Editorial

Targeting resolvins in cholestatic liver injury

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In general terms, the acute inflammatory reaction in conditions of infection or tissue damage is a response of the immune system to cope with survival and return to homeostasis. Temporarily, the reaction is initiated by edema followed by the progressive accumulation of polymorphonuclear leukocytes (PMN) and monocytes that differentiate into macrophages, with production of pro-inflammatory mediators such as leukotrienes (e.g., LTB4) and prostaglandins (e.g., PGE_2, PGI_2, PGF_2), which in excess may progress to chronic inflammation (1). Considering that the acute inflammatory response is a protective and self-limited phenomenon, its resolution is an active programmed reaction that is set in by specific pro-resolving mediators (SPMs), which are derived from n-3 polyunsaturated fatty acids (n-3 PUFAs). These include eicosapentaenoic acid (EPA) (C20:4n-3) and docosahexaenoic acid (DHA) (C22:6n-3) that are synthesized from the essential precursor α-linolenic acid (ALA) (C18:3n-3), which in contact with resolving exudates generate specific types of SPMs, namely, resolvins, protectins and maresins (1). Besides n-3 PUFAs, the n-6 PUFA arachidonic acid (ARA) (C20:4n-6) also acts as a precursor for the synthesis of a specific type of SPMs the lipoxins, either by the action of 5-lipoxygenase (e.g., lipoxin A_4 and B_4) or triggered by aspirin-dependent cyclooxygenase-2 (COX-2) acetylation that forms an intermediary transformed by 5-lipoxygenase into 15-epi-lipoxin A_4 (2). SPMs act in the pM to low nM range to interrupt PMN infiltration via signals that limit further PMN recruitment and tissue damage, with the concomitant enhancement of macrophage phagocytosis of apoptotic PMNs to attain resolution, the effective clearance of infecting microbes and tissue damage, with disappearance of the inflammatory exudate (1,2).

Resolvin D1 (RvD1), the SPM studied by Abshagen *et al.* (3), is synthesized from DHA by the action of aspirin-acetylated COX-2 and 5-lipoxygenase, although the process can proceed in the absence of aspirin, through the sequential catalysis of 15-lipoxygenase, 5-lipoxygenase and epoxide hydrolase (2). RvD1 exerts potent anti-inflammatory (diminished PMN infiltration) and pro-resolving (enhanced macrophage phagocytosis) effects, the underlying protective mechanism of action being associated with the counteraction on oxidative stress-related tissue injury caused by PMN activation, which involves the production of reactive oxygen species (ROS) by NADPH oxidase and hypochlorite by myeloperoxidase, in addition to proteases (1). RvD1 signaling is mediated by lipoxin receptor ALX/FPR2 and G-protein coupled receptor 32 (GPR32), which downregulate the activation of nuclear factor-κB (NF-κB), a redox-sensitive transcription factor that is central in inflammatory reactions (4).

Cholestatic liver diseases (CLDs) are related to bile transport obstruction conditions that slow biliary flow, which promote a cholestatic state with enhanced bile acid (BA) levels that induce BA cytotoxicity (5). The main cytotoxic mechanisms of BA include: (I) mitochondrial dysfunction associated with disruption of the mitochondrial membrane potential, enhancement in the production of ROS, with the consequent diminution in mitochondrial mass and DNA content altering respiratory functions; (II) ROS-dependent lipid peroxidation processes generating by-products that activate extracellular matrix cells and have direct

fibrogenic effects on activated hepatic stellate cells (HSCs); and (III) activation of NF-κB inducing the expression of inflammatory cytokines (5). In this scenario, Abshagen *et al.* (3) studied the influence of RvD1 administration on cholestatic liver fibrosis in the model of bile duct ligation (BDL) in mice, by means of daily doses of 2 ng RvD1/g (total of 50–60 ng/mouse) for 2, 5 and 14 days. Data reported indicate the adequacy of BDL protocol used, that developed cholestatic liver injury, concomitantly with an inflammatory response, activation of HSCs and collagen expression, and a proliferative response of hepatocytes and non-parenchymal cells, with the consequent increase in liver weight/body weight ratio. However, RvD1 treatment failed to modify most of the studied parameters, except for a significant and early diminution in the activity of HSCs and in the deposition of extracellular matrix at 2 days after BDL (3). Some drawbacks are encountered in the commented article. First, the low effectiveness of the RvD1 treatment may be ascribed to insufficient levels attained in blood and liver, a parameter that was not determined by the authors, despite the availability of specific ELISA kits for RvD1 currently accessible (5.0 pg/mL sensitivity; MyBioSource, California, USA; Thermo Fisher Scientific, Monza, Italy). Second, the lack of a previous dose-response study for RvD1 actions points to the possibility that doses higher than 50–60 ng/mouse (3) could have elicited significant results. In agreement with this prospect, (I) 100 ng RvD1/mouse three times per week via gavage from 5 to 21 days post-infection with *P. aeruginosa*, diminishes lung infection, inflammation and damage, promoting resolution *in vivo* in cystic fibrosis mice (6); (II) daily i.p. injections of 400–550 ng RvD1/rat for 21 days after a single dose of monocrotaline inducing right heart disease (RHD), prevents atrial fibrillation and suppresses inflammation and fibrotic/electrical remodelling by RHD (7); (III) low (100 ng/mouse) and high (300 ng/mouse) doses of RvD1 given in the last 2 weeks of a 4 weeks treatment with a methionine-choline deficient diet inducing non-alcoholic steatohepatitis (NASH), effectively improve liver oxidative stress, inflammation, steatosis and fibrosis, involving pro-inflammatory NF-κB downregulation and antioxidant Nrf2 activation (8); and (IV) using an ischemia/reperfusion injury protocol, the administration of 10 μg RvD1/mouse 10 min after reperfusion protects the kidney, as evidenced by the diminutions either in serum creatinine levels 24 and 48 h later, tissue fibrosis, leukocyte infiltration or macrophage activation (9). Interestingly, the administration of RvD1 alone in control experiments using 400–550 ng/rat (7) or 10 μg/mouse (9) did not induce changes in any of the parameters measured. Consequently, in experimental settings evaluating SPM effects, assessment of pick time of effects and the levels of circulating and tissue RvD1 achieved are crucial for obtaining reliable results. This is especially important considering that RvD1 is effectively inactivated by an eicosanoid oxidoreductase (EOR), which elicits dehydrogenation at carbon-17 to produce an inactive 17-oxo-RvD1 metabolite (10).

At present time, the study of the co-supplementation with different SPMs on the outcome of CLDs or other pathologies has not been implemented in preclinical or clinical investigations. Compared to monotherapies, combined protocols represent relevant strategies for disease preclusion or resolution, as they might use lower doses of the agents and shorter supplementation periods than the monotherapies, and the similar or different underlying mechanisms of action might lead to synergistic or additive effects, thus minimizing side effects (11). This proposal is supported by recent studies in the high-fat diet model of obesity in mice, in which the co-administration of hydroxytyrosol, the potent antioxidant component of extra virgin olive oil, and the metabolic regulator DHA that increases the hepatic RvD1 and RvD2 levels in control and high fat diet (HFD)-fed mice, fully prevents liver steatosis (12) and the associated mitochondrial dysfunction (13), eluding disease progression into more irreversible stages lacking effective therapies at present time.

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Footnote

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