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Editorials

The importance of fundamental pharmacology in fighting liver diseases

Liver disease causes millions of deaths worldwide each year, representing 4 % of all deaths. The main causes of death from liver disease are complications, such as cirrhosis and hepatocellular carcinoma (HCC) [1]. The most common causes of cirrhosis worldwide are viral hepatitis, alcohol abuse, and non-alcoholic fatty liver disease [1]. However, despite the significant public health problems that liver diseases represent, no effective pharmacological therapies to combat them are available. In this scenario, the search for the pathophysiological mechanisms involved in liver diseases can help identify cellular and molecular targets to develop new and more effective therapies to treat hepatic illnesses and reduce mortality associated with liver diseases. Moreover, research on the cellular and molecular mechanisms involved in liver pathology is a rational and effective way to identify new early non-invasive biomarkers of liver damage to detect the pathology for opportune treatment.

Understanding the molecular pathways involved in the progression of liver pathologies has led to new approaches for treating these diseases. For instance, fundamental researchers have found that exacerbated reactive oxygen species (ROS) production is a common causative factor in liver diseases. ROS attack proteins, lipids, and DNA, leading to necrosis, steatosis, fibrosis, cirrhosis, and ultimately HCC [2]. Therefore, antioxidants protect the liver. In this regard, fundamental researchers have found that deregulation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, a protein involved in the body's antioxidant response, plays a pivotal role in the development and progression of liver diseases; therefore, the pharmacological improvement of this pathway is associated with the attenuation of hepatic markers of oxidative stress, inflammation, fibrosis, and even prevention of HCC [3–7].

Basic research has demonstrated that apoptotic and injured hepatocytes release chemoattractant signals directed to cells of the immune system that are prone to be phagocytized by Kupffer cells and other macrophages that produce inflammatory cytokines such as interleukins (ILs) and tumor necrosis factor-alpha (TNF-α) [8]. Proinflammatory cytokines stimulate the activation of the nuclear factor kappa B (NF-κB) signaling pathway, the master inflammation factor, triggering the expression of several proinflammatory genes, including ILs and TNF-α, thus exacerbating inflammation and necrosis of liver cells [9]. Therefore, the NF-κB pathway is considered a suitable target for the treatment of liver diseases, and several drugs that protect the liver from injury block this pathway [4,9,10].

In recent years, considerable attention has been paid to several molecules that form the inflammasome protein complex, which is responsible for the maturation of inflammatory proteins. The most studied of these is the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3). In particular, the activation of the NLRP3 inflammasome plays a fundamental role in the development of liver diseases. Additionally, some studies have demonstrated that the maturation of IL-1β by the NLRP3 inflammasome is closely associated with the progression of liver inflammation and fibrosis. Consequently, the NLRP3 inflammasome pathway has become a therapeutic target, and several drugs downregulate it [10–13].

Fundamental studies have shown that activated hepatic stellate cells (HSCs) are the main producers of extracellular matrix proteins [14]. Therefore, the activation of these cells is considered a crucial step in fibrogenesis and liver cirrhosis, and efforts have been made to prevent or reverse their activation to interfere with the production of fibrotic tissue as an antifibrotic therapy [15]. Notably, transforming growth factor beta (TGF-β) is the most potent profibrogenic cytokine and a key driver of the activation, migration, and proliferation of HSCs and liver fibrosis through the activation of the TGF-β receptor and the phosphorylation of intracellular effector proteins called Smads [14,16]. Different protein kinases can phosphorylate Smad3 in the carboxyl terminus to form pSmad3C (this is the case of the TGF-β receptor) or in the linker region to form pSmad3L; this phosphorylation is achieved through the activity of mitogen-activated protein kinases (MAPK) [17,18]. pSmad3C is fibrogenic and part of the canonical Smad signaling pathway. In contrast, pSmad3L is mitogenic and triggers the proliferation of activated HSCs, exacerbating scar tissue deposition and promoting advanced cirrhosis [18,19]. Therefore, TGF-β, has become, since its discovery, a therapeutic target to attenuate fibrosis and HCC, because its inhibition downregulates the canonical and non-canonical fibrogenic signaling pathways of Smads proteins [20–22].

These examples demonstrate the importance of basic science and the impact of fundamental knowledge of molecular pathways on the development of molecular pharmacology. Owing to the knowledge of the different signaling pathways, we now know that pharmacologically modulating the molecular signaling of Nrf2 and NF-κB pathways can reduce oxidative stress and inflammation [3,4,6,7]. By regulating the activation of the NLRP3 inflammasome pathway, it is possible to reduce liver inflammation, fibrosis, and HCC [11]. In addition, by modulating the MAPK/TGF-β signaling pathways, the activation of HSCs and fibrogenesis can be reduced [10,22,23].

Based on basic science studies, several biomarkers of liver damage have been proposed; for example, alpha-smooth muscle actin, which is an indicator of HSC activation, is a potentially reliable and non-invasive biomarker for detecting early liver fibrosis [24]. In addition, fundamental pharmacological research has successfully incorporated docking molecular techniques into various drug discovery programs [25]. Using molecular docking, the conformations of ligands adopted within the binding sites of the macromolecular targets were studied computationally [25]. The combination of computational and experimental methods is useful for elucidating new mechanisms of action

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and for providing potential targets for the development of new therapeutic compounds [10,25].

Based on experimental pharmacology and basic research, new molecular targets can be discovered, therapeutic agents evaluated, and new markers of damage can be proposed for the treatment of liver diseases. In this regard, elucidating the molecular pathways involved in the development of liver diseases and the molecular mechanisms by which different compounds can affect these pathways will make pharmacological interventions more rational and specific, allowing for more effective and less toxic therapies. Therefore, the integration of basic and clinical sciences is essential for improving patient therapy, thereby reducing mortality associated with liver diseases.

Declaration of interests

None.

References

[1] Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. J Hepatol 2023;79:516–37. https://doi.org/10.1016/j.jhep.2023.03.017.

[2] Arauz J, Ramos-Tovar E, Muriel P. Redox state and methods to evaluate oxidative stress in liver damage: from bench to bedside. Ann Hepatol 2016;15:160–73. https://doi.org/10.5604/16652681.1193701.

[3] Ramos-Tovar E, Flores-Beltrán RE, Galindo-Gómez S, Vera-Aguilar E, Diaz-Ruiz A, Montes S, et al. Stevia rebaudiana tea prevents experimental cirrhosis via regulation of NF-κB, Nrf2, transforming growth factor beta, Smad7, and hepatic stellate cell activation. Phytother Res 2018;32:2568–76. https://doi.org/10.1002/ptr.6197.

[4] Vargas-Pozada EE, Ramos-Tovar E, Acero-Hernández C, Cardoso-Lezama I, Galindo-Gómez S, Tsutsumi V, et al. The antioxidant and anti-inflammatory activities of caffeine effectively attenuate non-alcoholic steatohepatitis and thioacetamide-induced hepatic injury in male rats. Can J Physiol Pharmacol 2023;101:147–59. https://doi.org/10.1139/cjpp-2022-0303.

[5] Oh CJ, Kim JY, Min AK, Park KG, Harris RA, Kim HJ, et al. Sulforaphane attenuates hepatic fibrosis via NF-E2-related factor 2-mediated inhibition of transforming growth factor-β/Smad signaling. Free Radic Biol Med 2012;52:671–82. https://doi.org/10.1016/j.freeradbiomed.2011.11.012.

[6] Ramos-Tovar E, Muriel P. Free radicals, antioxidants, nuclear factor-E2-related factor-2 and liver damage. J Appl Toxicol 2020;40:151–68. https://doi.org/10.1002/jat.3880.

[7] Ramos-Tovar E, Muriel P. Molecular mechanisms that link oxidative stress, inflammation, and fibrosis in the liver. Antioxidants (Basel) 2020;9:1279. https://doi.org/10.3390/antiox9121279.

[8] Bataller R, Brenner DA. Liver fibrosis. J Clin Invest 2005;115:209–18. https://doi.org/10.1172/JCI24282.

[9] Muriel P. NF-kappaB in liver diseases: a target for drug therapy. J Appl Toxicol 2009;29:91–100. https://doi.org/10.1002/jat.1393.

[10] Cardoso-Lezama I, Fuentes-Figueroa MÁ, Ramos-Tovar E, Márquez-Quiroga LV, Ortiz-Fernández A, Vargas-Pozada EE, et al. Nicotinic acid attenuates experimental non-alcoholic steatohepatitis by inhibiting the NLRP3 inflammasome/pyroptosis pathway. Biochem Pharmacol 2023;216:115762. https://doi.org/10.1016/j.bcp.2023.115762.

[11] Ramos-Tovar E, Muriel P. NLRP3 inflammasome in hepatic diseases: a pharmacological target. Biochem Pharmacol 2023:115861. https://doi.org/10.1016/j.bcp.2023.115861.

[12] Szabo G, Petrasek J. Inflammasome activation and function in liver disease. Nat Rev Gastroenterol Hepatol 2015;12:387–400. https://doi.org/10.1038/nrgastro.2015.94.

[13] Vargas-Pozada EE, Ramos-Tovar E, Rodriguez-Callejas JD, Cardoso-Lezama I, Galindo-Gómez S, Gil-Becerril K, et al. Activation of the NLRP3 inflammasome by CCl4 exacerbates hepatopathogenic diet-induced experimental NASH. Ann Hepatol 2023;28:100780. https://doi.org/10.1016/j.aohep.2022.100780.

[14] Lee Y, Friedman SL. Fibrosis in the liver: acute protection and chronic disease. Prog Mol Biol Transl Sci 2010:151–200. https://doi.org/10.1016/B978-0-12-385233-5.00006-4.

[15] Muriel P. The healthy and diseased extracellular matrix of the liver. In: Muriel P, editor. Hepatic fibrosis: mechanisms and targets. Elsevier; 2022. p. 1–23. https://doi.org/10.1016/C2021-0-02535-9.

[16] Duarte S, Baber J, Fujii T, Coito AJ. Matrix metalloproteinases in liver injury, repair and fibrosis. Matrix Biol 2015:147–56. https://doi.org/10.1016/j.matbio.2015.01.004.

[17] Matsuzaki K. Smad phospho-isoforms direct context-dependent TGF-β signaling. Cytokine Growth Factor Rev 2013;24(4):385–99. https://doi.org/10.1016/j.cytogfr.2013.06.002.

[18] Marra F, Arrighi MC, Fazi M, Caligiuri A, Pinzani M, Romanelli RG, et al. Extracellular signal-regulated kinase activation differentially regulates platelet-derived growth factor's actions in hepatic stellate cells, and is induced by in vivo liver injury in the rat. Hepatology 1999;30:951–8. https://doi.org/10.1002/hep.510300406.

[19] Matsuzaki K. Smad phosphoisoform signals in acute and chronic liver injury: similarities and differences between epithelial and mesenchymal cells. Cell Tissue Res 2012;347(1):225–43. https://doi.org/10.1007/s00441-011-1178-6.

[20] Gonzalez-Sanchez E, Vaquero J, Férnandez-Barrena MG, Lasarte JJ, Avila MA, Sarobe P, et al. The TGF-β pathway: A pharmacological target in hepatocellular carcinoma? Cancers (Basel) 2021;13:3248. https://doi.org/10.3390/cancers13133248.

[21] Akhurst RJ. Targeting TGF-β signaling for therapeutic gain. Cold Spring Harb Perspect Biol 2017;9 a022301. https://doi.org/10.1101/cshperspect.a022301.

[22] Vargas-Pozada EE, Ramos-Tovar E, Acero-Hernández C, Cardoso-Lezama I, Galindo-Gómez S, Tsutsumi V, et al. Caffeine mitigates experimental non-alcoholic steatohepatitis and the progression of thioacetamide-induced liver fibrosis by blocking the MAPK and TGF-β/Smad3 signaling pathways. Ann Hepatol 2022;27:100671. https://doi.org/10.1016/j.aohep.2022.100671.

[23] Vargas-Pozada EE, Ramos-Tovar E, Rodriguez-Callejas JD, Cardoso-Lezama I, Galindo-Gómez S, Talamás-Lara D, et al. Caffeine inhibits NLRP3 inflammasome activation by downregulating TLR4/MAPK/NF-κB signaling pathway in an experimental NASH Model. Int J Mol Sci 2022;23:9954.

[24] Cardoso-Lezama I, Ramos-Tovar E, Arellanes-Robledo J, Vargas-Pozada EE, Vásquez-Garzón VR, Villa-Treviño S, et al. Serum α-SMA is a potential non-invasive biomarker of liver fibrosis. Toxicol Mech Methods 2023;29:1–7. https://doi.org/10.1080/15376516.2023.2244061.

[25] Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules 2015;20:13384–421. https://doi.org/10.3390/molecules200713384.

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