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CD40: Lord of the endothelial cell

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CD40, a membrane-associated receptor, is a key activator of immune and vascular cells. In this issue of Blood, Pluvinet and colleagues reveal new features of human endothelial cells activated through CD40 that include inflammatory, thrombotic, and innate immune effects.

CD40 has a rich history as a prominent immune cell activator. CD40 is best known as the key mediator of B lymphocyte immunoglobulin class switch. It also serves as a major activator of antigen-presenting cells, such as macrophages and dendritic cells. More recently, it was discovered that CD40 is expressed on many types of human cells including tissue structural cells, such as fibroblasts, epithelial cells, and endothelial cells. On these cells, like classic immune cells, CD40 also serves as a major mediator of cell activation. For example, on endothelial cells, engagement of CD40 incites the production of adhesion molecules, cytokines, chemokines, and inflammatory mediators important for wound healing.

The natural ligand for CD40 is called CD40 ligand (CD40L; officially termed CD154) and can be expressed, after activation, on the surface of several cell types, including T lymphocytes and platelets. There is much interest in endothelial cell activation by CD40 ligand due to the potential consequences of this event, such as atherosclerotic progression, chronic inflammation, and organ rejection. Previously, blocking CD40 ligand was a therapeutic target in certain inflammatory diseases and in organ rejection as a pathway to inducing immune tolerance. However, due to human platelet expression of CD40L, thromboembolic events occurred in early clinical trials, setting back CD40L as an immune system target. However, these unanticipated side effects resulted in CD40 being vigorously pursued as a means to attenuate unwanted endothelial and other cell activation.

In this issue of Blood, Pluvinet et al. focus on the down-stream events triggered by T-cell delivery of CD40L to several types of human endothelial cells. Two complementary approaches were used to find and validate the down-stream consequences of CD40 signaling in endothelial cells. First, they used a human T-cell line that highly expressed CD40L to activate CD40-bearing human endothelial cells. Using genome wide transcriptional profiling, they identified many new genes not thought to be regulated by the CD40-CD40L pathway. Some of these were further validated using other methods, such as Northern blotting, Western blotting, immunohistochemistry, and a preclinical animal model of organ rejection. A second strength of their approach was the use of RNAi to knock down expression of CD40 in endothelial cells, further proving the importance of CD40 as a master switch that sets in motion a host of coordinated events.

Their work on CD40 signaling revealed the rapid and global response of endothelial cells after activation by T cells, including coordinated kinase and transcription factor changes impacting on inflammation, cell motility, and vascular tone. Two major findings of particular interest are highlighted in their article. The first involves a vasoactive peptide called apelin, which was highly down-regulated in endothelial cells after CD40-CD40L interaction. Apelin appears to play an important role as a blood vessel dilator and may have cardioprotective effects. The authors also postulate that down-regulation of endothelial apelin in an inflamed transplanted kidney is a major factor in dysregulation of fluid homeostasis associated with renal transplant rejection. The second highlighted finding is that CD40-stimulated endothelial cells up-regulate viral genes involved in host defense against viruses. These genes include those involved in detecting viral interactions of activated T cells and endothelial cells via the CD40-CD40L pathway leads to endothelial cell activation. In addition to the known proinflammatory mediators induced by this pathway, many potential new targets were also identified. Also discovered were mediators of hemodynamic dysfunction and coordinated enhancement of innate antiviral defenses.
RNA, such as TLR3, and in further activation of endothelial cells by up-regulating the IFNγ receptor. IFNγ binding to its receptor up-regulates CD40 expression, constituting an amplification pathway. Also of interest was the finding that certain proteins that permit viral entry were down-regulated by CD40. These include CXCR4, a chemokine receptor important for HIV entry into cells. These coordinated events appear to amplify innate immunity via the T-cell arm of adaptive immunity.

The work of Pluvinet et al provides much new information on human endothelial cell activation by CD40. Many of the genes and pathways identified herein require further validation. Moreover, endothelial cells are increasingly recognized as being diverse and differ from organ to organ and even within a single organ.7 Endothelial cell activation via delivery of CD40L from T cells may differ from organ to organ and even within a single organ.7 Pathways identified herein require further clarification. Many of the genes and pathways identified herein require further validation. An important role for CD40 signaling in atherosclerosis has been described.8-10 The role of CD40 in the pathogenesis of atherosclerosis has been recently reviewed.11

**REFERENCES**


**Is more better in myeloma?**

Guido Tricot

Rosiñol and colleagues report the results of a Spanish PETHEMA trial in this issue of *Blood*. Their study was an attempt to address the role of additional intensive treatments for patients failing to achieve a complete or nearly complete remission after a single autologous transplantation.

In spite of major advances in treatment over the past decade, multiple myeloma still remains a largely incurable disease. This has led some investigators to abandon any attempt to achieve a cure and treat myeloma as if it were a chronic disease, mainly relying on the novel drugs such as bortezomib, thalidomide, and lenalidomide with or without conventional chemotherapy at low doses. Others have further increased treatment intensity by introducing a second autotransplantation or an initial autologous transplantation followed by a reduced-intensity allogeneic transplantation in an attempt to obtain long-term survival or cure. Which of these different approaches is superior is still a matter of intense debate, although physicians need to remember that long-term outcome data (> 7 years) are available for transplantation, but not for the newer drugs. The PETHEMA patients either received a second autograft (second autologous stem cell transplantation [ASCT]) or an allograft with a reduced-intensity conditioning regimen (allo-RIC). Because of the older age of most myeloma patients, full myeloablative allotransplants are seldom used anymore. As is typical for such studies, a biological randomization was applied. The authors found that allo-RIC in the PETHEMA patient population resulted in a higher complete remission (CR) rate and a trend toward a longer progression-free survival. However, this procedure was associated with a higher treatment-related mortality and no benefit was observed in terms of event-free and overall survival. This again highlights the problem of allotransplantation for myeloma. Benefit from an allotransplant requires a graft-versus-myeloma effect, which is only seen in patients who develop graft-versus-host disease (GVHD), especially chronic GVHD. GVHD is associated with a high procedure-related mortality, which remains unacceptably high in myeloma and tends to occur later with allo-RIC. Of note, in this study the CR rate with high-dose melphalan prior to the second ASCT, now considered the gold standard, was not different than with allo-RIC. The major shortcomings of the study are the small numbers of patients included in the allo-RIC arm and the absence of information on the genetic features of patients enrolled in the study. Because genetic characterization is by far the most important prognostic factor in myeloma, it is difficult to assess if the groups going onto the second ASCT versus the allo-RIC arm are really comparable. Even the outcome results with a second ASCT are difficult to assess because of different conditioning regimens applied to these patients. As the authors rightfully conclude, allotransplantation in myeloma should only be performed in the context of a clinical trial because of its high treatment-related mortality. In contrast, a second ASCT has a less than 2% procedure-related mortality. Ultimately, the best results might be obtained by autotransplantation followed by maintenance therapy with the newer drugs as suggested by the Intergroupe Francophone du Myelome (IFM) study with thalidomide, or even better, maintenance therapy with a combination of the newer drugs as suggested by the recently published and encouraging preliminary data on Total Therapy 3. With the latter approach, the expectation of a median survival of more than 10 years for newly diagnosed myeloma patients has become a reality. To achieve a cure, a better understanding of the genetic makeup of the drug-resistant myeloma cells persisting after transplantation will be required, whether those drug-resistant cells represent myeloma stem cells or not.

**REFERENCES**

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