Nuclear Factor Erythroid-2 Linked Factor (Nrf2) as a Potential Mediator of Hepatotoxicity

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Abstract:

Hepatotoxicity is a term used to describe serious health complications of liver disease caused by a variety of factors. Nuclear factor erythroid-2 linked factor (Nrf2) as a potential mediator of hepatotoxicity via inflammatory and induction of oxidative stress, oxidation produces more toxic compounds caused more pathogenic cases; therefore, to maintain sufficient homeostasis, involve antioxidant materials and detoxification factors. Controlling cytokine activity in normal cells is a useful way to regulate the signaling pathway of Nrf2. Recent studies found a relation between each Nrf2 and NF-κB activation and drug-induced liver injury. This review presents a detailed and conformation update of Nrf2 roles in hepatotoxicity which considers that drug-induced liver injury is the main problem to draw attention in medical clinics and to develop new drugs with less harmful to the liver. In addition to that. Kept each of normal oxidation and cytokines levels is crucial responses for cells alteration and remaining to survive.

Key words: Nrf2, Hepatotoxicity, drug-induced liver injury.

العامل النووي(Nrf2) كعامل محفز للتسمم الكبدي

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الخلاصة:

مصطلح التسمم الكبدي يستخدم لوصف المضاعفات الصحية الخطيرة لأمراض الكبد الناجمة عن مجموعة متنوعة من العوامل. العامل النووي (Nrf2) كعامل محفز للتسمم الكبدي عن طريق تحريض الإجهاد الالتهابي والتأكسدي . تنتج الأكسدة العديد من المركبات السامة مسببة العديد من الحالات المرضية لذلك للحفاظ على التوازن الكافي ، يتطلب توفر مضادات الأكسدة وعوامل إزالة السمية . التحكم في نشاط السيتوكين في الخلايا الطبيعية تعتبر طريقة مفيدة لتنظيم مسار إشارات (Nrf2) . الدراسات الحديثة وجدت العلاقة مابين تنشيط العامل النووي (Nrf2) و NF-κB مع تاثير العقاقير المحفزة لاصابة الكبد .في هذه المراجعة سنقوم بشرح التفاصيل واخر المستجدات بخصوص Nrf2 ودوره في التسمم الكبدي التي تعتبر دواء المحفز لاصابة الكبد من اهم المشاكل التي تسترعي الانتباه في العيادات السريرية وكذلك في تطوير أدوية جديدة أكثر أمانًا. بالإضافة إلى ذلك الحفاظ على مستويات الاكسدة الطبيعية ومستوى السيتوكينات هما من العوامل الاساسية للتكييف وادامة الخلايا.

الكلمات المفتاحية: Nrf2 , التسمم الكبدي, الدواء المحفز لاصابة الكبد.

Background

Nrf2-Keap1 Signaling Pathway

Nrf2-Keap1 is a protein responsible of transcribed and regulating the Nuclear factor erythroid-2 linked factor (Nrf2) expression, it is found in the cytoplasm and accumulates in the nucleus, where it functions as a transcription activator released by Keap1, belongs to the family of a transcription

factor called Cap'n'collar (CNC), which divided into seven domain (Neh1-Neh7) (Figure-1), the N-terminal domains influenced the stabilities and predominant of Nrf2 by Keap1 binding, while the Neh5 domains are managing the localization of cytoplasm for Nrf2's transcription and regulation Nrf2 expression [1]

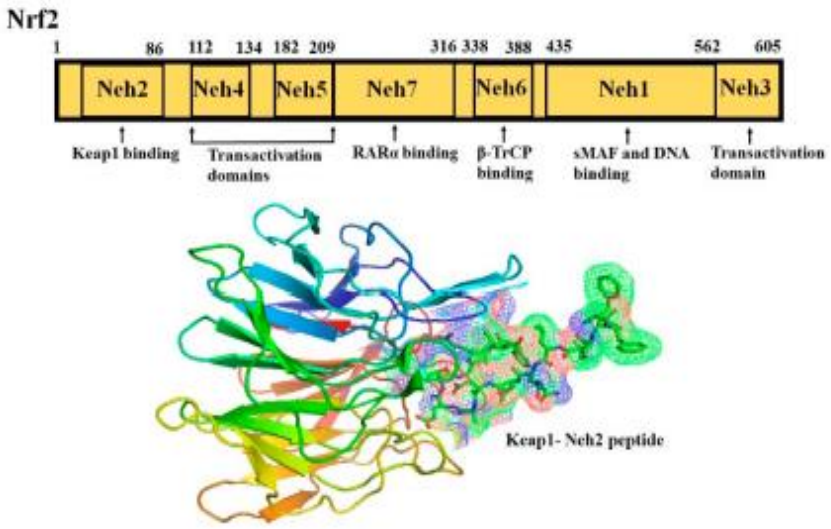

Figure (1): A surface presentation of the Kelch domain (carton) with peptide from Neh2 domain of Nrf2[1]

Kelch repeats, on the other hand, are responsible for accelerating the binding of Keap1's to p62 and Nrf2, as shown in Figure 2. [2]

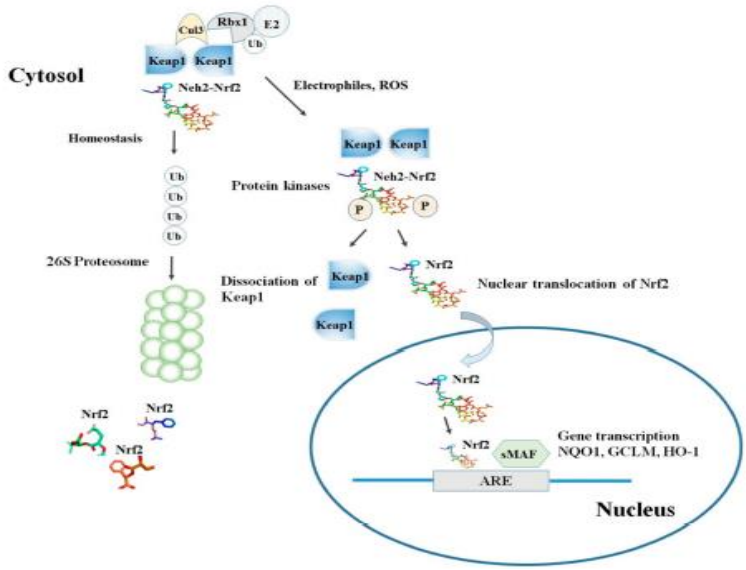

Figure (2): Mediator associated the binding of Keap1 to protein (p62) and Nrf2(2)

Hepatotoxicity produces by different mechanisms.

One of the most remarkable biomarkers of hepatic injury is lipid peroxidation since certain hepatotoxicants need metabolic activation to generate reactive intermediates involved in liver disease [3] therefore activated or induced by certain genes involved antioxidant protection is very necessary, glutathione (GSH) system is the most essential process that defends against hepatotoxicity [3] and oxidative stress (4). Nrf2 acts as an important part of this process. [5].

Also, the complication of liver injury is characterized by exacerbating inflammatory responses such as cytokine and chemokine production, as well as changes in the extracellular matrix composition. [6] Excessive levels of reactive oxygen species are more harmful to cells; it involves molecules that have unpaired electrons obtained from the reduction of oxygen which is unstable and become more reactive when reacted with adjacent molecules. Superoxide radicals, hydroxyl radicals, and peroxyl radicals are examples of oxygen-centered radicals, while H2O2 and singlet oxygen are examples of oxygen-centered non-radicals. Antioxidants are substances that delay or prevent free radicals from damaging the cell by scavenging reactive oxygen species, the human system has a variety of process ways to combat oxidative stress. [7]. Oxidation and cytokines are survival responses to adverse drug reactions that are dependent on an active transcription factor (Nrf2). Tumour necrosis factor (TNFα) mediates intracellular signaling through activating the Nuclear Factor Kappa B (NF-κB) transcription factors. (Nrf2) mediates oxidation responses and death receptors signaling.

Drugs induce liver injury to activate TNF-α which mediates NF-κB signaling. Nrf2 enhances the effect of the TNFα signal pathway as synergistic toward oxidative which amplified TNFα sensitization [8]. All these mediators are part of some important physiological functions like the signal transduction pathway and protect microorganisms (neutrophil, eosinophil, and macrophage) during inflammations. [9] Inflammation can be classified as either acute or chronic. Acute inflammations describe the rapid response of innate immune components to a challenge. [10,11]

The role of Nrf2 overexpression on liver enzymes

Hepatocellular toxicities markers, such as increased levels of aspartate and alanine transaminase (AST, ALT) or total bilirubin, are associated with suppression of (NF-κB) activation by intrinsic hepatotoxicity drugs that stimulate the (Nrf2) response and sensitize toward Tumour necrosis factor (TNFα) which induce cytotoxicity [8] Although elevated liver enzymes can reflect glutathione depletion, lipid peroxidation, and increase production of reactive oxygen species. [12] increased levels of Alanine Aminotransferase enzyme upon normal ranges related to acute hepatocellular injury can lead to liver failure [13, 14]. Tissue distribution of NrF2 is in kidneys, muscles, lungs, heart, liver, and brain, Nrf2 expressions in high concentrations in these sites [15].

add them to show the tissue distribution in tumor overexpression of Nrf2 induced 6-phosphogluconate dehydrogenase and glucose -6- phosphate dehydrogenase which involve stimulating cell proliferation [16] Furthermore, promote Nrf2 associate with increased levels of hepatocellular carcinoma and metastasis [17].

Respective pathology

Genetic pathways of Nrf2 can demonstrate via de novo malignant tumor (18) that similar to the mechanism of atherosclerosis which involve synthesis in the liver (19)

Therapeutic Strategies

Drug-induced liver injury increases levels of (Nrf2) targeting usually correlate with Nuclear Factor Kappa B (NF-κB) such as diclofenac, carbamazepine, and ketoconazole, making people more sensitive to TNF-mediated cytotoxicity. (8)

The hepatocyte has a complex protection mechanism against damage, one of which is the antioxidant enzyme such as Superoxide dismutase.

Most drugs derived from plants like turmeric, resveratrol, and plant pigment (quercetin), as well as synthetic compounds like Esbriet (pirfenidone) and oltipraz, may be an excellent choice for treating oxidative diseases. [20] Several

studies have shown the abilities of these drugs to prevent liver injury. [21-23]

Conclusion

This review showed that Nuclear Factor Erythroid-2 Linked Factor (Nrf2) has a strong role in hepatotoxicity which considers drug-induced liver injury.

Recommendation

Because of the significant potential function of the (Nrf2) transcription factor, further clinical trials are required to investigate the impact of (Nrf2) as a potential mediator of hepatotoxicity.

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References

1- Krajka-Kuźniak V. Paluszczak J. Baer-Dubowska W. The Nrf2-ARE signaling pathway: An update on its regulation and possible role in cancer prevention and treatment. Pharmacol. Rep. 2017; 69: 393–402.
2- Hayes, J.D. McMahon. M. NRF2 and KEAP1 mutations: permanent activation of an adaptive response in cancer. Trends Biochem. Sci. 2009; 34: 176–188.
3- Jie L. Kai Connie W. Yuan-Fu L. et al. NRF2 Protection against Liver Injury Produced by Various Hepatotoxicants. Oxidative Medicine and Cellular Longevity.2013; 2013:1-8.
4- Tang, W. Jiang, Y.F. Ponnusamy, M.; Diallo, M. Role of Nrf2 in chronic liver disease. World J. Gastroenterol. 2014; 20: 13079–13087
5- Xu, D. Xu, M. Jeong, S. Qian, Y. Wu, H. Xia, Q. Kong X. The role of Nrf2 in liver disease: Novel molecular mechanisms and therapeutic approaches. Front. Pharmacol. 2019; 9:1428.
6- Galicia-Moreno. M. Gutierrez-Reyes G. The role of oxidative stress in the development of alcoholic liver disease. Rev. Gastroenterol. México. 2014; 79:135–144.
7- Ramos-Tovar E. Muriel P. Free radicals, antioxidants, nuclear factor - E2-related factor-2 and liver damage. J. Appl. Toxicol. 2020;40: 151–168.
8- Bram Herpers, Steven Wink, Lisa Fredriksson . Activation of the Nrf2 response by intrinsic hepatotoxic drugs correlates with suppression of NF-κB activation and sensitizes toward TNFα-induced cytotoxicity. Archives of Toxicology volume. 3016; 90:1163–1179.
9- Li S. Tan, H.Y. Wang, N. Zhang, Z.J. Lao L. Wong, C.W. Feng Y. The role of oxidative stress and antioxidants in liver diseases. Int. J. Mol. Sci. 2015; 16: 26087–26124.
10- Inam S. Yassir M. Israa B. Nrf2 as a modulator of oxidative stress. Al Mustansiriyah Journal of Pharmaceutical Sciences, 2019;21(3):25-32.
11- Abdul Muhaimen A. Monther F. Ayad k. Design, Synthesis, and Acute Anti-inflammatory Assessment of New 2-methyl Benzoimidazole Derivatives Having 4-Thiazolidinone Nucleus. Al Mustansiriyah Journal of Pharmaceutical Sciences, 2019;19(4):151-160.
12- Dongwei X. Min X. and Seogsong J. The Role of Nrf2 in Liver Disease: Novel Molecular Mechanisms and Therapeutic Approaches. Frontiers in Pharmacology. 2019; 9: 1428.
13- Chan K. Han XD. Kan YW. An important function of Nrf2 in combating oxidative stress: detoxification of acetaminophen. Proc. Natl. Acad. Sci. The USA. 2001; 98:4611–16.
14- Zhou R. Tardivel A. Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to

inflammasome activation. Nat. Immunol. 2010; 11:136–40.

15- Moi P. Chan K. Asunis I. Cao A. Kan YW. Isolation of NF-E2-related factor 2 (NRF2), an NF-E2-like basic leucine zipper transcriptional activator that binds to the tandem NF-E2/AP1 repeat of the beta-globin locus control region. Proceedings of the National Academy of Sciences of the United States of America. 1994;91 (21): 9926 30.

16- Zhou J. Zhang X. Tang H. Yu J. Zu X. Xie, Z.Yang, X. Hu, J. Tan, F. Li Q. et al. Nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2) in autophagy-induced hepatocellular carcinoma. Clin. Chim. Acta. 2020; 506; 1–8.

17- Xu, D. Xu M. Jeong S. Qian Y.Wu H.; Xia Q. Kong X. The role of Nrf2 in liver disease: Novel molecular mechanisms and therapeutic approaches. Front. Pharmacol. 2019; 9: 1428.

18- DeNicola GM. KaGarethA. Humpton TJ. Gopinathan A. Wei C. Frese K. et al. Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. Nature. 2011; 475 (7354): 106–9.

19- Barajas B. Che N. Yin F. Rowshanrad A. Orozco LD. Gong KW. et al. NF-E2- related factor 2 promotes atherosclerosis by effects on plasma lipoproteins and cholesterol transport that overshadow antioxidant protection. Arteriosclerosis, Thrombosis, and Vascular Biology. 2011; 31 (1): 58–66.

20- Marina G. Silvia Lucano L. Hugo Christian Monroy R. Roles of Nrf2 in Liver Diseases: Molecular, Pharmacological, and Epigenetic Aspects. Antioxidants 2020; 9 (980):1-23.

21- Robledinos-Anton N. Fernandez-Gines R. Manda G. Cuadrado, A. Activators and inhibitors of Nrf2: A review of their potential for clinical development. Oxid. Med. Cell. Longev. 2019;14: 9372182.

22- Kaibori M, Yanagida H, Yokogawa N, Hijikawa T, Kwon AH, Okumura T, Kamiyama Y. Effects of pirfenidone on endotoxin-induced liver injury after partial hepatectomy in rats. InTransplantation proceedings 2004 Sep 1 (Vol. 36, No. 7, pp. 1975-1976). Elsevier.

23- Hamadi N, Mansour A, Hassan MH, Khalifa-Touhami F, Bacary O. Ameliorative effects of resveratrol on liver injury in streptozotocin-induced diabetic rats. Journal of biochemical and molecular toxicology. 2012 Oct;26(10):384-92.