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TNFalpha-signaling in drug-induced liver injury

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Stellingen

behorende bij het proefschrift

TNF α -signaling in drug-induced liver injury

1. Chemicals that show strong Nrf2 activation as well as a perturbation of NF- κ B signaling have a significant drug-cytokine cytotoxic synergy, which is predictive for DILI (*this thesis*).
2. Enhanced drug-induced translation processes initiate PERK-mediated CHOP signaling, thereby sensitizing towards caspase-8-dependent TNF α -induced apoptosis (*this thesis*).
3. The de(ubiquitinase) A20 is a master regulator in the life-death decision upon TNF α stimulation in drug-induced hepatotoxic responses, which, in turn, is kept under control by a network of genes that control its expression level (*this thesis*).
4. TNF α enhancement of diclofenac cytotoxicity in HepG2 cells is an excellent model system to study the detailed molecular mechanism(s) of inflammatory stress signaling in DILI (*this thesis*).
5. Early gene expression is not dependent on the inducing signal intensity, whereas the expression of later genes requires persistent nuclear localizations of the transcription factor (NF- κ B) (Tay *et al*, Nature 2010).
6. Increased activation of hepatic Nrf2 is more important for the detoxification and elimination of electrophiles than reactive oxygen species (Reisman *et al*, Toxicological Sciences, 2009).
7. The liver injury induced by drug/LPS co-exposure can be reproduced by substituting TNF α administration for LPS, which supports the critical importance of this cytokine in the pathogenesis (Shaw *et al*, Journal of Pharmacology and Experimental Therapeutics, 2009).
8. Hepatic cytotoxicity responses are governed by multi-pathway signaling network balance (Cosgrove *et al*, Molecular Biosystems, 2010).
9. One has to dare exposing him-/herself to the unknown in order to be successful and be able to move forward, both in science and in life.
10. Patience is a virtue...also when trypsinizing HepG2 cells.
11. It is fascinating how many and complex processes are needed for life to exist. But it is even more fascinating how seldom they actually fail.
12. It is wise to know what you are looking for, before you start looking for it (Winnie the Pooh).