

Novel insights into toxic and chronic liver disease

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Novel insights into toxic and chronic liver disease: From molecular pharmacology to clinical practice

Miguel E. Zoubek Aranda

Maastricht, woensdag, 29 september 2021 om 13.00 uur

I) Ibuprofen has been convincingly associated with hepatotoxicity, presenting with short latency and cytolytic features, and can potentially progress to a severe condition.

II) Prospective data analysis from Spain and Latin-America demonstrated a higher frequency of ibuprofen DILI cases than reported elsewhere. The clinical presentation of ibuprofen DILI varies between patients and lacks a characteristic drug signature.

III) Cytoplasmic JNK activation in hepatocytes and other non-LPCs is a hallmark of human and murine ibuprofen-induced acute liver injury. Functional *in vivo* analysis demonstrated a pivotal role of hepatocyte-specific JNK2 in mediating protection.

IV) Hepatocytic JNK1/2 appear to have combined effects in protecting mice from APAP- and CCl₄-induced liver injury. JNK inhibition with SP600125 shows off-target effects.

V) Methylprednisolone use can induce severe liver injury, often with an autoimmune phenotype, particularly in patients with multiple sclerosis and Graves' ophthalmopathy.

VI) JNK2 shows a stage-dependent role during CLD progression in NEMO^{Ahepa} mice. Notably, siJnk2 delivery to hepatocytes ameliorated hepatitis, fibrogenesis and HCC initiation and, thus, might be an attractive therapeutic option against CLD.

VII) The functionality of the FasL/Fas axis can interfere in the inflammation-driven tumorigenesis in an experimental model of CLD, which may provide an alternative therapeutic strategy and extend the current limitations in tumor therapy against HCC.

To conclude this dissertation, I would like to share diverse quotes that inspired me during my time as a PhD candidate:

“The more you know, the more you know you don't know”. —Aristotle (384 bc-322bc)

“Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world”. —Louis Pasteur (1822-1895)

“The task of science is to stake out the limits of the knowable, and to center consciousness within them”. —Rudolf Virchow (1821-1902)

“There are no small problems. Problems that appear small are large problems that are not understood”. —Santiago Ramón y Cajal (1852-1934)

*“The best diagnostic tool (for a pathologist) is a microscope connected to the brain”.
—Hans Popper (1903-1988)*