Images

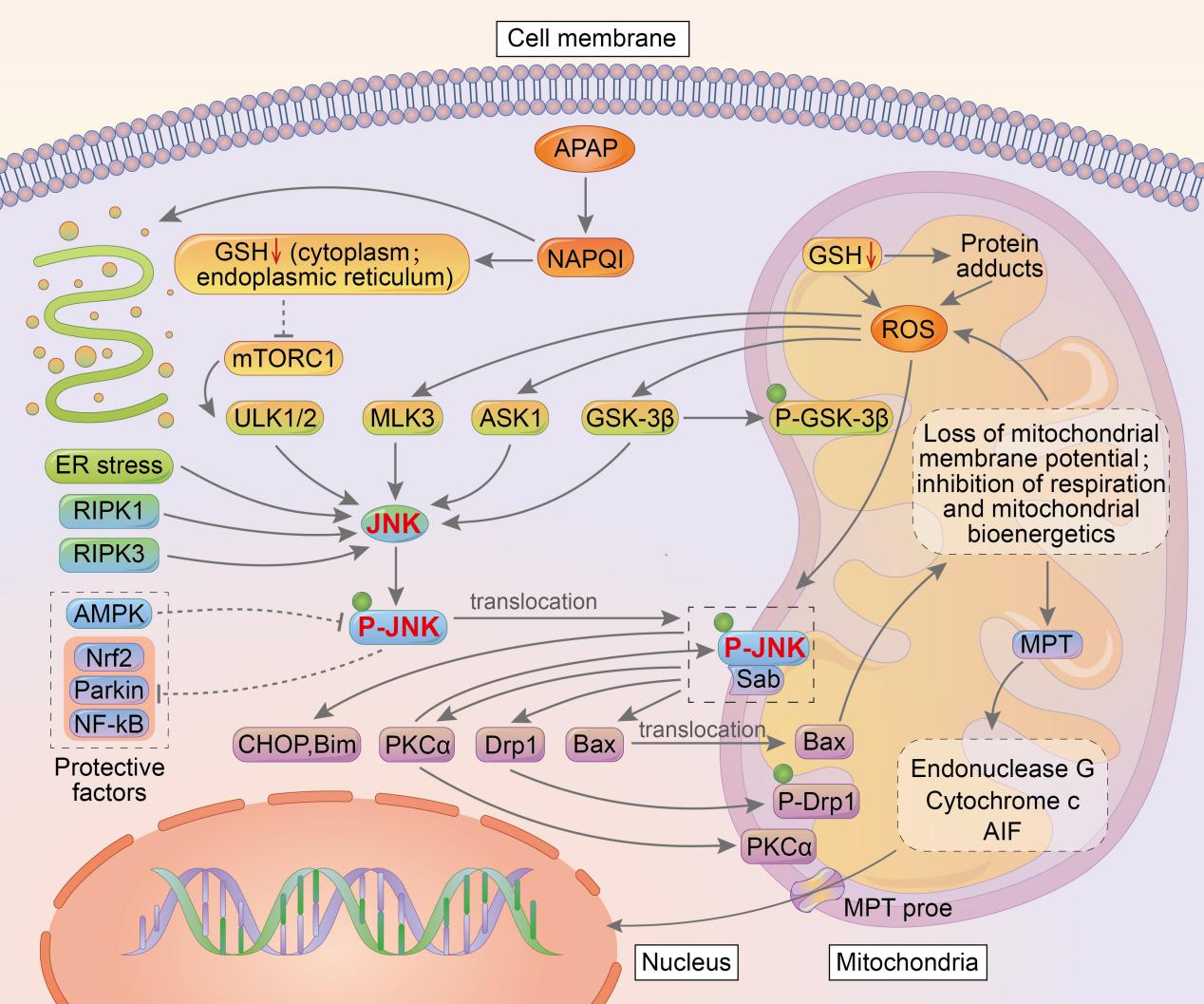


Figure1: The JNK signaling pathway during APAP-induced liver injury. An overdose of APAP produces excessive NAPQI, depletes GSH in the cytoplasm, endoplasmic reticulum and mitochondria, forms mitochondrial protein adducts, damages the electron transport chain and induces initial oxidative stress as well as the production of ROS. In addition, MAP3K, including MLK3, ASK1 and GSK3βis activated， and then leads to JNK activation through MAP2k. Moreover, mTORC1 is inhibited during APAP-induced liver injury and this blocks the phosphorylation of ULK1/2, increases the level of activated ULK1/2 then acts on JNK. The upstream molecules of JNK also include RIPK1 and RIPK3. Endoplasmic Reticulum(ER) stress is also as an important mechanism of APAP-induced liver injury and JNK is a biomarker of ER stress. Notably, phosphorylated JNK translocates to the mitochondria and binds to the adaptor protein, Sab. The downstream molecules of p-JNK, i.e. Bax and Drp1 also translocate to the mitochondria. Furthermore, the downstream events of p-JNK also include PKC-α, CHOP and Bim. Bax particularly induces mitochondrial dysfunction, MPT and continuous production of ROS. In addition, the ROS produced in the mitochondria play an essential role in the sustained activation of JNK. Notably, the MPT pores open and endonuclease G, cytochrome C and AIF are released into the cytoplasm and translocate to the nucleus. Finally, the death or injury of liver cells occurs.

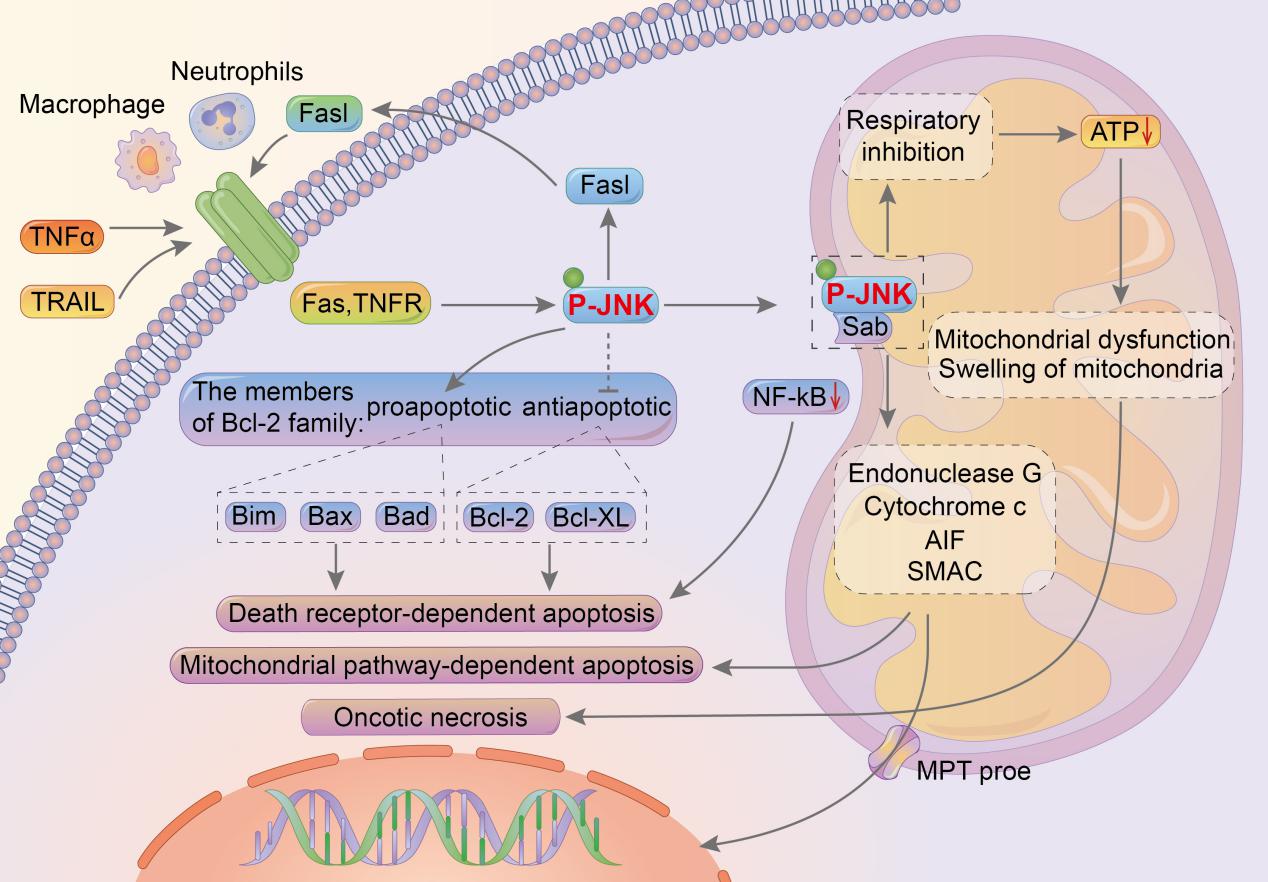


Figure2: JNK mediates APAP-induced death of liver cells. p-JNK promotes the secretion of FasL in an autocrine or paracrine fashion. In addition, production of TNF-α and TRAIL increases in the context of inflammation and these molecules are associated with the corresponding death receptors. Moreover, the JNK signaling pathway is activated to amplify oxidative stress during APAP-induced hepatotoxicity. Thereafter, JNK mediates death receptor-dependent apoptosis. Additionally, p-JNK translocates to the mitochondria and activates the downstream apoptotic events to mediate apoptosis through the mitochondria/caspase9 pathway. Furthermore, p-JNK in the mitochondria induces the downstream events in the mitochondria. For instance, the MPT pores open, mitochondrial respiration is inhibited and ATP synthesis is decreased resulting to insufficient energy for apoptosis. Finally, mitochondrial swelling and oncotic necrosis occurs.