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Interleukin-17 in Drug Toxicity

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Editorial

Drug-induced tissue injury is the most common cause for termination of preclinical and clinical trial processes of drug development. Many drugs approved for clinical use have been withdrawn from market or have been advised to use with caution because of unexpected adverse effects noticed during postmarketing surveliance. Based on their relative importance in human health, some pharmaceuticals with relatively less drug toxicity, such as tolrestat, lumiracoxib and arotinin, have been approved in certain countries for use in patients, but not worldwide. Moreover, the surge in new drugs for human use has also increased the morbidity and mortality associated with adverse drug reactions. Although, over the years, investigative toxicology studies have unraveled mechanisms behind adverse drug reactions, the underlying pathogenesis of many drug toxicities are still unknown. Immune cells and inflammation have been attributed to majority of toxic effects of chemicals and drugs. The immune system may either be protective or detrimental to the host. For example, in cisplatin-induced kidney injury, dendritic cells, T regulatory cells and IL-10 attenuate, whereas T cells, NK cells and IL-17 aggravate nephrotoxicity [1,2]. Recently, interleukin-17 research has gained much importance as a drug target for autoimmune and inflammatory diseases.

IL-17 family of cytokines, particularly IL-17A, is emerging as critical mediator of inflammatory diseases and adverse drug reactions. IL-17 family consists of cytokines IL-17A (also referred to as IL-17), IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F. IL-17A and IL-17F share highest homology both in sequence and biological functions, and are primarily produced by Th17 cells. Other less characterized sources of IL-17A and IL-17F are γδ T cells, NK cells, neutrophils and macrophages. IL-23 produced by dendritic cells and macrophages is critical for maintenance and expansion of Th17 cells. The heterodimer IL-23 is made of p40 that is shared with IL-12, and p19 subunits. IL-17E regulates parasitic and allergic inflammation, and is produced mainly by Th2 cells, mast cells, basophils, eosinophils and epithelial cells. The functions of IL-17B, IL-17C and IL-17D are largely unknown, except few recent studies on IL-17C pro-inflammatory functions in mucosal immunity and autoimmune diseases. IL-17 family cytokines exerts their biological functions mainly through heterodimers of IL-17RA with IL-17RB, IL-17RC, IL-17RD and IL-17RE, where IL-17RA serves as a common subunit. For example, IL-17RA and IL-17RC recognizes both IL-17A and IL-17F, whereas IL-25 binds to IL-17RA and IL-17RB. Although, several investigators have reported induction of IL-17 cytokines in toxic tissue injury, studies examining its *in vivo* role using IL-17A deficient mice or neutralizing antibody are limited to two drug toxicity investigations, cisplatin nephrotoxicity [3] and halothane hepatitis [4], and three chemically induced tissue damage studies, alpha-naphthylisothiocyanate (ANIT)-induced liver injury [5] and Dextran Sodium Sulfate (DSS) and trinitrobenzenesulfonic acid (TNBS)-induced colitis [6,7]. Furthermore, these investigations were restricted to IL-17A but not to other members of IL-17 cytokine family.

IL-17A in Nephrotoxicity: Cisplatin is a very effective chemotherapeutic agent commonly used against many solid organ malignancies. Since the approval by the U.S. Food and Drug Administration in 1978, cisplatin has been extensively used as a principle agent against wide range of cancers. Cisplatin elicits its antitumor functions by crosslinking DNA. The major concern of cisplatin therapy is nephrotoxicity occurring in 25-35% of treated patients. In spite of its toxicity on kidneys, cisplatin continues to be widely prescribed worldwide as much as 70% of anticancer treatments at an approximate $2 billion annual sales. IL-17A has been described as mediator of inflammation and tissue injury in human and experimental renal diseases. Most recently in 2014, Chan and colleagues reported the pathogenic function of endogenous IL-17A and IL-17A producing cells in cisplatin nephrotoxicity using mice deficient in IL-17A and various IL-17A-producing immune cells [3]. In their very elaborate study, the authors noticed very high expression of IL-17A in kidneys as early as 24 hrs after cisplatin injection before any noticeable functional or histological signs of kidney injury. Interestingly, the expression of IL-17A decreased to basal levels in kidneys at later intervals when renal dysfunction and tissue injury were evident. Mice deficient in IL-17A as well as mice treated with anti-IL-17A antibody showed marked reduction in renal dysfunction and tissue injury, suggesting IL-17A mediation in cisplatin nephrotoxicity. Likewise, mice deficient in RORγt, the key transcription factor required for IL-17A production by Th17 cells, were found protected from cisplatin-induced kidney injury. IL-17A is produced in response to varied stimulus, including activation of Toll-like Receptors (TLRs) and inflammasome. Mice deficient in TLR2 and ASC (a subunit of multiprotein inflammasome complex) showed less renal IL-17A production and dysfunction than controls, suggesting TLR and inflammasome-mediated production of IL-17A in cisplatin nephrotoxicity.

Inflammation is one of the key mediators of nephrotoxic kidney injury. Leukocytes and their secreted cytokines and chemokines exacerbate cisplatin-induced renal tubular injury. Subsequent to establishing IL-17A mediation in cisplatin nephrotoxicity, the authors investigated the source of IL-17A production. The major source of IL-17A was found to be renal neutrophils followed by Th17 cells. The infiltration of neutrophils, but not Th17 cells was minimal in IL-17A deficient mice, suggesting IL-17A dependent and independent migration of leukocytes in cisplatin nephrotoxicity. In addition to neutrophils and Th17 cells, the authors examined the role of γδ T cells and NK cells in IL-17A-mediated augmentation of cisplatin nephrotoxicity. Cisplatin treatment did not impact the course or magnitude of renal dysfunction or tissue injury in mice deficient in γδ

T cells as compared to controls. Likewise, Rag1 deficient mice reconstituted with IL-17A deficient T cells showed renal dysfunction almost similar to that of controls. Depletion of neutrophils using anti-Ly6g antibody had very minimal protective effect on renal function but not on tissue injury. However, depletion of neutrophils in addition to NK cells ameliorated cisplatin nephrotoxicity, and an additional exogenous administration of IL-17A neutralizing antibody did not offer any added protection against cisplatin-induced kidney injury. These interesting findings suggest that the innate immune cells such as neutrophils and NK cells are the key drivers of IL-17A-mediated cisplatin nephrotoxicity. These findings distinguish from the pathogenesis of autoimmunity where Th17 cells of the adaptive immune system mediate inflammation and tissue injury. This elegant investigation on cisplatin nephrotoxicity is the only study in which the functional significance of endogenous IL-17A and its source has been examined in great detail using mice deficient in IL-17A, RORγt, Th17 cells, neutrophils, NK cells and γδ T cells.

IL-17A in Hepatitis: Halothane is an inhalational general anesthetic and is one of the drugs in the WHO's list of essential medicines. A small percentage of adults, but not children, exposed to halothane develop life threatening fulminant hepatitis with a mortality rate of 30-70%. Trifluoroacetyl radicals of halothane formed in the liver are believed to mediate halothane hepatitis. In 2009, Kobayashi and colleagues published the inflammatory function of IL-17A in a mouse model of drug-induced liver injury [4]. Treatment of mice with halothane caused marked increase in serum IL-17A levels as early as 24 hrs after administration. The significance of elevated plasma IL-17A levels after halothane administration was examined using IL-17A specific neutralization antibody. Mice treated with halothane and IL-17A antibody showed striking decrease in serum alanine and aspartate aminotransferases than control group of mice. Likewise, exogenous administration of recombinant IL-17A with halothane caused worsening of liver injury. Although this study has not been performed in IL-17A deficient mice, this first investigation using IL-17A neutralizing antibody provides clear evidence that IL-17A is detrimental in drug-induced liver injury.

Subsequent to examining the function of IL-17A in halothane hepatitis, Kobayashi and colleagues investigated IL-17A role in ANIT-induced liver injury in mice [5]. ANIT causes hepatic and biliary cell damage due to its high concentrating ability resulting from repeated cycles of secretion and reuptake in the liver. Mice treated with ANIT showed marked induction of RORγt in liver. In ANIT treated mice, neutralization of IL-17A with specific antibody attenuated liver injury with a decrease in the levels of serum alanine and aspartate aminotransferases and infiltration of neutrophils. Furthermore, exogenous administration of IL-17A along with ANIT caused remarkable increases in serum aminotransferases and liver neutrophil infiltration. These exogenous IL-17A and anti-IL-17A antibody administration studies signify the importance of IL-17A in ANIT-induced toxic liver injury.

IL-17 in Colitis: Although all reported findings point towards IL-17A as a mediator of toxic tissue injury, studies on chemically induced inflammatory bowel disease have provided contradictory results. In 2004, Ogawa and colleagues reported an inhibitory function of IL-17A in DSS-induced colitis [6]. Contrary to their hypothesis, mice treated with IL-17A antibody developed severe weight loss, rectal prolapse, and colon shortening with marked tissue injury. These exacerbated changes of colitis were reduced in mice administered with recombinant IL-17A suggesting a significant anti-inflammatory function of IL-17A in intestine. Contrary to these observations, Zhang and colleagues in 2006 reported an inflammatory function for IL-17A in TNBS-induced colitis in mice [7]. In their experiments, IL-17RA deficient mice elicited less weight loss, colonic inflammation and leukocyte infiltration to TNBS than controls. Considering IL-17RA role as a common subunit for the entire family of IL-17 receptors, it is possible that all IL-17 cytokine family members, rather than IL-17A alone, are inhibited in IL-17RA deficient mice in the latter model of colitis.

Many preclinical studies conducted during the past decade have firmly established the proinflammatory function of IL-17A in autoimmunity and inflammatory diseases. These promising findings have resulted in various biologicals, mainly monoclonal antibodies, targeting IL-17A or its production pathways in diseases like psoriasis, rhematoid arthirits, asthma, multiple sclerosis, crohn's disease and others. The drugs that are in phase 2 and phase 3 clinical trials include secukinumab from Novartis and ixekizumab from Eli Lilly against IL-17A, brodalumab from Amgen and MedImmune against IL-17 receptor, MK-3222 from Merck and CNTO 1959 from Janssen Biotech against p19 subunit of IL-23, and ustekinumab from Janssen Biotech against p40 subunit of IL-23 and IL-12. Although the studies on IL-17A function in toxic or drug-induced tissue injury are limited to few preclinical investigations, the reported findings undoubtedly indicate that IL-17A inhibition is protective from drug toxicity. The availability of different monoclonal antibodies targeting various stages of IL-17 production provides a greater opportunity to investigate their protective function against sterile injury of toxins or drugs in patients.

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