



CONTEMPORARY REVIEW

Contributions of Costimulatory Molecule CD137 in Endothelial Cells

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ABSTRACT: CD137 (4-1BB, tumor necrosis factor receptor superfamily 9) is a surface glycoprotein of the tumor necrosis factor receptor family that can be induced on a variety of immunocytes and nonimmune cells, including endothelial cells and smooth muscle cells. The importance of CD137 in immune response has been well recognized; however, the precise biological effects and underlying mechanisms of CD137 in endothelial cells are unclear. A single layer of cells called the endothelium constitutes the innermost layer of blood vessels including larger arteries, veins, the capillaries, and the lymphatic vessels. It not only acts as an important functional interface, but also participates in local inflammatory response. This review covers recent findings to illuminate the role of CD137 in endothelial cells in different pathophysiologic settings.

Key Words: atherosclerosis ■ CD137 ■ CD137L ■ endothelial cell ■ vascular inflammation

Tumor necrosis factor superfamily and tumor necrosis factor receptor superfamily are important cellular signaling pathways involved in apoptosis, inflammation, tissue development, and lymphocyte homeostasis, such as CD137/CD137L, OX40/OX40L, CD40/CD40L, and Fas-FasL. The interaction between CD137 and CD137L (its ligand) is the second signal for activating T lymphocytes and is involved in cellular immune responses, immune tolerance, and other reactions. CD137 has been found to be expressed not only in immune cells, but also in vascular cells. CD137-positive blood vessels have been identified in atherosclerotic lesions, tumors, and vasculitis.¹ CD137 is mainly expressed by activated endothelial cells (ECs) and smooth muscle cells (SMCs). Notably, ECs are the primary component of the endothelial lining of the circulatory system (blood and lymph), which are considered major participants in and regulators of inflammatory reactions. Endothelial dysfunction induced by the activation of CD137 signaling effectively induces a state of inflammation, which plays a critical role in a variety of pathological conditions. Currently, excellent

reviews are available on the role of CD137 in the immune system and immunotherapy.^{2,3} In this article, a review of the literatures focusing on the evidence of the implication of CD137 in the biological effects of ECs was conducted on PubMed and Google Scholar.

SEARCH STRATEGY

Our literature search was performed in PubMed and Google Scholar with no language limitation. The search strategy involved combining the following keywords: CD137, 4-1BB, CD137L, 4-1BBL, ECs, endothelium, inflammation, vascular, and vessel. Publications should be between January 1990 to September 2020, including various types of CD137 and endothelium-related articles.

STRUCTURE AND REGULATION OF CD137

CD137 is a type I transmembrane glycoprotein receptor characterized by the presence of cysteine-rich domains.

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For Sources of Funding and Disclosures, see page 8.

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Nonstandard Abbreviations and Acronyms

CRDs	cysteine-rich domains
DCs	dendritic cells
ECs	endothelial cells
EV	extracellular vesicle
mAbs	monoclonal antibodies
SMCs	smooth muscle cells
TECs	tumor ECs
TET2	ten-eleven translocation protein methylcytosine dioxygenase 2
TME	tumor microenvironment
TRAF	tumor necrosis factor (TNF) receptor-associated factor

As in most of the tumor necrosis factor receptor superfamily members, CD137 exists in a membrane-bound, soluble form. Although some studies have shown that CD137 exists as a monomer and dimer, it has recently been suggested that CD137 is a functional trimer complex that exists on cell surfaces. It has also been confirmed that CD137 is predominantly expressed in most immune cells, including activated CD4⁺ and CD8⁺ T cells, natural killer cells, natural killer T (natural killer T cell) cells, and CD4⁺CD25⁺ regulatory T cells. CD137 is also expressed on myeloid cells, such as monocytes, neutrophils, mast cells, eosinophils, and dendritic cells (DCs).⁴ In vascular cells, CD137 is expressed in an activation-dependent manner.⁵ CD137L, a ligand of CD137, is a type II membrane glycoprotein of the tumor necrosis factor superfamily that is expressed on antigen-presenting cells, such as monocytes, macrophages, DCs, and activated B cells.⁵ CD137L can also be cleaved to generate a soluble form, sCD137L.⁶ The interaction of CD137 and CD137L is limited to CRDs. Mouse and human CD137L are mainly combined with CRDII and CRDIII, respectively. Both CRDII and CRDIII contain cysteines that can form a typical CRD structure. Although CD137L is considered to be the major binding partner for CD137, CD137 can bind to other receptors, including fibronectin, vitronectin, laminin, collagen VI, and galectin-9. However, the function of these combined structures has not yet been completely understood.² Notably, sCD137 antagonizes CD137/CD137L interaction by competing with membrane CD137 for binding to CD137L, serving as a natural genetic regulator of CD137 signaling.⁷

Upon activation by CD137L or agonist monoclonal antibodies (mAbs), CD137 binds to TRAF (tumor necrosis factor [TNF] receptor-associated factor) proteins, including TRAF1, TRAF2, and TRAF3, to form a CD137 signalosome, which can induce transubiquitination via the Ubc13-mediated K63-linked polyubiquitination

of transforming growth factor beta-activated kinase 1-binding protein 1/2/3 with the subsequent activation of nuclear factor- κ B and extracellular signal-regulated kinases via inhibitor of nuclear factor kappa-B kinase β and NEMO (nuclear factor- κ B essential modulator) and mitogen-activated protein kinases via mitogen-activated protein kinases/extracellular signal-regulated kinases 1. Deubiquitination of polyubiquitination chains by K63 deubiquitinases is required to quench this pathway. CD137 can also become internalized upon ligation with anti-CD137 antibody during K63 polyubiquitination.⁸ Anti-CD137 mAbs, recombinant CD137-Fc fusion proteins and cell transfer, implantation techniques, and CD137 and CD137L knockout mice have been used to specifically block CD137 or CD137L signals.⁹

ROLE OF CD137 IN VASCULAR DISORDERS

Role of CD137 in Atherosclerosis

Atherosclerosis is a chronic inflammatory lesion of the arterial wall. Endothelial dysfunction and morphological damage cause leukocyte-EC adhesion, vasoconstriction, platelet aggregation, oxidative stress, smooth muscle proliferation, and thrombosis.¹⁰ Many traditional risk factors that promote the formation of ECs damage and induce EC apoptosis, which results in localized endothelial denudation and contributes to the formation of plaque erosion and the development of acute coronary syndrome. Thus, endothelial dysfunction is involved in arteriosclerosis through various pathways.¹¹

The expression of CD137 is generally upregulated in atheroma-associated vascular cells in both mouse and human atherosclerotic plaque lesions *in vivo*. It is also inducible in ECs and vascular SMCs by proinflammatory stimuli *in vitro*.¹² Apoe^{-/-}CD137^{-/-} mice fed with both chow and high-fat diets showed significantly reduced atherosclerotic areas in the aorta compared with their Apoe^{-/-}CD137^{+/+} counterparts, suggesting that CD137 promotes atherogenesis.¹³ However, a lack of change in atherosclerotic plaque size was observed in a bone marrow transplantation experiment, which showed only the deprivation of vascular CD137.¹³ This may have occurred because the extent of the contribution of EC modulation by CD137 is different in the overall atherosclerotic process. Further research is needed to determine whether the characteristics of plaques change in mice undergoing bone marrow transplantation.

The CD137/CD137L interaction on the EC surface results in endothelium activation and subsequently increases the expression of adhesion molecules and proinflammatory cytokines, including vascular cell

adhesion molecule-1, intercellular adhesion molecule-1, monocyte chemoattractant protein-1, and interleukin-6.¹³ ECs interact with peripheral blood monocytes as an initiating step in atherosclerosis. Proinflammatory cytokines and adhesion molecules promote leukocyte recruitment and migration into vascular inflammation sites to exacerbate the inflammatory response and the progression of atherosclerosis in Apoe^{-/-} mice treated with CD137 agonist antibody. Quek et al also reported that the expression of CD137 on ECs can result in an E-selectin- and intercellular adhesion molecule-1-dependent increase in the number of interacting THP-1 cells.⁷ In contrast, CD137-deficient ECs or blocking of CD137 function is effective against monocyte and THP-1 recruitment and attachment.^{7,13} The CD137 signaling-induced inflammatory process is amplified in atherosclerotic lesions through bidirectional signaling of T cells expressing CD137, macrophages expressing CD137L, and ECs expressing both CD137 and CD137L, thus generating localized, intercellular inflammatory signaling loops within the vessel wall.^{9,13} CD137L is also expressed in other cell types, including DCs and activated B cells.¹⁴ However, whether CD137/CD137L signaling contributes to the interaction between ECs and these cells in atherosclerosis remains to be investigated.

An extracellular vesicle (EV) is a membrane-bound vesicle released from healthy cells and activated/apoptotic cells, which mediates intercellular communication via transporting nucleic acids (RNA and DNA), lipids, and proteins.¹⁵ EVs arising from ECs can modulate inflammation, regulate circulating inflammatory cells such as macrophage and monocyte migration, and cell adhesion. Endothelial EVs also transfer messages to SMCs, which is a key event in atherosclerotic development. Endothelial EVs in atherosclerotic lesions may generate either protective or harmful effects, depending on the context.¹⁶ Notably, EVs derived from activated ECs via CD137 signaling play a detrimental role in the progression of atherosclerosis in Apoe^{-/-} mice. The activation of CD137 signaling in ECs increases the expression of interleukin-6 in EVs via the Akt-nuclear factor- κ B pathway. Moreover, the transfer of interleukin-6 via CD137 EVs to recipient CD4⁺T cells can result in the activation of Th17 cell differentiation and upregulation of target protein IL-17. Such upregulation of IL-17 is associated with enhanced EC apoptosis and inhibition of cell viability, along with an increased expression of soluble intercellular adhesion molecule-1, monocyte chemoattractant protein-1, and E-selectin, therefore inducing positive feedback on local inflammation of blood vessels.¹⁷ However, the effect of CD137 stimulation on the differentiation of Th17 cells is controversial. In experimental autoimmune encephalomyelitis, CD137 stimulation suppresses the differentiation of Th17 cells and increases the production of regulatory T cells.¹⁸

CD137 agonist is one of the most potent costimulators of T cells that plays a key role in the polarization of T-cell immune responses. CD137-induced alterations in the differentiation of T-lymphocyte subsets contribute to the bidirectional effects of immunoenhancement versus immunosuppression on cell-mediated immunity.¹⁹ EVs produced by ECs also participate in the crosstalk between the endothelium and smooth muscles.²⁰ Evidence of intracellular communication between ECs and SMCs via endothelial EVs has also been found with the transfer of the TET2 (ten-eleven translocation protein methylcytosine dioxygenase 2).²¹ This protein is associated with the phenotypic transformation of vascular SMCs, endothelial dysfunction, and inflammation via the modification of DNA methylation.²² Notably, EC-derived EVs generated from the activation of CD137 inflammatory stimulation exhibit downregulated TET2. This specific reduction of TET2 in endothelial EVs induces a synthetic and proliferative phenotype of SMCs and intimal hyperplasia after arterial injury. In contrast, EVs overexpressing TET2 inhibit the prophenotypic transformation and intimal hyperplasia induced by CD137 signaling.²³

Endothelial dysfunction and apoptosis resulting from dysregulated oxidative stress can trigger the formation of thrombi.¹⁸ Nuclear factor erythroid 2-related factor 2 regulates intracellular redox balance and extracellular oxidative stress in ECs.²⁴ Moreover, activation of CD137 signaling using agonist-CD137 recombinant protein (CD137L) promotes endothelial apoptosis by modulating both nuclear factor erythroid 2-related factor 2 and nuclear factor- κ B pathways. This subsequently induces the production of reactive oxygen species and increases the expression of proinflammatory cytokine genes, including interleukin-6, IL-1 β , and tumor necrosis factor- α . Notably, reactive oxygen species upregulate proapoptotic proteins, such as Bax and cleaved caspase-3, and downregulate antiapoptotic proteins, such as Bcl2, thereby inducing EC apoptosis.²⁵ The mechanism underlying the effects of CD137 signaling on human umbilical vein endothelial cells also includes the diacyl glycerol-PKC (protein kinase C) signaling pathway. Stimulation of human umbilical vein endothelial cells with anti-CD137 antibody leads to the rapid formation of inositol triphosphate, which in turn upregulates diacyl glycerol levels and PKC activity and consequently results in the translocation of PKC from the cytosol to the plasma membrane. However, anti-CD137L antibodies suppress the activation of the diacyl glycerol-PKC signaling pathway in human umbilical vein endothelial cells.²⁶ However, it was found that anti-CD137 antibodies stimulate the proliferation of mouse brain vascular ECs, whereas inhibitory anti-CD137 antibodies have an inhibitory effect on proliferation.²⁷ The reasons underlying this difference may stem from the organ-specific endothelial action

in response to the activation of the CD137 costimulatory system. Notably, administering agonist-CD137 antibodies is more efficacious than administering the natural CD137 ligand because CD137L can be inhibited by sCD137.²⁸

Because of the instability of the microenvironment in plaques, nourishing blood vessels can lead to abnormalities and serious defects during the process of development, resulting in immaturity and rupture.²⁹ As a key feature of vulnerable atherosclerotic plaques, excessive angiogenesis is considered an independent predictor of cardiovascular risk. We found that the agonistic anti-CD137 antibody is a promoter of angiogenic processes in atherosclerotic plaques of Apoe^{-/-} mice. The activation of CD137 signaling markedly induces angiogenesis and EC migration, accompanied by an increase in the phosphorylation of recombinant human mothers against decapentaplegic homolog (Smad1/5) and nuclear translocation of p-Smad1/5, which consequently promote the expression and translocation of the nuclear factor of activated T cells 1. Therefore, activation of CD137 signaling aggravates angiogenesis in atherosclerotic lesions by modulating the Smad1/5-nuclear factor of activated T cells 1 pathway.²⁷ Several studies have shown that atherosclerosis is associated with genetic polymorphism.³⁰ Recent studies have shown that single nucleotide polymorphisms exist in the genes encoding human CD137 and impart increased susceptibility to atherosclerosis. Söderström et al showed that the minor T allele of rs2453021 was associated with decreased CD137 mRNA expression and an increased carotid intima-media thickness, a widely used measurement of subclinical atherosclerosis; however, it was not associated with an increased risk of coronary artery disease.³¹ Hence the distinct vascular sites may be differently affected because of natural variations in the anatomical and functional properties. The authors also reported increased expression of CD137 mRNA in murine carotid atherosclerotic and atherothrombotic lesions compared with control vessels.³² Zhang et al showed that 3 single nucleotide polymorphisms (rs161827, rs161818, and rs161810) in the CD137 gene were associated with ischemic stroke in patients with carotid lesions; moreover, rs161827 is significantly associated with stroke in patients with diabetes mellitus.³³ These results suggest that functional single nucleotide polymorphisms of CD137 may affect the development of noncardiac vascular atherosclerosis by changing the expression and activity of CD137, thereby modulating the downstream biological effects.

In summary, in addition to other groups, we identified that inflammation and EC death induced by the activation of CD137 signaling result in the initiation of atherosclerosis and transition of stable plaques to a vulnerable plaque (Figure 1). Promotion of the angiogenic process exacerbates the risk of plaque rupture

and thrombosis formation (Figure 2). Figure 3 describes the underlying molecular pathways for these processes. Therefore, the effects of CD137 on ECs are observed in lesions throughout the progression of atherosclerosis, contributing to interactions between ECs and various inflammatory cells.³⁴ Although CD137 represents a promising potential therapy to ameliorate multiple aspects of atherosclerotic plaque progression in atherosclerotic mice, more studies are needed on atherosclerotic human models. Moreover, the role of CD137 in the crosstalk between ECs and SMCs remains to be further investigated.

Role of CD137 in Vasculitis

Vasculitis is a pathological condition of blood vessels resulting from inflammatory changes in vessel walls of different sizes (large, medium, and small), different types (arteries, veins, and capillaries), and different sites (visceral organs and skin).³⁵ Patients with vasculitis showed CD137 overexpression in the blood vessels (arteries, microvessels, and venules) of the skin that facilitated recruitment of circulating monocytes; moreover, both ECs and SMCs expressed CD137 in the vessel wall. Furthermore, CD137 was uniformly expressed throughout the vessel wall to ensure continuous migration of monocytes.¹ However, CD137 expression and function in different types of vasculitis including large vessel vasculitis, Kawasaki disease, and antineutrophil cytoplasmic antibody-associated vasculitis are not entirely known and need further studies.

Graft vascular disease is a common cause of death in the first year after heart transplantation.³⁶ Although the authors did not investigate the expression of CD137 on ECs, it is preferentially expressed in both alloactivated CD4⁺ or CD8⁺ T cells during alloimmune responses. Moreover, blocking the CD137/CD137L pathway in CD137 deficient mice or using an anti-CD137L monoclonal antibody contributes to a long-term survival of grafts partially via attenuating coronary vasculopathy.³⁷ Further research studies are warranted to determine whether inhibiting CD137 together with other costimulatory signaling pathways such as CD40 and CD28 would have a greater effect on the suppression of immune rejection.

ROLE OF CD137 IN LYMPHATIC ECS

Generally, the lymphatic system is regarded as an important factor in inflammatory processes and immune functions. The inflammatory response of the lymphatic endothelium depends on specific stimuli and context.³⁸ CD137 is predominantly expressed by lymphatic endothelial cells of inflamed human skin rather than the lymphatic vessels of noninflamed samples. Furthermore, CD137 expression in lymphatic endothelial

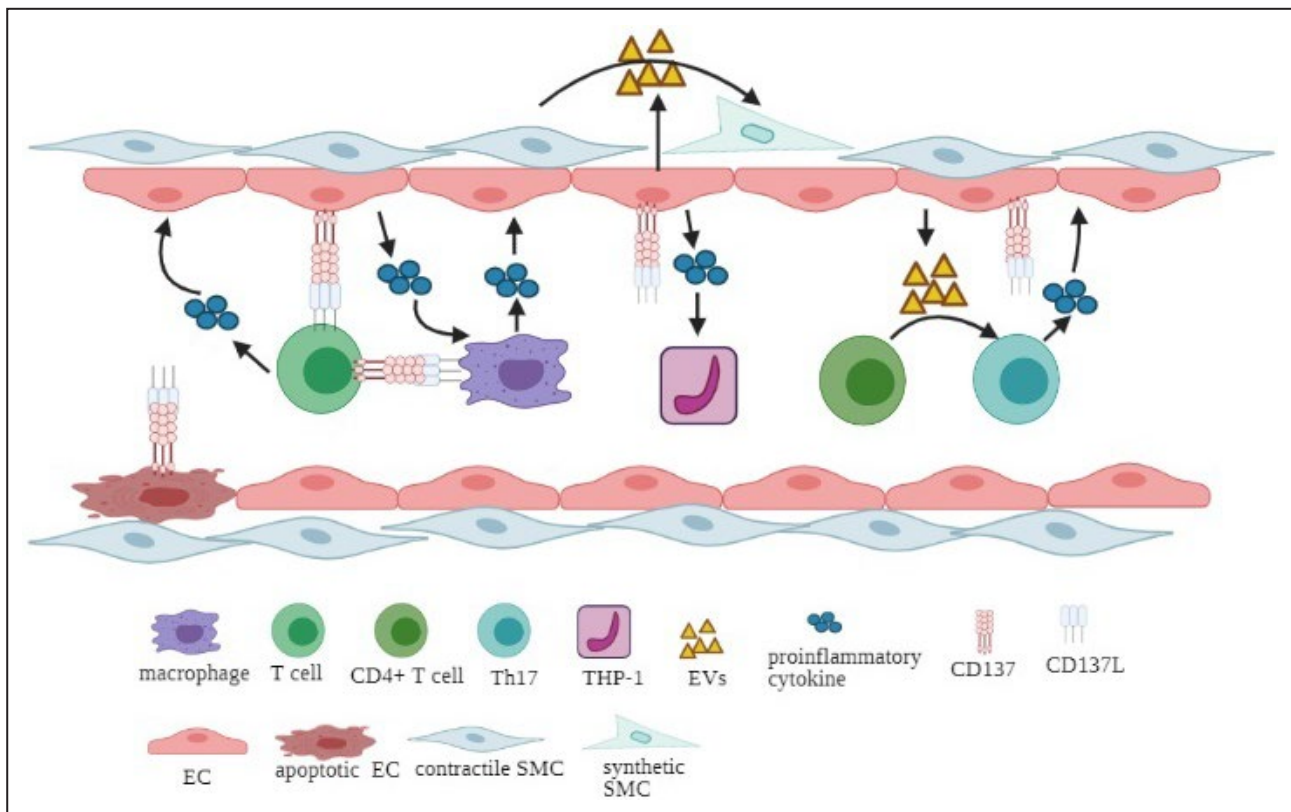


Figure 1. Activation of CD137 signaling in ECs helps recruit inflammatory cells, resulting in a positive feedback loop in inflammation.

Meanwhile, the activation of CD137 signaling by CD137L, a ligand of CD137, in ECs promotes the apoptosis of ECs. Furthermore, EVs released from activated ECs by CD137/CD137L mediate phenotypic transformation of SMCs and induce differentiation of CD4⁺ T cells into Th17 cells. ECs indicates endothelial cells; EVs, extracellular vesicles; and SMCs, smooth muscle cells.

cells is induced during inflammation by tumor necrosis factor- α , lipopolysaccharides, and IL-1 β . Activation of CD137 signaling with an agonistic mAb promotes the nuclear translocation of nuclear factor- κ B, which in turn increases the expression of vascular cell adhesion molecule-1 and chemokine (C-C motif) ligand 21.³⁹ It has been established that chemokine (C-C motif) ligand 21 is the lead chemokine mediating DC attraction from tissues to lymphatic nodes.⁴⁰ As a result, treatment with a CD137 agonistic antibody induces DC accumulation close to lymphatic vessels.³⁹ Interestingly, CD137 has not been detected in murine lymphatic endothelial cells in inflammatory experimental settings.³⁹ This is believed to be because of the different cross-species expression patterns of CD137, even in the same pathological setting. Collectively, these data suggest that CD137 induces inflammatory chemokines and adhesion molecules that participate in DC trafficking.

ROLE OF CD137 IN TUMOR ECS

Tumor cells are usually present in a complex environment comprising inflammatory immune cells, stromal cells, vascular ECs, cytokines, and chemokines. This

microenvironment is called the tumor microenvironment (TME).⁴¹ The evolution of vascular ECs to tumor ECs (TECs) is the result of shaping of the TME and plays a key role in tumor progression. TECs can recruit inflammatory cells into the TME.⁴² Immune cells have a natural antitumor effect at the beginning of tumor invasion, and they also abnormally transform to a protumor phenotype during tumor progression, assisting tumor immune escape and distant metastasis.⁴³ Hence, establishing an effective antitumor immune response is key to the success of antitumor therapy.

Immunohistochemical staining showed that CD137 is present in the blood vessels of most malignant tumors; in contrast, in vascular ECs in benign tumors and inflammatory lesions, the antigen was detected to a minor degree.⁴⁴ This suggests, on the one hand, that the expression of CD137 by ECs is inducible rather than constitutive and probably indicates the activation of these cells. The induction of CD137 expression on TECs may be a result of the lack of oxygen, such as in the TME.¹⁹ Upregulated surface CD137 in mouse ECs has been reported in the presence of hypoxia, whereas CD137 has been rarely demonstrated under normoxic culture conditions.⁴⁵ On the other hand, such variety of

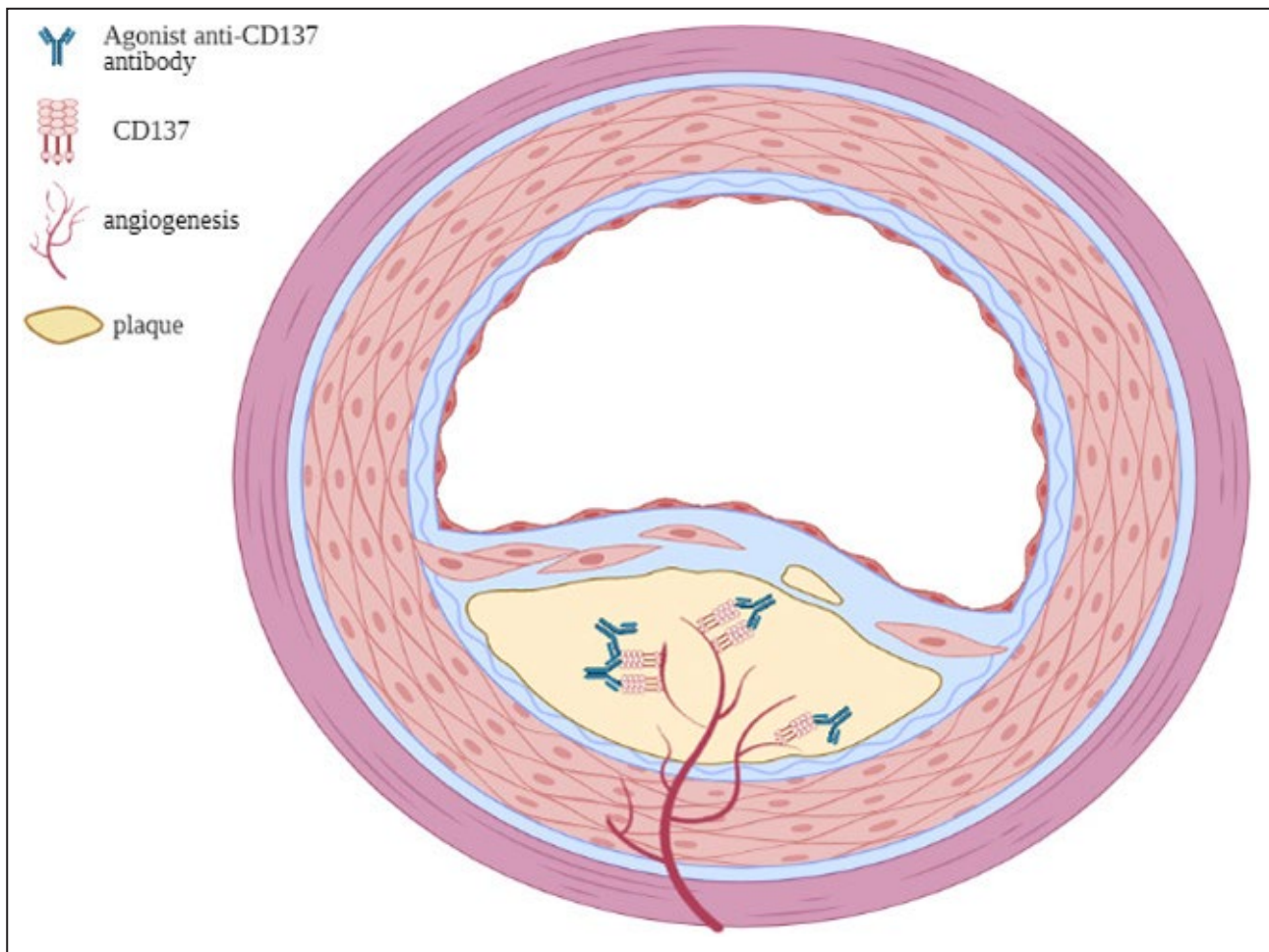


Figure 2. Activation of CD137 signaling by agonistic anti-CD137 antibodies promotes atherosclerotic angiogenesis.

expression patterns also depends on the types and developmental stages of cancer. Interestingly, CD137 has been found to be consistently positive in the capillaries and venules of normal lungs. In contrast, in vessels containing SMCs in media, ECs have been found to be generally negative.⁴⁶ It should be noted that the embryonic origins of ECs in pulmonary microvessels and large blood vessels are different.⁴⁷ Therefore, the expression of CD137 is likely to be dependent on regional factors from microenvironmental cues in the lung. Type I cell-mediated immune response is the main immune threat for malignant cells. Notably, the CD137/CD137L interaction is critical for potentiating type I immune responses for immune surveillance.⁴⁸ In the presence of CD137 on the surface of TECs, stimulation with agonist CD137 mAbs results in increased recruitment of CD8⁺ T cells into the malignant tissue via the upregulation of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin. In turn, such increase in T-cell recruitment into tumor sites via CD137 further enhances local inflammation by producing

more chemokines and proinflammatory cytokines.⁴⁵ Therefore, the aim of CD137 expression on ECs is to stimulate antigen-experienced T cells instead of priming naive T cells as professional antigen-presenting cells. However, as mentioned above, agonistic anti-CD137 antibodies may accelerate atherosclerosis in humans. Hence, to specifically provide costimulation to the TME, intratumorally injecting proper doses of the CD137 antibody may be a better option for the treatment of tumors. sCD137 can also be overexpressed in TECs. Release of sCD137 may serve to suppress T-cell activation by binding to CD137L and blocking the CD137/CD137L costimulatory system, thus reducing the immune activity against tumors.⁴⁹ Programmed death-ligand 1 is a molecule that binds to programmed death-1 to negatively regulate T-cell activation. It has also been reported that programmed death-ligand 1 is expressed by TECs that induce TEC tolerance in tumor-specific T cells.⁵⁰ Therefore, the mechanism underlying how an anti-CD137/programmed death-ligand 1 bispecific antibody changes an immunosuppressive

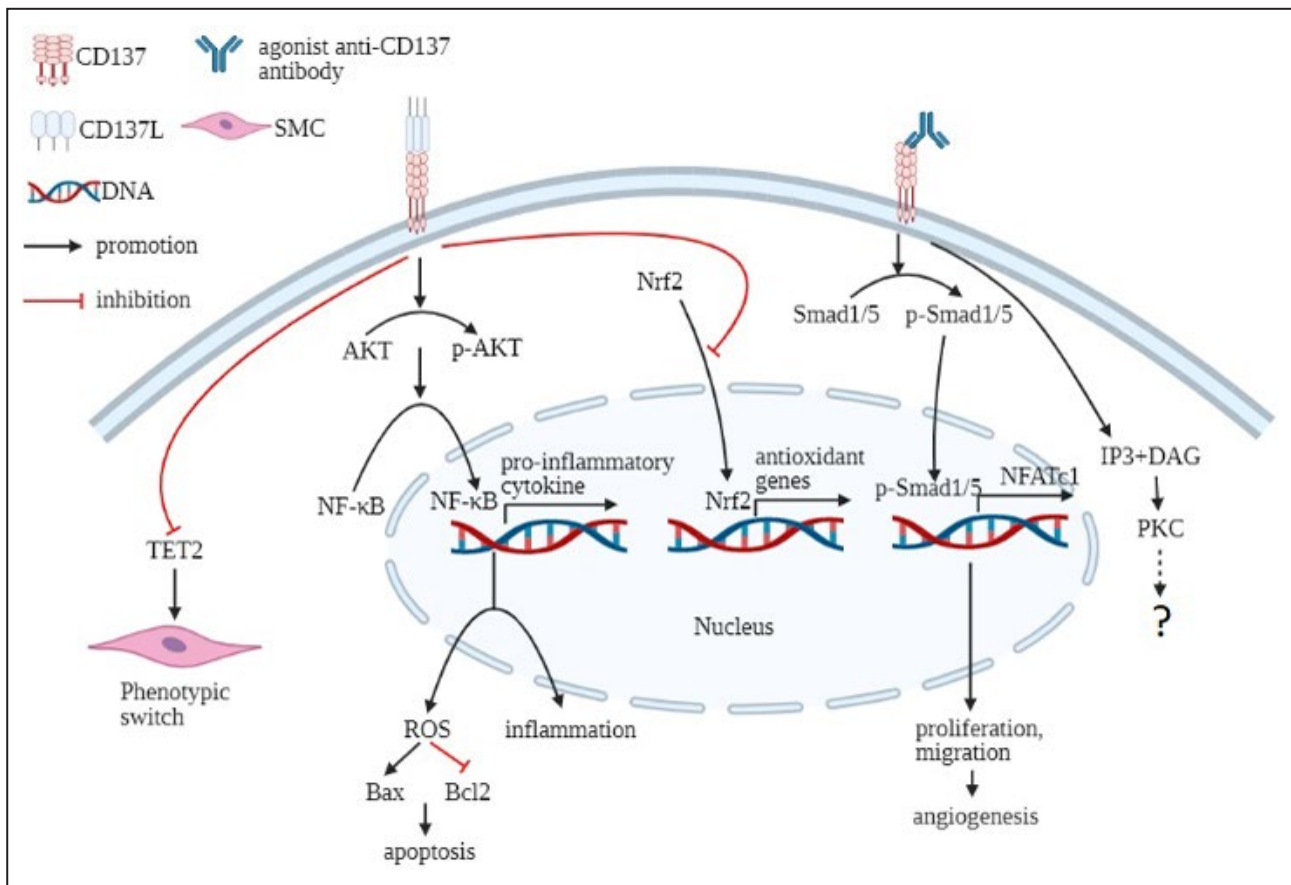


Figure 3. Molecular pathways linking the CD137 signaling pathway to ECs.

DAG indicates diacyl glycerol; ECs, endothelial cells; Nrf2, nuclear factor erythroid 2-related factor 2; PKC, protein kinase C; ROS, reactive oxygen species; SMCs, smooth muscle cells; and TET2, ten-eleven translocation methylcytosine dioxygenase 2.

TME into an immunostimulatory one may partially stem from its alteration of the immunological characteristics of TECs.⁵¹

It is important to selectively deliver antiangiogenic agents or vascular disrupting agents to tumor tissues while minimizing potential side effects. Hence, markers that can distinguish between physiological and pathological angiogenesis are urgently needed. It has been found that mouse CD137 is a prime candidate gene for distinguishing between physiological and pathological angiogenesis.⁴⁹ Selective expression of CD137 on TECs may allow the application of TEC-targeted immunotherapy for angiogenesis.⁴⁹ Antiangiogenic drugs have a positive effect on tumor immunity therapy. Immunization with DC-EC hybrids and CD137-specific mAbs can induce antiangiogenic immunity through the activation of self-antigen-selective immune responses by EC-specific CD8⁺ T and CD4⁺ lymphocytes, which result in the inhibition of B16-F10 melanoma and MC38 colon adenocarcinoma growth.⁵² Notably, Palazon et al found that anti-CD137 mAbs alone have no antiangiogenic effects *in vivo*.⁴⁵ These results highlight the need for combination therapies involving agonist-CD137

antibodies and other antibodies or vaccines/drugs/reagents.

In summary, CD137-mediated antitumor responses partially depend on the ability of TECs to increase T-cell recruitment into tumor sites and to target newly formed blood vessels. Moreover, CD137 is expressed not only in TECs, but also in immune cells. The therapeutic effects of CD137 signaling depend on the synergistic action of these cells.

CONCLUSION

The understanding of the molecular mechanisms of CD137 that affect EC behavior during specific pathophysiological stimuli has expanded remarkably in recent years. Studies on atherosclerosis, cancer, and vasculitis have greatly enriched our knowledge regarding the key aspects of CD137 in the endothelium, including inflammation, angiogenesis, and apoptosis. Despite the progress made, our understanding is still in its infancy as several aspects of CD137 expression and function remain to be elucidated. For instance, determining the role and effects of CD137 on ECs at all stages of atherosclerosis, identification of the active

components in EVs released from the activated ECs by CD137/CD137L signaling, determining the role of these EVs in SMCs, and the precise mechanisms of immunotherapy using agonistic anti-CD137 in a CD137-rich expression tumor microenvironment need further explorations.

Therapy targeted at CD137, whether via the activation or inhibition of this costimulatory system, depends on the disease setting. Given the varying mechanisms of vascular bed heterogeneity in different organs in health and disease, selective targeting of CD137 will prevent side effects of normal tissues. Hence, safer and more effective doses, drug delivery, and combinational therapy are currently a hotspot in clinical research.

ARTICLE INFORMATION

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Sources of Funding

This work was supported by the National Natural Science Foundation of China (81670405), Natural Science Foundation of Jiangsu Province (BK20181227), Social Development Foundation of Zhenjiang (SH2018043), Six Talent Peaks Project in Jiangsu Province (WSN-126), and Cardiovascular Disease Clinical Research Center of Zhenjiang (SS2018008).

Disclosures

None.

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