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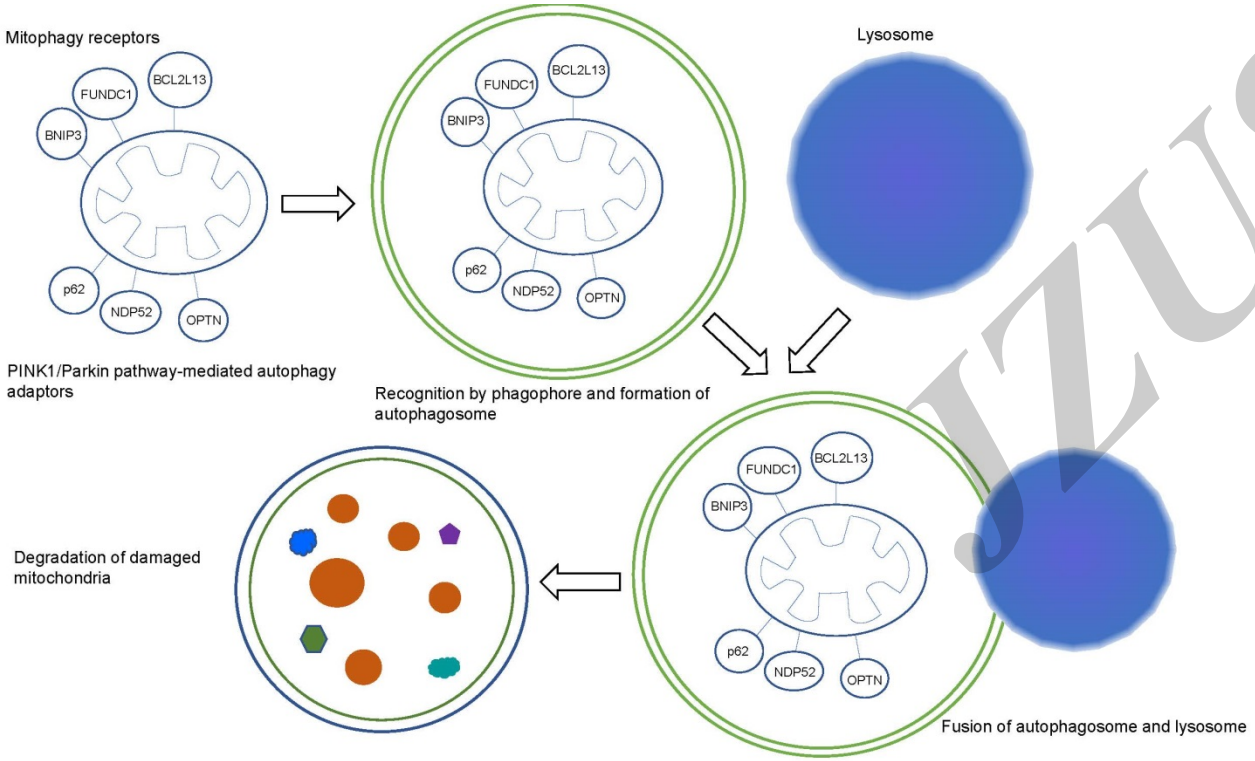
Roles of the Keap1/Nrf2 pathway and mitophagy in liver diseases

Key words: Nrf2 signaling pathway; Mitophagy; Liver diseases

Research Summary

This review mainly focused roles of the Nrf2 signaling pathway and mitophagy, and the relationship between them, in various hepatic diseases (nonalcoholic fatty liver disease, viral hepatitis, alcoholic liver disease, drug-induced liver injury, autoimmune hepatitis, hepatic ischemia–reperfusion injury and liver cancer).



Liver Diseases	Roles of Nrf2 signaling pathway	Roles of mitophagy
Metabolic dysfunction-associated steatotic liver disease	Nrf2 is upregulated to repress obesity and hepatic lipidoses and enhance antioxidative capacity.	Either defective or excessive mitophagy aggravates MASLD.
Viral hepatitis	Nrf2 inhibits HBV and HCV replication.	Mitophagy promotes HBV replication, thus accelerating HBV-related liver cancer; Mitophagy may also suppresses HBV replication. Mitophagy supports HCV replication, maturation and release.
Alcoholic liver disease	Nrf2 is activated to attenuate oxidative stress in ALD; Nrf2 is also inhibited in several alcohol-feeding modes.	Mitophagy accelerates alcohol metabolism and prevents liver damage.
Drug-induced liver disease	Nrf2 is upregulated to fight against DILI.	Mitophagy protects liver from APAP injury through suppression of NF-κB, the NLRP3 inflammasome and IL-1β; Parkin-knockout mitophagy protects APAP injury.
Hepatic ischemia–reperfusion injury	Nrf2 is suppressed to aggravate hepatic IRI; however, Nrf2 is also elevated to improve hepatic IRI.	Mitophagy attenuates hepatic ischemia–reperfusion injury.
Liver Carcinoma	Nrf2 prevents against carcinogenesis in normal cells and promotes tumor cells in cancer tissues.	Mitophagy suppresses liver cancer in the initial stage; while supports the development of liver cancer in the formed tumors.

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Innovation points

- The review explained the totally different roles of Nrf2 signaling pathway in the diverse hepatic diseases, for example, Nrf2 sometimes suppressed, sometimes contributed to HCC.
- The review hinted that the protective role of mitophagy in the majority of hepatic diseases, however, it may also supported the development of HCC in the later stage.
- Nrf2 pathway and mitophagy are the two vital pathways in the homeostasis of the internal environment. The relationship between them is precise.

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