cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Functional and Structural Features of Cholangiocytes in Health and Disease

Luca Maroni,[1] Bai Haibo,[2] Debolina Ray,[3] Tianhao Zhou,[3] Ying Wan,[2] Fanyin Meng,[2,3,4] Marco Marzioni,[1,*] and Gianfranco Alpini[2,3,4,*]

[1]Department of Gastroenterology and Hepatology, Università Politecnica delle Marche, Ancona, Italy; [2]Scott & White Digestive Disease Research Center, Scott & White, Temple, Texas; [3]Department of Medicine, Division Gastroenterology, Texas A&M University Health Science Center, Temple, Texas; [4]Research, Central Texas Veterans Health Care System, Temple, Texas

SUMMARY

Important pathophysiological changes occur in cholangiocytes in response to injury. These will be addressed in the review, with particular emphasis on neuroendocrine factors and morphogenic signaling pathways activated in reactive cholangiocytes.

Cholangiocytes are the epithelial cells that line the bile ducts. Along the biliary tree, two different kinds of cholangiocytes exist: small and large cholangiocytes. Each type has important differences in their biological role in physiologic and pathologic conditions. In response to injury, cholangiocytes become reactive and acquire a neuroendocrine-like phenotype with the secretion of a number of peptides. These molecules act in an autocrine/paracrine fashion to modulate cholangiocyte biology and determine the evolution of biliary damage. The failure of such mechanisms is believed to influence the progression of cholangiopathies, a group of diseases that selectively target biliary cells. Therefore, the understanding of mechanisms regulating cholangiocyte response to injury is expected to foster the development of new therapeutic options to treat biliary diseases. In this review, we discuss the most recent findings in the mechanisms driving cholangiocyte adaptation to damage, with particular emphasis on molecular pathways that are susceptible of therapeutic intervention. Morphogenic pathways (Hippo, Notch, Hedgehog), which have been recently shown to regulate biliary ontogenesis and response to injury, are also reviewed as well as the results of ongoing clinical trials evaluating new drugs for the treatment of cholangiopathies. *(Cell Mol Gastroenterol Hepatol 2015;1:368–380; http://dx.doi.org/10.1016/j.jcmgh.2015.05.005)*

Keywords: Biliary Epithelium; Primary Biliary Cirrhosis; Primary Sclerosing Cholangitis.

The liver, the largest gland in the body, is endowed with critical metabolic functions that involve digestion of food and clearance of toxic substances. At the level of the bile canaliculus, hepatocytes secrete bile, which is then carried to the duodenum through a complex network of bile ducts lined by cholangiocytes.[1–3]

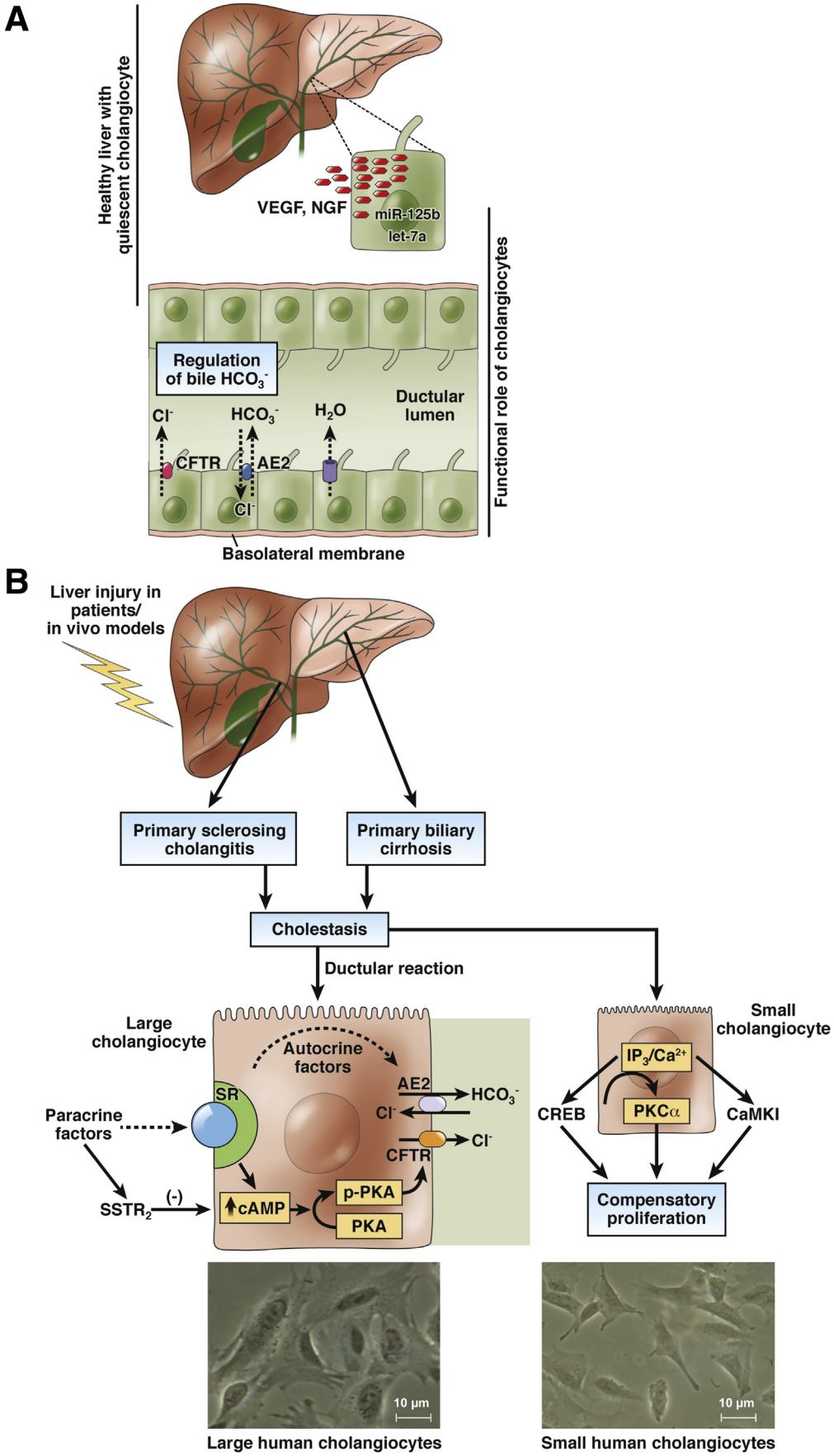
Under physiologic conditions, cholangiocytes actively contribute to the final composition and volume of bile secretion by basal and hormone-regulated events.[4] In normal conditions, one of the most important and well-studied functions of cholangiocytes is secretin-induced release of bicarbonate into bile. The binding of secretin to the secretin receptor (SR) on the basolateral membrane of cholangiocytes leads to the formation of adenosine 3′,5′-cyclic monophosphate (cAMP), protein kinase A (PKA)-dependent phosphorylation of cystic fibrosis transmembrane conductance regulator (CFTR), and the subsequent extrusion of Cl^- in the lumen of bile ducts. Driven by the Cl^- gradient across the plasma membrane, the activation of the apical Cl^-/HCO_3^- anion exchanger 2 (AE2) culminates in the net excretion of bicarbonate in bile,[5] with passive influx of water (Figure 1). As a result, cholangiocytes participate to up to 40% of the so-called bile salt–independent bile flow.[6]

Cholangiocytes are the specific target of a heterogeneous group of human diseases, termed cholangiopathies, that have deep consequences on the biology of these cells.[7] In the present review, we discuss the differences in the structure and function of cholangiocytes and underline the main findings in biliary pathophysiology of the last 10 years. The clinical implications of ongoing research are also specifically addressed.

*Authors share senior authorship.

Abbreviations used in this paper: BA, biliary atresia; BDL, bile duct ligation; cAMP, adenosine 3′,5′-cyclic monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator; FSH, follicle-stimulating hormone; FXR, farnesoid X receptor; GnRH, gonadotropin-releasing hormone; Hes, Hairy/Enhancer of split homolog; Hh, Hedgehog; HNF, hepatocyte nuclear factors; IL, interleukin; IP3, D-myo-inositol 1,4,5-triphosphate; LATS1/2, large tumor suppressor homolog 1/2; miR, microRNA; MT, melatonin; NGF, nerve growth factor; NICD, Notch intracellular domain; OCA, obeticholic acid; PBC, primary biliary cirrhosis; PBP, peribiliary plexus; PKA, protein kinase A; PSC, primary sclerosing cholangitis; RBP-Jκ, recombination signal binding protein immunoglobulin Jκ; Sox-9, sex-determining region Y-box 9; SR, secretin receptor; TGF, transforming growth factor; TGR5, G protein-coupled bile acid receptor; VEGF, vascular endothelial growth factor; UDCA, ursodeoxycholic acid; YAP, Yes-associated protein.

2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2015.05.005


A
Healthy liver with quiescent cholangiocyte
VEGF, NGF
miR-125b
let-7a
Regulation of bile HCO_3^-
Ductular lumen
Cl^-
HCO_3^-
H_2O
CFTR
AE2
Cl^-
Basolateral membrane
Functional role of cholangiocytes
B
Liver injury in patients/ in vivo models
Primary sclerosing cholangitis
Primary biliary cirrhosis
Cholestasis
Ductular reaction
Large cholangiocyte
Autocrine factors
SR
Paracrine factors
$SSTR_2$
(-)
cAMP
p-PKA
PKA
AE2
HCO_3^-
Cl^-
Cl^-
CFTR
Small cholangiocyte
IP_3/Ca^{2+}
PKCα
CREB
CaMKI
Compensatory proliferation
10 μm
Large human cholangiocytes
10 μm
Small human cholangiocytes