and lymphocytic-lineage immune cells [T-helper type 2 (Th2) lymphocytes and innate lymphoid type 2 (ILC2) cells], and CD200R expression is upregulated in M2 macrophages and Th2 lymphocytes by IL4 and mediates immunosuppressive effects (32,34-36). Interaction between CD200 and CD200R leads to the phosphorylation of tyrosine 302 in the NPxY motif of CD200R, which recruits the Dok2-RasGAP complex to repress Ras-ERK signaling in myeloid cells (33). *Cd200* knockout mice are prone to collagen-induced arthritis and experimental autoimmune encephalomyelitis owing to the activation and expansion of macrophages and microglial cells, respectively (37). *Cd200* knockout mice are also resistant to chemically induced skin tumorigenesis owing to decreased immune tolerance (38), whereas compared with CD200- B16 melanoma cells, CD200+ B16 melanoma cells exhibit enhanced tumorigenesis owing to the expansion of myeloid-lineage cells and increased tumor angiogenesis in *Cd200r* knockout mice (39). CD200-CD200R signaling plays a critical role in cancers and noncancerous diseases through the regulation of immunity and angiogenesis.

In a clinical study, cell-surface CD200 expression on B lymphocytes was upregulated in 100% (n=87) of patients with B-cell chronic lymphocytic leukemia (B-CLL) compared with healthy donors (40), whereas cell-surface CD200 expression on blast cells was detected in 56% (136/244) of patients with AML (41). CD200 immunostaining is frequently detected in B-CLL (100%, n=21), hairy cell leukemia (100%, n=12), mediastinal large B-cell leukemia (100%, n=8), classical Hodgkin lymphoma (92%, 12/13) and multiple myeloma (77%, 10/13) among B-cell lymphoproliferative disorders (42). CD200 immunostaining is also detected in solid tumors, such as basal cell carcinoma (100%, n=9), papillary thyroid carcinoma (100%, n=10), gastrointestinal carcinoid tumors (95%, 78/82), pancreatic neuroendocrine tumors (93%, 56/60), Merkel cell carcinoma (84%, 125/149), small cell lung carcinoma (83%, 60/72), renal cell carcinoma (71%, 5/7) and ovarian cancer (67%, 6/9) (43). In addition, CD200 expression is upregulated in cancer-associated fibroblasts (44) and infiltrating CD4+ T lymphocytes (45) in

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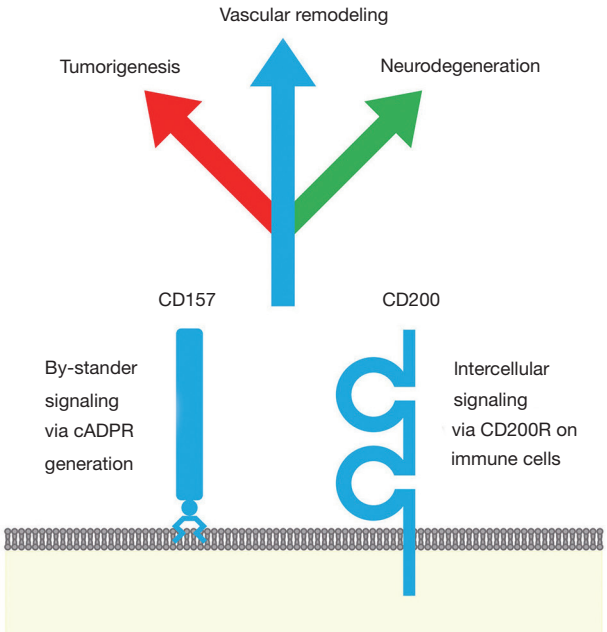

Figure 1 CD157 and CD200 in vascular regeneration, tumorigenesis and neurodegeneration. CD157 (BST1) is a glycosylphosphatidylinositol-anchored ectoenzyme that produces cyclic ADP-ribose (cADPR). CD200 (OX-2) is expressed on endothelial cells, lymphocytes, pancreatic islet cells, neurons and cancer-associated fibroblasts and is a transmembrane-type ligand for the CD200R receptor, which is expressed on myeloid- and lymphoid-lineage cells. CD157 and CD200 are coexpressed on endothelial stem cells. CD200 and CD200R are coexpressed on mammary gland stem cells. CD157 is expressed on Paneth cells, which support intestinal stem cells. CD157 is expressed in acute myeloid leukemia, B-cell precursor acute lymphoblastic leukemia, mesothelioma and ovarian cancer, whereas CD200 is expressed in B-cell lymphoproliferative disorders, such as chronic lymphocytic leukemia and classical Hodgkin lymphoma, and solid tumors, including basal cell carcinoma, papillary thyroid carcinoma, pancreatic neuroendocrine tumors, Merkel cell carcinoma, small cell lung carcinoma and ovarian cancer. The CD157 single-nucleotide polymorphism rs11724635 is associated with the risk of Parkinson's disease. Neuronal CD200 expression is downregulated in the postmortem brain of patients with Alzheimer's disease, multiple sclerosis or Parkinson's disease. CD157 and CD200 are involved in a variety of physiological and pathological processes at the crossroads of vascular remodeling and immune regulation.

patients with lung cancer or classical Hodgkin lymphoma, respectively. Because CD200 transduces immunosuppressive signals through CD200R on myeloid-lineage cells and T lymphocytes, CD200 expression on tumor cells, cancer-associated fibroblasts and CD4+ T lymphocytes can induce immune evasion through the expansion of M2-like macrophages and regulatory T (Treg) cells (46) and reduced infiltration of CD4+ and CD8+ T lymphocytes and natural killer cells (39) into the tumor microenvironment.

Anti-CD200 monoclonal antibodies (mAbs) (47) and engineered CD8+ T lymphocytes expressing CD200R-CD28 chimeric proteins (CD200R-IFP T cells) (48) have been developed as investigational therapeutics targeting the immunosuppressive CD200-CD200R signaling cascade. Antagonistic anti-CD200 mAbs show antitumor effects in a mouse model of B-CLL, whereas engineered chimeric CD200R-CD28 T lymphocytes showed antitumor effects in a mouse model of erythroleukemia. However, because inflammation and immune tolerance are both involved in tumorigenesis (49,50), preclinical mouse-model experiments have revealed context-dependent functions of CD200-CD200R signaling in tumor progression (39,51) and tumor suppression (52,53). The exploration of biomarkers predicting antitumor effects without severe adverse effects related to autoimmunity is necessary for the clinical application of CD200-CD200R signaling-targeted therapeutics.

Neuronal CD200 immunostaining in the central nervous system (CNS) is downregulated in the postmortem brain of patients with Alzheimer's disease (54), multiple sclerosis (55) or Parkinson's disease (56), which are characterized by CNS destruction mediated in part through inflammation triggered by β-amyloid, β-synuclein and α-synuclein, respectively (57-59). The defect in Cd200 expression in *Cd200* knockout mice leads to enhanced microglia/macrophage activation in the CNS and accelerated neurodegeneration (37), whereas the upregulation of neuronal Cd200 expression in *Wld*^{S} mice leads to decreased microglia/macrophage accumulation in the CNS and decelerated neurodegeneration (60). CD200 can protect the CNS from neurodegeneration through the maintenance of the blood-brain barrier (61), suppression of microglia/macrophage-mediated inflammation (37) and promotion of FGFR-dependent neuronal survival (62). A CD200-Fc fusion protein (63), an adeno-associated virus expressing CD200 (AAV-CD200) (64) and an agonistic anti-CD200R mAb (63) have been developed as investigational drugs that stimulate CD200 signaling for neuroprotection; however, these drugs still remain in preclinical stages.

CD157 and CD200 are surface markers of stem/niche cell populations in tissue or tumor microenvironments (*Figure 1*). CD157 is a GPI-anchored ectoenzyme that generates cyclic ADP-ribose and functions as an integrin-

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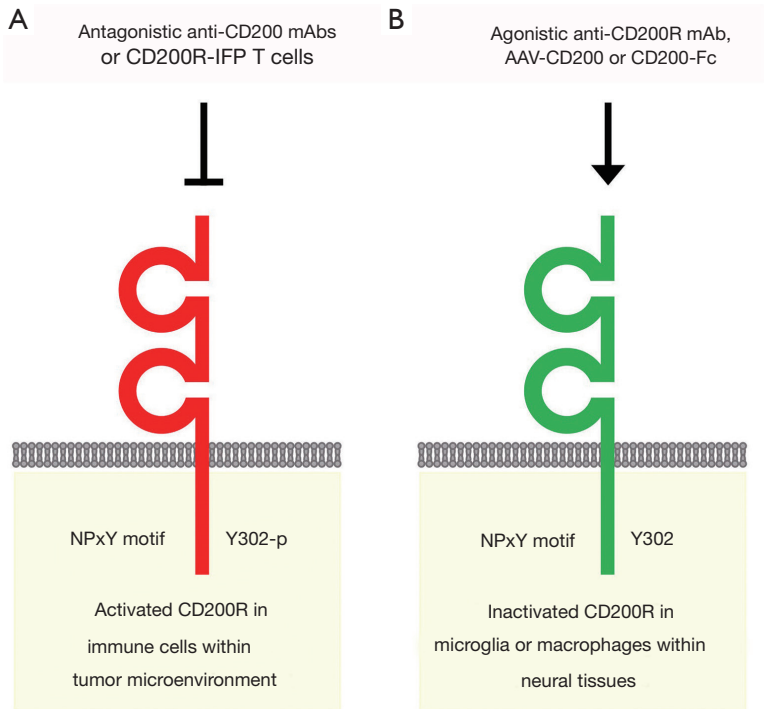

Figure 2 CD200 signaling-targeted therapeutics. (A) Investigational drugs inhibiting CD200 signaling. Antagonistic anti-CD200 monoclonal antibodies (mAbs) and engineered CD8+ T lymphocytes expressing CD200R-CD28 chimeric proteins (CD200R-IFP T cells) are investigational therapeutics that block the CD200-CD200R signaling cascade for the treatment of cancer patients with immune evasion. (B) Investigational drugs activating CD200 signaling. An agonistic anti-CD200R mAb, an adeno-associated virus expressing CD200 (AAV-CD200) and a CD200-Fc fusion protein are investigational therapeutics that stimulate anti-inflammatory CD200-CD200R signaling for neuroprotection in patients with neurodegenerative diseases. However, the context-dependent functions of CD200 signaling in angiogenesis and immunity in the central nervous system (CNS) and tumor microenvironment should be further investigated for future clinical application of CD200 signaling-targeted therapeutics.

interacting protein, whereas CD200 is a transmembrane-type ligand that transduces immunosuppressive signals through CD200R. CD157 and CD200 are involved in a variety of pathophysiological processes, such as vascular regeneration, tumor progression and inflammation-related neurodegeneration (*Figure 1*). Anti-CD200 mAbs and CD200R-IFP T cells are investigational drugs that inhibit CD200 signaling for the treatment of cancer patients with immune evasion (*Figure 2A*), whereas an agonistic anti-CD200R mAb, AAV-CD200 and CD200-Fc are investigational drugs that activate CD200 signaling for the treatment of patients with neurodegenerative diseases (*Figure 2B*). The context-dependent functions of CD200-CD200R signaling in tumor and neuroinflammatory microenvironments should be further investigated before CD200-CD200R signaling-targeted therapeutics are applied in the clinic in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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