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Connexins: Mediators, Targets and Biomarkers of Liver Toxicity

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Gap junctions are a group of specialized cell junctions that arise from the docking of 2 hemichannels of adjacent cells. These hemichannels are composed of 6 connexins (Cx), which constitute a family of approximately 21 transmembrane proteins that are expressed in a cell-specific way [1-3]. In liver, C×32 is the dominant connexin species in parenchymal cells (i.e. hepatocytes), while the non-parenchymal liver cell population (e.g. stellate cells and Kupffer cells) mainly harbours C×43 [3-6].

Connexins and their channels contribute to cellular signaling in 3 ways. First, gap junctions establish a circuit for direct intercellular communication by controlling the exchange of vital metabolites and secondary messengers between neighbouring cells. Secondly, hemichannels, besides serving as structural precursors of gap junctions, form a pathway for extracellular communication, as they allow the trafficking of a number of biochemical messengers between the cytoplasm of individual cells and their extracellular environment. Thirdly, connexin proteins participate in intracellular communication, by directly interacting with critical homeostasis regulators or by affecting their expression independently of their role as building blocks of hemichannels or gap junctions [2,7,8].

Cx32-based gap junction communication between hepatocytes supports the execution of a number of typical liver functions, including drug metabolism, albumin secretion, ammonia detoxification, glycogenolysis and bile secretion [3-6]. Furthermore, connexin-based signaling, in all its facets, is involved in the control of liver cell growth [2,7] and liver cell death [2,8]. Inherent to this pivotal role in the maintenance of homeostasis, *in casu* in the liver, connexins and their channels are frequent targets of hepatotoxicity. Indeed, a plethora of chemicals negatively affect hepatocellular Cx32 protein levels and gap junctional communication, including environmental pollutants, biological toxins, organic solvents, pesticides, pharmaceuticals, peroxides, metals and phthalates. Since many of these compounds are tumor promoters or epigenetic carcinogens, inhibition of liver gap junctions has been proposed as a promising biomarker of non-genotoxic hepatocarcinogenicity [3,5,9].

The involvement of hepatic connexin-related signaling in the response to chemical insults is bidirectional, as gap junctions not only are sensors, but also mediators of liver toxicity. However, their exact role in this process remains unclear. Thus, Cx32 knock-out mice are more susceptible to both spontaneous [10] and chemical-induced liver [10,11] tumors, which advocates a cytoprotective function for Cx32-based cellular communication. In sharp contrast a number of reports demonstrating that animals which express a dominant negative mutant of Cx32 are resistant to liver injury evoked by carbon tetrachloride [12] or acetaminophen [13], thereby suggesting that Cx32-related signaling aggravates hepatotoxicity. In line with this finding, a recent study showed that pharmacological inhibition of hepatic Cx32-based communication reduces serum alanine aminotransferase levels, inflammation and histopathological evidence of hepatocyte cell death in the liver of acetaminophen-overdosed animals [14]. Such reports clearly underscore the high potential of exploiting connexin channels as drug targets in the treatment of liver toxicity and pathology. Nevertheless, future steps into this direction should be focused on the development of drugs that are able to disentangle hemichannel signaling and gap junction communication. Indeed, although controversial, the current view is that hemichannels, unlike gap junctions, generally act as pathological pores [7,8], thus necessitating distinction between these 2 types of connexin-based channels when intending novel therapeutic strategies.

Connexins are not only of great therapeutic value, but seem equally promising from a clinical diagnostic perspective. In this regard, administration of acetaminophen to rats results in *de novo* expression of Cx43 in hepatocytes, which is co-localised with caspase 3, a key regulator of apoptotic cell death [13]. Cx43 is not naturally occurring in hepatocytes and its production in these cells is also induced by many other hepatotoxicants as well as in several liver pathologies. The mechanism that drives this event, which usually parallels the loss of endogenous Cx32 expression, is unclear, though may rely on the transcriptional machinery [15]. Anyhow, Cx43 represents a novel and general "stress" liver biomarker, which will undoubtedly be cordially welcomed by clinical toxicologists.

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