C3b as a ligand and have defects referable to complement regulation of APCs and B cells in addition to T cells. Notwithstanding the systemic nature of their defect, the observation of vaccine-specific antibody responses in which the Th2 cell-dependent isotypes (human immunoglobulin G4 [IgG4] and IgE) were most diminished (Pekkarinen et al., 2015) suggests that analyses of the functional subsets of circulating Tfh or memory Tfh cells in people with mutated CD46 will be important. CD46 phenotypes run the gamut from normal health in the absence of CD46 expression to atypical hemolytic uremic syndrome to some patients with common variable immunodeficiency. Yet more broadly, then, understanding why the spectrum of perturbations in adaptive immunity of CD46-mutated people is so broad offers the possibility of important insights into the modifiers of phenotype in vivo and human susceptibility to disease.

REFERENCES

Kolev, M., Dimeloe, S., Le Friec, G., Navarini, A., Arbore, G., Povoleri, G.A., Fischer, M., Belle, R., Loeliger, J., Razik, L., et al. (2015). Immunity *42*, this issue, 1033–1047.

Kwan, W.H., van der Touw, W., Paz-Artal, E., Li, M.O., and Heeger, P.S. (2013). J. Exp. Med. *210*, 257–268.

Lajoie, S., and Wills-Karp, M. (2013). Immunity *39*, 1000–1002.

Lee, K., Gudapati, P., Dragovic, S., Spencer, C., Joyce, S., Killeen, N., Magnuson, M.A., and Boothby, M. (2010). Immunity *32*, 743–753.

Pekkarinen, P.T., Heikkilä, N., Kisand, K., Peterson, P., Botto, M., Daha, M.R., Drouet, C., Isaac, L., Helminen, M., Haahtela, T., et al. (2015). Eur. J. Immunol. *45*, 915–921.

Ricklin, D., Hajishengallis, G., Yang, K., and Lambris, J.D. (2010). Nat. Immunol. *11*, 785–797.

Strainic, M.G., Liu, J., Huang, D., An, F., Lalli, P.N., Muqim, N., Shapiro, V.S., Dubyak, G.R., Heeger, P.S., and Medof, M.E. (2008). Immunity *28*, 425–435.

Truscott, S.M., Abate, G., Price, J.D., Kemper, C., Atkinson, J.P., and Hoft, D.F. (2010). Infect. Immun. *78*, 5295–5306.

Yang, K., Shrestha, S., Zeng, H., Karmaus, P.W., Neale, G., Vogel, P., Guertin, D.A., Lamb, R.F., and Chi, H. (2013). Immunity *39*, 1043–1056.

Zeng, H., Yang, K., Cloer, C., Neale, G., Vogel, P., and Chi, H. (2013). Nature *499*, 485–490.

HGF Guides T Cells into the Heart

Dennis Wolf,[1] Jie Li,[1] and Klaus Ley[1,*]
[1]Division of Inflammation Biology, La Jolla Institute for Allergy and Immunology, La Jolla, CA 92037, USA
*Correspondence: klaus@liai.org
http://dx.doi.org/10.1016/j.immuni.2015.06.001

Expression of distinct homing receptors guides adaptive immune cells to antigen-rich tissue. In this issue of *Immunity*, Komarowska et al. (2015) describe an autocrine loop that is initiated by cardiac-expressed hepatocyte growth factor to direct T cells into the heart during inflammation and cardiac transplant rejection.

T cells are the main determinants of adaptive immunity. Their presence in target tissue is regulated by the expression of distinct sets of adhesion and chemokine receptors and required to fulfill their immunological function. Naive and effector/memory T cells are distinguishable by their adhesion factor signatures: naive T cells can home only to lymph nodes (via CCR7, L-selectin, and the integrin LFA-1), whereas antigen-experienced T cells can travel to almost any tissue via many chemokine receptors and adhesion molecules (Ley, 2014; Mora and von Andrian, 2006). In order to return to the tissue where the antigen is present, there must be tissue tropism to allow a site-directed action of adaptive immunity. This is best documented for homing to the skin and the gastrointestinal tract. Migration of primed T effector/memory cells to skin involves the chemokine receptors CCR4, CCR10, and CCR8 (McCully et al., 2012). T cells activated in the mesenteric lymph nodes display higher expression of CCR9 and $\alpha_4\beta_7$ integrin (Zabel et al., 1999), which allows their subsequent homing to the gut. Beyond these findings, it has been challenging to identify unique tissue-homing signatures. For instance, T cell accumulation in atherosclerosis has been proposed to be dependent on a variety of chemokines, including CCR5, CCR7, CXCR3, and CXCL10 among others, but observations mainly stem from global knock-out mouse models. Because these chemokine receptors are also expressed on other immune cells, such as dendritic or myeloid cells, their specific role in T cell homing remains unclear (Li and Ley, 2015).

If adhesion and chemokine receptors are indeed executing T cell homing, then what are the mechanisms imprinting T cells initially to recall the origin of the antigen exposure? Do tissue-derived factors induce specific sets of adhesion factors on T cells? In this issue of *Immunity*, Komarowska et al. (2015) set out to address this experimentally, by investigating the role of hepatocyte growth factor (HGF) in T cell homing to the heart. Although it has been proposed previously that the chemokine receptors CXCR3 (and its ligand CXCL10) as well as CCR4 are contributing to T cell accumulation during heart transplantation (Hancock et al., 2001; Hüser et al., 2005), it was unknown how the myocardium

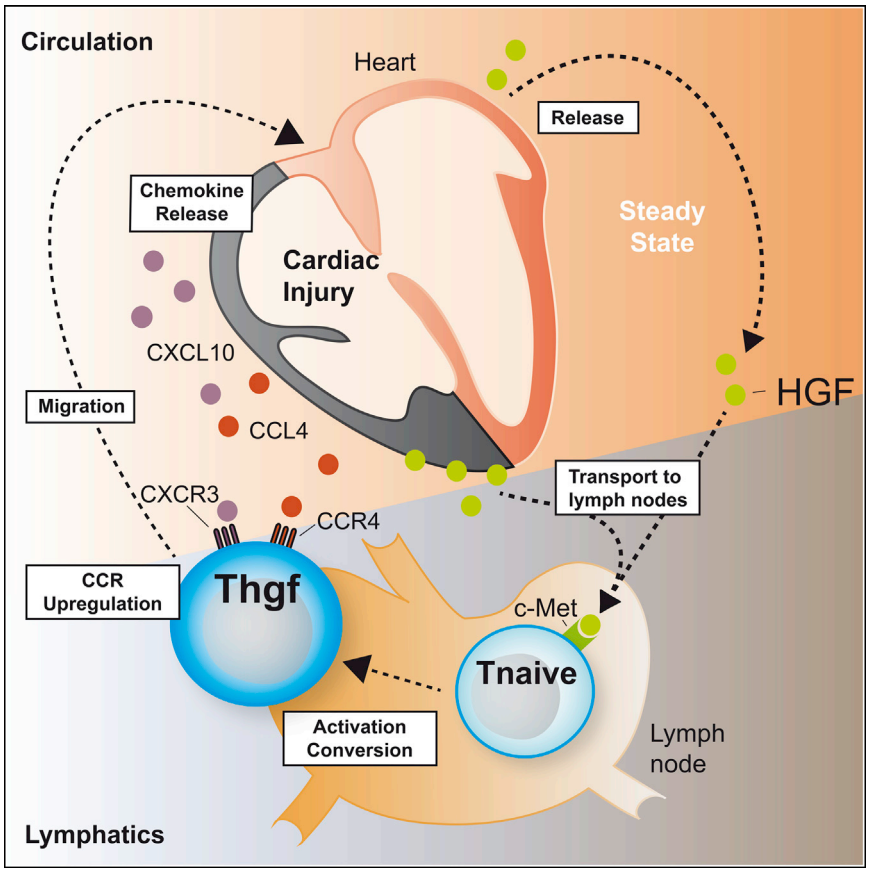

Figure 1. HGF's Proposed Mechanism in T Cell Cardiotropism
Hepatocyte growth factor (HGF) is expressed by healthy heart tissue and transported to lymph nodes, possibly by dendritic cells or passively. Binding to its receptor c-Met on naive T cells (Tnt) induces signaling by Akt-STAT3-dependent pathways, resulting in higher expression of c-Met itself and of the chemokine receptors CXCR3 and CCR4. Under inflammatory conditions, cardiac tissue releases higher levels of the chemokines CXCL10 and CCL4, which serve as signal for HGF-primed T (Thgf) cells to home to the heart. Also, injured cardiac tissue releases more HGF, which in turn might retain T cells in close proximity by increasing chemokine receptor expression on recruited T cells. This mechanism might further be supported by enhanced expression of some chemokines by Thgf, including CCL3-5, 17, and 22 (not depicted).

imprints cardiotropism during priming and differentiation of heart-specific T cells and whether such imprinting would take place in inflamed tissue or the draining lymph nodes. Findings from Komarowska et al. (2015) suggest that HGF might be a master regulator of T cell cardiotropism.

The centerpiece of Komarowska et al. (2015)'s study is a series of in vitro and in vivo experiments, in which a 7-day treatment with HGF in parallel with strong induction of TCR signaling via anti-CD3 and anti-CD28 stimulation enhanced responsiveness to the chemokines CXCL10 and CCL22 in migration assays in vitro, as well as directing cells to the peritoneal cavity in mice. These effects were dependent on binding of HGF to its receptor c-Met and induction of an intracellular signaling cascade involving Akt and STAT3 engagement. In part, c-Met ligation increases responsiveness to the canonical G protein-coupled (GPCR) chemokine receptor family pathways, which include the chemokine receptors CCR4 and CXCR3, which bind CCL22 and CXCL10, respectively. That these pathways are relevant is supported by a loss of HGF's migratory effects after treatment with pertussis toxin, a potent inhibitor of Gαi-dependent chemokine receptor signaling. However, the authors surprisingly found that HGF-stimulated T cells did not respond to CCL5, even though its receptor CCR5 is expressed. Instead, HGF induced secretion of several chemokines, including CCL3, CCL4, CCL5, CCL17, and CCL22, and increased expression of the chemokine receptors CCR4 and CXCR3. The authors conclude that this mechanism represents an autocrine loop, by which T cells—once primed by HGF—stimulate both receptors and their ligands to re-direct T cells to target tissue.

Notably, HGF was not sufficient to alter chemokine expression in T cells in an immediate fashion. Instead, only a prolonged and constant exposure during 7 days in vitro resulted in upregulation of the HGF receptor c-Met and increased susceptibility to HGF. Naive T cells expressed much lower amounts of c-Met than activated T effector/memory cells. The authors found that HGF is expressed in cardiac tissue—presumably by cardiomyocytes, although the exact cellular source was not tested—but only after a strong inflammatory stimulus such as LPS and not under steady-state conditions. In line with the author's hypothesis, adoptively transferred T cells that were primed in vitro with HGF for 7 days homed preferentially to the heart. An additional set of experiments, in which the relative contribution of the homing receptors CXCR3, CCR4, and CCR5 was tested in knock-out mice, revealed that these receptors acted synergistically to direct adoptively transferred T cells to the heart. Finally, the authors demonstrated clinical relevance by showing that treatment with the c-Met inhibitor PHA-665752 protected mice from cardiac allograft rejection, but not from skin allograft rejection—a finding that further supports a tissue-specific role of the proposed mechanism in disease. This was confirmed in a sophisticated human heart xenograft model, where human heart biopsies were transplanted into *scid* mice followed by injection of human HGF-treated T cells. Confirming the mouse work, HGF-primed T cells homed preferentially to the heart, proposing that these new findings might also be relevant in humans.

A somewhat unanswered question in the work from Komarowska et al. (2015) is how the HGF-c-Met axis contributes to sequential T cell priming and recall events in cardiac immunity. The authors propose that cardiac HGF might be transported to draining lymph nodes and deposited in close proximity of endothelial and dendritic cells—supported by

HGF co-localization with the endothelial marker CD31 and the dendritic cell marker CD11c by microscopy. It is possible that dendritic cells take up HGF and travel from the myocardium to lymph nodes, but this was not formally tested. The authors argue that T cells interacting with HGF in lymph nodes will be primed for a cardiotropic chemokine-receptor signature during simultaneous antigen presentation and co-stimulation (Figure 1). It is indeed plausible that expression of cardiotropic chemokine receptors might guide T cells into the heart. However, what is the role of enhanced chemokine secretion by T cells in response to HGF? Is this an autocrine loop that keeps primed T cells in the lymph node for some time or do HGF-treated cells exhaust after prolonged HGF treatment and stop chemokine secretion? The authors did not test different durations of HGF stimulation followed by an absence of HGF to clarify this. Thus, it is possible that HGF deposition in the injured myocardium might induce the relevant chemokines that serve as direct homing signals. In the latter case, increased chemokine and chemokine receptor expression by T cells themselves would help to retain T cells in the myocardium. Indeed, some observations support the idea that full differentiation into functional T effector/memory cells might require antigen presentation and second activation in non-lymphoid tissue (Ley, 2014). HGF might be a co-factor required for such tissue-specific activation and retention in the heart.

Beyond the findings presented in the current study, some remaining questions will have to be answered in the future. First, this study required anti-CD3 and anti-CD28 stimulation to exert HGF's activating effects on T cells, which raises the question whether weaker TCR-signaling events, as would be expected from natural antigen stimulation by APCs, would induce the same cardiotropic signatures in vivo. Second, the authors find that besides CCR5, both CCR4 and CXCR3 are required for T cell homing. This is unexpected, because T helper (Th) cell lineage commitment typically results in modified chemokine receptor expression, defining CXCR3 as landmark of Th1 and CCR4 of Th2 cell polarization (Sallusto et al., 1998).

Taken together, the results presented by Komarowska et al. (2015) introduce a new paradigm for cardiac T cell tropism. In addition, the data are exciting because they raise the potential to alter tissue-tropism of T cells that might modulate T cell-mediated pathology in the heart—and relevant therapeutic compounds are already available.

REFERENCES

Hancock, W.W., Gao, W., Csizmadia, V., Faia, K.L., Shemmeri, N., and Luster, A.D. (2001). J. Exp. Med. *193*, 975–980.

Hüser, N., Tertilt, C., Gerauer, K., Maier, S., Traeger, T., Assfalg, V., Reiter, R., Heidecke, C.D., and Pfeffer, K. (2005). Eur. J. Immunol. *35*, 128–138.

Komarowska, I., Coe, D., Wang, G., Haas, R., Mauro, C., Kishore, M., Cooper, D., Nadkarni, S., Fu, H., Steinbruchel, D.A., et al. (2015). Immunity *42*, this issue, 1087–1099.

Ley, K. (2014). F1000Res. *3*, 37.

Li, J., and Ley, K. (2015). Arterioscler. Thromb. Vasc. Biol. *35*, 40–49.

McCully, M.L., Ladell, K., Hakobyan, S., Mansel, R.E., Price, D.A., and Moser, B. (2012). Blood *120*, 4591–4598.

Mora, J.R., and von Andrian, U.H. (2006). Trends Immunol. *27*, 235–243.

Sallusto, F., Lenig, D., Mackay, C.R., and Lanzavecchia, A. (1998). J. Exp. Med. *187*, 875–883.

Zabel, B.A., Agace, W.W., Campbell, J.J., Heath, H.M., Parent, D., Roberts, A.I., Ebert, E.C., Kassam, N., Qin, S., Zovko, M., et al. (1999). J. Exp. Med. *190*, 1241–1256.

Another TLO in the Wall: Education and Control of T Cells in Atherosclerotic Arteries

Lucas Onder[1] and Burkhard Ludewig[1,*]
[1]Institute of Immunobiology, Kantonsspital St. Gallen, St. Gallen 9007, Switzerland
*Correspondence: burkhard.ludewig@kssg.ch
http://dx.doi.org/10.1016/j.immuni.2015.05.022

Atherosclerosis is a lipid-storage disease of arteries that is exacerbated by chronic inflammatory processes. In this issue of *Immunity*, Hu et al. (2015) demonstrate that T cell responses in atherosclerotic lesions are controlled in tertiary lymphoid organs in the arterial wall.

Atherosclerosis is a multifactorial cardiovascular disease that is characterized by elevated lipid amounts in the blood and deposition of lipids in and subsequent chronic inflammation of the arterial wall. The immune system already detects small changes in the integrity of the blood vessel wall and reacts with macrophage and T cell infiltration into early subendothelial "fatty streaks" (Hansson and Hermansson, 2011). With progressive deposition of low-density cholesterol and formation of cholesterol crystals, more immune cells infiltrate the vascular lesion, leading to enhanced production of collagens and fibrotic remodeling of the atherosclerotic plaque. Uncontrolled growth and destabilization of