3D visualization of the biliary tree by X-ray phase-contrast computed tomography

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The hepatic biliary network is a complex 3D mesh of interconnected conduits of different sizes (Roskams et al. 2008). Bile canaliculi which are the finest branches of the biliary network secrete bile, fluid consisting of water, electrolytes, organic molecules such as bile acids, conjugated bilirubin, cholesterol, and phospholipids. Hepatic bile, which is transported into the intestine via the bile ducts, has different physiological functions like solubilization of lipids and fats, drug transport, and xenobiotic excretion (Strazzabosco 1997; Esteller 2008; Jansen et al. 2017). Chronic exposure to hepatotoxic compounds and various pathological conditions such as primary biliary cirrhosis induce a proliferative response of the cholangiocytes that line the bile ducts. This response is known as the ‘ductular reaction’ (Alpini et al. 1997; Kaneko et al. 2015; Gouw et al. 2011; Roskams and Desmet 1998; Vartak et al. 2016). Bile duct ligation in rodents is known to induce clinically relevant cholestatic symptoms, making it highly suitable to study ductular reactions (Tag et al. 2015). Recently, we have demonstrated that ductular reactions follow a highly reproducible sequence of interlobular duct remodeling, where proliferation of cholangiocytes first causes corrugation of the luminal duct surface leading to a strong increase in surface area (Vartak et al. 2016). This increase in surface area is further enhanced by duct branching, branch elongation, and looping. By these processes, a relatively sparse mesh of interlobular ducts around the portal vein transforms to a much denser ductular mesh within 21 days after bile duct ligation (Vartak et al. 2016). Ductular responses were also analyzed after the administration of hepatotoxic chemicals including CCl₄ (Kaneko et al. 2015). In this study, newly formed biliary branches extended into

the pericentral necrotic area induced by CCl₄ suggesting that ductular reactions infiltrate into the damaged tissue areas.

In a recent report, Qin and colleagues from Tianjin, China utilized X-ray phase-contrast computed tomography for the visualization of ductular proliferation in 3D, in a bile duct ligation model (Qin et al. 2017). The contrast in this novel imaging modality arises from the phase shift in X-rays induced while transmission through heterotrophic tissue (Qin et al. 2017). As an interferometry-based technique, it has a much higher sensitivity than absorption-based X-ray imaging. Large sections of tissue up to the size of an entire rodent liver lobe may be reconstructed in 3D with distinguishable signal characteristics of tissue substructures. This is demonstrated in the visualization of the microvasculature of entire liver lobes (Qin et al. 2017). The technique has sufficient resolution and signal-to-noise ratio to detect, segment, and visualize even single interlobular bile ducts with diameters smaller than 20 µm to study their architecture and surface properties. The results of this 3D visualization by X-ray phase-contrast computed tomography confirm the previous findings from confocal reconstructions of KRT19-stained bile ducts (Vartak et al. 2016). In particular, ductular elongation, increased ramification, and increased surface corrugation were observed with a net effect of an increased intraluminal surface area (Qin et al. 2017). However, the imaging modality presented by Qin et al. does not require immunostaining (Vartak et al. 2016) or use of contrast reagents (Kaneko et al. 2015) and is inherently ‘label-free’. Furthermore, as an X-ray based technique, it is in principle applicable as a non-invasive method in vivo which will not have the limitations of a restricted optical field of view.

Hepatotoxicity and changes in tissue morphology that occur in clinically common pathological conditions such as cholestasis represent a major focus of research in toxicology (Luo et al. 2017; Rodrigues et al. 2018; Paech et al. 2017; Leist et al. 2017; Schenk et al. 2017; Hammad et al. 2017, 2014). Visualization and functional analyses of biliary tract domains such a bile canaliculi and ducts remain a major

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challenge (Deharde et al. 2016; Luckert et al. 2017), requiring animal models and tissue extraction as cholestasis cannot yet be reliably simulated in vitro (Stöber 2016; Grinberg et al. 2014; Godoy et al. 2013, 2016). Hence, Qin and colleagues are to be congratulated for expanding the repertoire of tools available for non-invasive in vivo high-resolution 3D imaging of the biliary tract.

Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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