Comment on Donners et al, page 4596

CD40/TRAFA6 switch in neointimal hyperplasia

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An article by Donner and colleagues in this issue of Blood describes a specific role for the CD40L/CD40/TRAFA6 signaling axis in neointima formation upon carotid injury. In this model, several key parameters of neointimal remodeling are demonstrated to be dependent on CD40 signaling through the TRAF6 binding site, but not the TRAF2,3,5 binding site.

CD40 receptor is a member of the TNF receptor family with a prominent role in the regulation of adaptive immune response. The receptor’s stimulation by specific CD40 ligand (CD40L) results in activation of macrophages, B cells, and dendritic cells. Vascular cells also express CD40, and stimulation by CD40L mediates inflammatory responses in the vascular wall. The 2 major signaling mediators downstream of CD40 are TRAF2 and TRAF6. Whereas TRAF2 function seems to be confined to the signaling of the TNF receptor family, TRAF6 seems to function more broadly as a mediator of IL-1 and Toll-like receptor signaling.1 TRAF2 and TRAF6 have distinct binding sites in the CD40 intracellular domain, structurally different from each other.

CD40/CD40L signaling appears to underlie a number of cardiovascular pathologies, and elevated levels of soluble CD40L have been shown to predict cardiovascular events. Previously published analyses of animal models have demonstrated opposing effects of CD40L knock-out (KO) on arteriosclerosis2 and acute collar-induced arterial injury.3

The study by Donner et al shows that, upon carotid ligation, neointima formation is substantially reduced in CD40 KO, which is attributed to bone marrow–dependent functions. Indeed, the study documents defective infiltration of CD40-null leukocytes to endothe-lium, which might result in reduced infiltration of inflammatory cells into the vessel wall. Analysis of the neointima of CD40−/− animals showed dramatic reduction in CD45-positive cells. Similar reduction is observed in animals expressing CD40 receptor with impaired TRAF6 binding site (CD40−T6), but not TRAF2 binding site (CD40−T2). These analyses conclusively demonstrate that CD40/TRAFA6 regulates infiltration of pro-inflammatory cells into the vessel wall and, consequently, neointima formation. Intriguingly, the effect of CD40L KO was minimal compared with CD40 KO, suggesting the possibility of an alternative CD40 ligand. CD40L interaction with αIIb/β3 integrins in thrombosis4 also complicates analysis while suggesting that the phenotypes of CD40L and CD40-null mice are not completely identical.

The intriguing novelty of the study by Donner and colleagues lies in its demonstration of a functional dichotomy downstream of CD40. In CD40L and CD40 KO animals, as well as in the case of CD40-T6 mutants, carotid ligation leads to reduced leukocytes infiltration, vessel restructuring, and metalloproteinase activity. However, CD40 mutation with an impaired TRAF2,3,5 binding site (CD40-T2) has no such effect.

REFERENCE

Comment on Gowda et al, page 4723

IL-21 as new therapy for CLL?

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Based on observations that IL-21 stimulates apoptosis in CLL cells (see figure) and additively enhances the cytotoxicity of fludarabine or rituximab, Gowda and colleagues propose the introduction of IL-21 in combination therapy with fludarabine and rituximab.

Chronic lymphocytic leukemia (CLL) is still considered an incurable disease, despite recent progress due to the development of agents such as fludarabine and antibodies (rituximab, alemtuzumab); thus, additional therapeutic approaches are highly desired.

IL-21 triggers the antibody–dependent cellular cytotoxicity (ADCC) exerted by natural killer (NK) cells on rituximab–coated syngeneic or allogeneic CLL cells in all patients, including those resistant to apoptosis induction by IL-21. IL-21 appears, therefore, more interesting than other NK–stimulatory cytokines, such as IL-2 and IL-12, that present the disadvantage of simultaneously favoring the proliferation of CLL cells and/or preventing...
KSHV LANA’s expanding bag of tricks

Andrew J. Barbera and Kenneth M. Kaye

In this issue of Blood, Di Bartolo and colleagues report that KSHV targets the TGF-β signaling pathway in latently infected tumor cells.

Kaposi sarcoma–associated herpesvirus (KSHV) infection has a causative role in Kaposi sarcoma (KS), primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD). In tumor cells, the virus predominantly exists in a latent state in which the viral genome is maintained as a multicopy episome (or episome). Latently infected cells express only several of the virus’s approximately 100 genes. These few genes exert critical effects on the host cell that deregulate its growth.

The KSHV latency-associated nuclear antigen (LANA) is the predominant viral antigen expressed during latent infection. Several key functions have been attributed to LANA. A critical obstacle that an episomal virus (which is not integrated into cell chromosomes) must overcome is to maintain its genetic material in proliferating cells. LANA fills this void by ensuring that the KSHV genome is replicated during each cell cycle. LANA then tethers newly replicated KSHV genomes to mitotic chromosomes, thereby using a “piggyback” mechanism to ensure KSHV DNA distribution to daughter–cell nuclei.

In addition to its role in genome maintenance, LANA also exerts effects on transcription and cell growth. Tumor viruses such as KSHV often directly deregulate critical cell-growth pathways, rather than relying on the
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