Title
Lipid Metabolites

Journal
Transplantation, 102(6)

ISSN
0041-1337

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Publication Date
2018-06-01

DOI
10.1097/tp.0000000000002206

Peer reviewed

This article emphasizes on the importance of sex on graft immunogenicity and alloimmune responses. Both genetic aspects and hormonal levels appear to drive those processes. It will be exciting to see more research in this area to potentially refine clinical treatments. Moreover, an improved understanding will allow assessing a potential impact of sex disparities in organ allocation.

Selective Targeting of Engineered T Cells Using Orthogonal IL-2 Cytokine-receptor Complexes

Sockolosky JT, Trotta E, Parisi G, et al. *Science*. 2018; 359(6379):1037–1042.

Adoptive transfer of tumor-reactive T cells may inducing clinical antitumor immunity. However, producing sufficient quantities of cells that remain effective after transfer continues to be a challenge. Interleukin-2 (IL-2) improves survival of tumor-reactive T cells. Notably, IL-2 causes both stimulatory and suppressive T-cell responses and can be toxic based on the activity of the IL-2 receptor (IL-2R). It is therefore conceivable that the balance between natural IL-2R and host responses will limit toxicities. Thus, there may be a potential advantage if IL-2 can be precisely targeted to a specific cell type of interest.

In their recent publication in *Science*, the authors present a mouse model in which the IL-2R was modified so that T cells could only react with a specific mutant IL-2 cytokine, called *ortho*IL-2. This substance played a potent role as a proliferative cytokine, capable of activating cytotoxic T-cell function and T-cell inflammatory pathways, but was nontoxic at all doses evaluated.

The differential activity of *ortho*IL-2 on both T-cell expansion and function may be due to an increased bioavailability of *ortho*IL-2 for T cells. Furthermore, alternative host factors influenced by IL-2 (but not *ortho*IL-2) may influence the function of transplanted T cells.

An example of this is the effect of IL-2 and *ortho*IL-2 treatment on host CD4+ and CD8+ T cells. Interferon gamma, as well as several other inflammatory cytokines, is increased by IL-2, but not by *ortho*IL-2 treatment. This ability to decouple direct IL-2 activity on transplanted T cells from indirect host bystander effects may have important therapeutic implications to specifically enrich transduced T cells and reduce toxic effects of IL-2. Those observations may also be of relevance for tolerance protocols in organ transplantation.

Game Changer

Lipid Metabolites: The Alarm Signal to Trigger Liver Ischemia-reperfusion Injury

Bibo Ke, MD, PhD[1] and Jerzy W. Kupiec-Weglinski, MD, PhD[1]

Hepatic dysfunction or failure caused by ischemia-reperfusion injury (IRI) remains a major unresolved clinical problem affecting outcomes after orthotopic liver transplantation while representing a key obstacle to expanding the donor pool. Several factors have been implicated in the pathophysiology of hepatic IRI, including anaerobic metabolism, changes in mitochondrial membrane permeability, intracellular calcium overloading, adenosine triphosphate (ATP) depletion, oxidative stress/reactive oxygen species (ROS) generation, liver Kupffer cell and neutrophil activation as well as cytokine and chemokine release.[1] *ROS* produced by activated Kupffer cells are key molecules in the progression of local *inflammation* in the early phase of hepatic IRI that cause direct tissue injury and subsequent hepatocellular death. Moreover, ROS initiate the release of endogenous mediators known as damage-associated molecular patterns (DAMPs) activating innate immunity and *inflammatory* responses.[1] Subsequently, signaling pathways triggered by DAMPs recruit circulating macrophages and dendritic cells to ischemic livers. Innate immune cells, in turn, secrete inflammatory cytokines (eg, IL-6 and TNF-α) that activate key players of the adaptive immune response, including T cells exacerbating hepatocellular damage.

Received 31 January 2018. Revision 5 February 2018.

Accepted 6 February 2018.

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The authors declare no funding or conflicts of interest.

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ISSN: 0041-1337/18/10206-0887

DOI: 10.1097/TP.0000000000002206

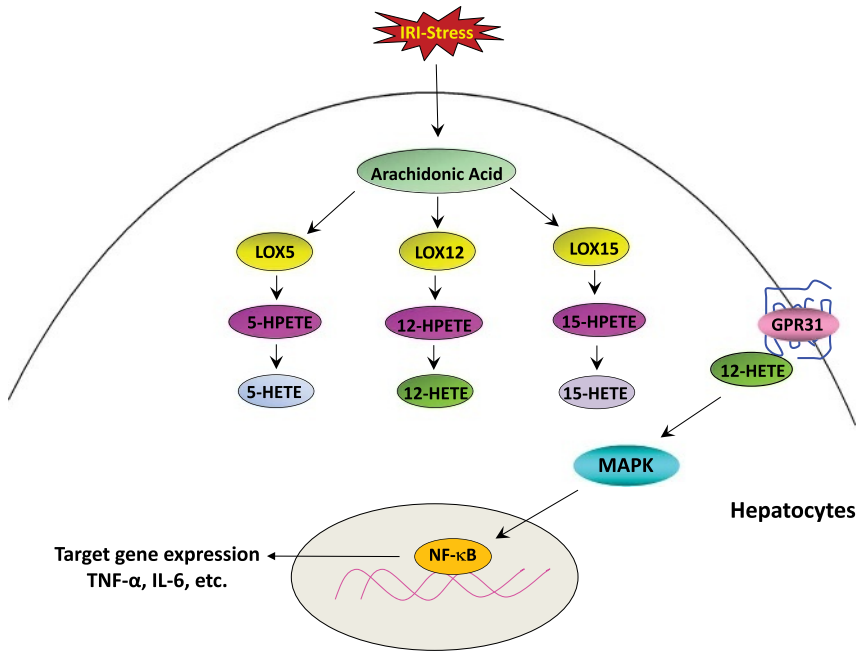

FIGURE 1. Schematic illustration of crosstalk between arachidonic acid metabolism and inflammation. LOXs catalyze the oxygenation of arachidonic acid and are classified as LOX5, LOX12, and LOX15 per the oxygenation sites in arachidonic acid as a substrate. All LOX isoforms generate the lipid primary product hydroperoxides (HPETEs). LOX5 metabolizes arachidonic acid to 5-HPETE, which is converted to 5-HETE and leukotrienes. LOX12 metabolizes arachidonic acid to 12-HPETE, which is further converted to 12-HETE or to various hepoxilins. LOX15 metabolizes arachidonic acid principally to 15-HPETE, subsequently converted to 15-HETE. In IR-stressed hepatocytes, 12-HETE can directly bind to G-protein coupled receptor GPR31 to activate MAPK pathway, which results in activation of NF-κB target genes to trigger liver inflammation. 12-HPETE, 12-hydroperoxyeiocsatetraeoic acid; 5-HPETE, 5-hydroperoxy-eicostetraeoic acid.

Previous studies have probed mechanisms through which DAMPs recognize Toll-like receptors, receptors for advanced glycation end-products, nucleotide-binding oligomerization domain-like receptors, retonic acid inducible gene-I-like receptors, C-type lectin receptors, and DNA sensors.[1] Clearly, signaling cascades contributing to IR-induced hepatocellular damage are diverse and complex.

A recent study by Zhang and coworkers[2] provides novel view on mechanisms that drive IRI by showing that lipid metabolic signaling may play a key role in triggering IRI-induced hepatocellular damage. The authors found that activation of the arachidonate 12-lipoxygenase (ALOX12)-12-hydroxyeicosatetraenoic acid (12-HETE)-G-protein-coupled receptor 31 (GPR31) pathway was instrumental in IRI-induced liver injury. Lipoxygenases (LOXs) are essential for *arachidonic acid* (AA) metabolism in both humans and animals. Humans express 5, 12 (platelet-type and leukocyte-type), and 15-lipoxygenase (LOX5, LOX12, and LOX15), whereas mice only express the leukocyte-type LOX12 that is functionally closest to human LOX15.[3] These different LOXs have significant species-specific variations in their downstream products (Figure 1). The leukocyte-type arachidonate LOX12 (ALOX12) catalyzes the oxygenation of cellular arachidonic acid to 12-HETE.[3] Indeed, under inflammatory conditions, arachidonic acid can be released from the cell membrane in response to various cytokines.[4] Although it has been reported that ALOX12 and its metabolic mediator 12-HETE generated by murine macrophages may play an anti-inflammatory role in some disease models,[5,6] more recent evidence shows that 12-HETE activates immune cells to orchestrate a local inflammatory response resulting in tissue injury.[7] Taken together, data available until now indicate that the ALOX12-12-HETE pathway is pivotal for innate immune-driven inflammatory responses.

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In their *Nature Medicine* publication, Zhang and coworkers[2] used an unbiased integrative "omics" approach showing that ALOX12 and its metabolite 12-HETE contributed to hepatocellular damage during the ischemia stage. Inhibiting 12-HETE production mitigated IRI-induced liver damage in mice, pigs, and nonhuman primates. Moreover, the authors demonstrated that ALOX12-mediated 12-HETE triggered IRI-induced liver inflammation by directly binding to *G-protein coupled receptor* 31 (GPR31). These data suggest that the ALOX12-12-HETE-GPR31 axis is required for hepatic IRI. To confirm their findings, the authors used ALOX12-deficient and hepatocyte-specific ALOX12 transgenic mice and found that ALOX12 deficiency induced hepatocellular necrosis, inflammatory cell accumulation, and inflammatory cytokine/chemokine production. In contrast, ALOX12 overexpression in hepatocyte-specific transgenic mice exacerbated hepatocellular damage and inflammatory responses in IRI-stressed livers. Interestingly, deficiency of ALOX12 diminished 12-HETE levels, whereas augmented ALOX12 expression promoted 12-HETE production both in vitro and in vivo. Furthermore, blocking 12-HETE production

ameliorated hepatic IRI and inflammatory responses, demonstrating the potential pathogenic role of ALOX12-12-HETE signaling in IRI.

Zhang and coworkers also showed that ALOX12-12-HETE–mediated liver inflammation through cell signaling metabolite GPR31 expressed on inflammatory cells leading to the synthesis and secretion of inflammatory cytokines and chemokines.[8] Although many G protein–coupled receptors can serve as receptors for lipid metabolites, Zhang et al identified GPR31 as a key receptor for 12-HETE triggering liver IRI.

Hypoxia can directly activate Kupffer cells that are a major source of ROS produced during the early postischemic period. Moreover, ROS generated by neutrophils contribute additionally to oxidative stress. Indeed. macrophages and neutrophils have been identified as key-players in hepatic IRI. Myeloid specific ALOX12-deficient mice may thus be useful for dissecting the mechanistic crosstalk between ALOX12 and ROS signaling pathways. The authors also demonstrated that treatment of primary hepatocytes with 12-HETE activated NF-κB and mitogen-activated protein kinase (MAPK) signaling, whereas inhibition of 12-HETE diminished NF-κB/MAPK activation and inflammatory programs initiated by IRI. However, potentially protective antiapoptotic survival factors produced by hepatocyte NF-κB and JNK need to be considered as well.[9] As both NF-κB and JNK not only prevent apoptosis but also promote inflammatory response,[10] the cellular location of NF-κB/JNK activity appears critical.

Of note, the interesting preclinical data by Zhang may not have direct clinical application. The leukocyte-type LOX12, found in mice, rats, cows, and pigs but not humans, shares 73% to 86% amino acid with human ALOX15, but only 57% to 66% with human platelet-type ALOX12.[3] Nevertheless, the data by Zhang provide novel and fascinating links between metabolism, inflammation, and hepatic IRI that will hopefully translate into much needed novel clinical applications.

REFERENCES

1. Zhai Y, Busuttil RW, Kupiec-Weglinski JW. Liver ischemia and reperfusion injury: new insights into mechanisms of innate-adaptive immune-mediated tissue inflammation. *Am J Transplant*. 2011;11:1563–1569.
2. Zhang XJ, Cheng X, Yan ZZ, et al. An ALOX12-12-HETE-GPR31 signaling axis is a key mediator of hepatic ischemia-reperfusion injury. *Nat Med*. 2018;24:73–83.
3. Yamamoto S, Suzuki H, Ueda N. Arachidonate 12-lipoxygenases. *Prog Lipid Res*. 1997;36:23–41.
4. Lambeau G, Gelb MH. Biochemistry and physiology of mammalian secreted phospholipases A2. *Annu Rev Biochem*. 2008;77:495–520.
5. Morgan AH, Dioszeghy V, Maskrey BH, et al. Phosphatidylethanolamine-esterified eicosanoids in the mouse: tissue localization and inflammation-dependent formation in Th-2 disease. *J Biol Chem*. 2009;284:21185–21191.
6. Dioszeghy V, Rosas M, Maskrey BH, et al. 12/15-Lipoxygenase regulates the inflammatory response to bacterial products in vivo. *J Immunol*. 2008;181:6514–6524.
7. Dobrian AD, Lieb DC, Cole BK, et al. Functional and pathological roles of the 12- and 15-lipoxygenases. *Prog Lipid Res*. 2011;50:115–131.
8. Sun L, Ye RD. Role of G protein-coupled receptors in inflammation. *Acta Pharmacol Sin*. 2012;33:342–350.
9. Papa S, Bubici C, Zazzeroni F, et al. Mechanisms of liver disease: cross-talk between the NF-kappaB and JNK pathways. *Biol Chem*. 2009;390:965–976.
10. Han MS, Barrett T, Brehm MA, et al. Inflammation mediated by JNK in myeloid cells promotes the development of hepatitis and hepatocellular carcinoma. *Cell Rep*. 2016;15:19–26.

People in Transplantation

Mehmet Haberal, MD: Transplant Pioneer, Entrepreneur, President-elect, The Transplantation Society

You were born in Pazar, a small town on the coast of the black sea in the east of Turkey. What shaped you during your early years and what motivated you to start a career in Medicine?

MH: I spent most of my elementary school years in a small school in the village. In my final year of elementary school, my family moved to Zonguldak—a city in the Black Sea area, known for its coal mines. I finished middle and high school there, and it was in my second year of high school that I finalized my decision for a future profession. Until that time, I had always imagined becoming an engineer. However, when I made a list of all possible career paths, I realized that medicine would be ideal: not only would I be able to help people, but I would probably still be able to integrate many other areas that interested me into Medicine!

You have been a pioneer of organ transplantation in Turkey with many 'firsts' in living and deceased donor kidney and liver transplantation. What is your most memorable surgery? What is your most memorable patient?

MH: I think my most memorable surgeries will always be those "firsts"—especially the first successful kidney transplant

Received 30 November 2017.
Accepted 27 November 2017.
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The author declares no conflicts of interest.

ISSN: 0041-1337/18/10206-0888
DOI: 10.1097/TP.0000000000002063