Role of TNF-α and the NF-κB pathway in drug-induced organ injuries

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Stellingen

Behorende bij het proefschrift

Role of TNF–α and the NF–κB signalling in drug–induced organ injuries

1. *In vitro* exposure of kidney and liver cells with a combination of a drug and TNF-α is an advanced model to study the mechanisms involved in inflammation-mediated aggravation of toxicant-induced injury *in vivo* (this thesis).

2. Co-treatment with cisplatin and TNF-α switches on a strong pro-apoptotic and pro-inflammatory program which is related to altered NF-κB/JNK/c-Jun balance (this thesis).

3. RelB is required for the cisplatin/TNF-α-induced cytoskeletal reorganization and onset of apoptosis in renal cells by controlling a Rho kinase-dependent signalling network (this thesis).

4. Delay in p65 translocation accompanied with general NF-κB inhibition is a common mechanism in the TNF-α-mediated aggravation of drug-induced toxicity in kidney and liver cells (this thesis).

5. An integrated drug safety evaluation involving ´omics´ techniques, subsequent modeling approaches and improved *in vitro* systems that mimick the *in vivo* situation will reduce the future attrition rate of drugs due to safety concerns (this thesis).

6. Whether cells mount an adaptive or maladaptive stress response depends to a large extent on the nature and duration of the stress as well as the cell type (Fulda et al, Int J Cell Biol. 2010).

7. Toxicant-induced biochemical perturbations lead to changes in gene expression to adapt to the new environment (Stevens JL et al, Toxicol Lett. 2000).

8. Although the last decade has witnessed remarkable advances in the fundamental molecular biological aspects of the cytokine tumor necrosis factor (TNF), we still do not know in detail how cells choose between life and death after TNF stimulation in relation to drug toxicity (Bertazza and Mocellin, Front Biosci. 2008).

9. The integration of diverse stimuli to achieve cell type- and stimulus-specific responses depends on the type of NF-κB dimeric complexes formed within the cell (Hoffmann and Baltimore, Immunol Rev. 2006).

10. The best solution to find your way is to first get lost (based on an African proverb).

11. Only by travelling you can test the veracity of stereotypes.

12. A cell is like a human being, it has to choose wisely between different paths to adapt to its environment and survive.

Giulia Benedetti, Bron, March 2013