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ESSENTIALS Chronic liver disease is responsible for most of the clinical burden of liver disease. Chronic liver injury can occur via a variety of mech- anisms, including sterile inflammation and activation of innate and adaptive immunity. Despite the diversity of disease aetiologies and the ability of the liver to regenerate, a significant minority of patients with chronic liver disease proceed to liver fibrosis and eventually cir- rhosis, which is defined histologically by regenerative hepatocyte nodules surrounded by fibrous bands of matrix. Ongoing liver injury stimulates the development of a myofibroblast cell type which is responsible for matrix remodelling, haemodynamic changes, and immune cell regulation. This typically results in repair without significant modification of the basic liver structure. In a few subjects, this repair process results in alterations of the basic structure of the liver with loss of hepatocyte mass, deposition of collagen, and the development of hypertension in the portal venous system. Although cirrhosis is well defined histologically, there is a spec- trum of severity. In early cirrhosis, patients are asymptomatic but with increasing derangement in hepatic function and portal hypertension, patients can decompensate and develop ascites, coagulopathy, en- cephalopathy, jaundice, renal failure, oesophageal varices, and spon- taneous bacterial infections. Management is focused on removing or reducing ongoing liver injury, and managing cirrhosis-related complications by the use of low-salt diets, diuretics, β-blockers, endoscopic therapy, vasopres- sors, and antibiotics. There is, as yet, no definite role for antifibrotic medications. Introduction The clinically relevant outcomes of chronic injury to the liver paren- chyma are directly dependent on the development of liver cirrhosis or hepatocellular cancer, which is usually secondary to the develop- ment of cirrhosis. Chronic parenchymal injury to the liver stimu- lates a number of adaptive changes including ongoing hepatocyte proliferation, immune cell infiltration and activation, myofibroblast differentiation, and matrix remodelling. These adaptive changes appear universal, but result in the development of cirrhosis in approximately 20% of patients. The aetiology, severity, and duration of

the injury are important, as are poorly defined genetic factors, and the presence of more than one insult seems to accelerate the rate of disease progression. Therapies for cirrhosis are under development, some targeting the individual diseases and others seeking to prevent or modify fibrosis. Removal of scar tissue from a fibrotic organ would still leave a dam- aged organ, but the liver may be uniquely suited for antifibrotic ther- apies due to its well-known capacity to regenerate. For hepatocellular cancer, reducing the burden of cirrhosis is likely the best preventa- tive approach, but current therapies are focused primarily on man- agement after hepatocellular cancer has developed, rather than reducing the risk of hepatocellular cancer development. Aetiology and pathogenesis of liver injury Globally the major aetiological factors for chronic liver disease are viral hepatitis (B and C), alcoholic steatohepatitis, and nonalcoholic steatohepatitis (NASH). Analysis of chronic liver injury by hepatitis B virus (HBV) and hepatitis C virus (HCV) is an exercise in simi- larities and differences. The contrasts are that most adults infected by HBV mount an effective immune response and clear viraemia within 6 months, whereas for HCV chronic infection is typical. After loss of HBV viraemia, subjects maintain a replication capable strand of HBV DNA in the hepatocyte nucleus, but loss of HCV viraemia can result in a total loss of virus. Of relevance to liver injury, both vir- uses are not cytopathic, and liver injury and subsequent adaptive re- sponses are due to the immune response initiated by viral infection. Liver injury in chronic HBV infection In addition to not being cytopathic, HBV also has a low ability to initiate innate immune responses (natural killer (NK) and nat- ural killer T (NKT) cells). In most patients, however, there is a multispecific CD8+ and CD4+ T-cell response, and also the produc- tion of neutralizing autoantibodies. In the absence of neutralizing antibodies, there is chronic infection and usually the persistence of some degree of a T-cell response. The CD4+ T-cell response is important in maintaining a CD8+ and B-cell response, and the CD8+ T-cell response is key to the production of antiviral cytokines (predominantly interferon (IFN)-γ), and crucially cytotoxicity 15.21 Pathobiology of chronic liver disease Wajahat Z. Mehal

 towards hepatocytes. The scale of the anti-HBV T-cell response is modified by a number of viral components, including the hepa- titis B surface antigen and hepatitis B envelope antigen. The site of priming of the CD8+ T cells determines functional capacity of the activated CD8+ T cell, with antigen presentation by nonprofessional antigen-presenting cells such as hepatocytes resulting in a low level of cytotoxicity, generically referred to as exhaustion. A sig- nificant mechanism in the exhausted phenotype is the absence of costimulatory molecules such as programmed cell death 1 (PD1) on the antigen-presenting cell. CD8+ T cells have a key role in clearing HBV from infected hep- atocytes via cytolytic and noncytolytic means, and are likely the drivers of liver injury in chronic HBV infection. CD8+ T cells spe- cific for viral antigens temporarily stop in the sinusoids using plate- lets as an intermediaries to bind to the sinusoidal endothelium. From this position they can make contact with multiple hepatocytes and sample if individual hepatocytes are expressing an antigen/major histocompatibility complex with affinity for their T-cell receptor. An adequate recognition will result in the production of IFN-γ and possible hepatocyte death. An important implication of this is that loss of endothelial fenestration, as occurs in chronic liver injury, may limit the ability of CD8+ T cells to clear HBV-infected hepatocytes. Liver injury in chronic HCV infection HCV shares the lack of cytolytic action with HBV but contrasts with it in stimulating a more diverse immune response, which is subverted from being fully effective in multiple ways. One reason for this pleotropic response is that HCV is highly mutable, and mu- tants that are not targeted by the current immune response become dominant. Hepatocytes generate predominantly a type III IFN re- sponse via

stimulation of a variety of nucleic acid receptors. HCV has developed multiple strategies to inhibit the production of these immune responses, including inhibition of cellular translation, degradation of signalling molecules, blocking of Toll-like receptor (TLR)-3 signalling, and upregulation of anti-inflammatory path- ways. HCV infection also results in dysfunction of many immune cells, including dendritic cells, by uncharacterized pathways. There are multiple reports of HCV infection altering the function of innate immune cells such as NK and NKT cells, but a consensus has not developed. An indirect effect of modulating NK cells' function by HCV is on liver fibrosis. For example, reduction of IFN-γ is expected to reduce liver injury, but promote fibrogenesis. There is a HCV-specific T-cell response after infection, and the strength and scope of this response is a key determinant of reso- lution of infection. CD4+ and CD8+ T cells are both needed for viral clearance, and as for HBV CD4+ T cells provide a stimula- tory role for CD8+ T cells, which are responsible for cytotoxicity towards hepatocytes. In the absence of clearing acute infection, the prolonged antigenic stimulation of CD8+ T cells results in a state of functional hyporeactivity. In contrast to a clear role for CD8+ T cells in liver injury, the universally present B-cell response results in the development of antibodies which are usually not neutralizing, and appear to have no role in the development of liver injury. Alcoholic and nonalcoholic steatohepatitis Alcoholic and nonalcoholic hepatitis are characterized by hepatocyte steatosis, ballooning, liver inflammation, and fibrosis. Nonalcoholic hepatitis is typically due to overnutrition and obesity. Both share many features, and central to the development of the disease pheno- type appears to be the presence of chronic metabolic and oxidative stress in hepatocytes, resulting in hepatocyte death. A crucial feature of the disease is the development of an inflammatory response. Such inflammation that occurs after cell death, in the absence of patho- gens, is termed sterile inflammation, and the cellular circuit respon- sible for it has been identified (Fig. 15.21.1). The term 'damage-associated molecular patterns' (DAMPs) is broadly applied to self-molecules which have the ability to ac- tivate inflammation, and these are proposed to explain immune responses to tissue injury. A large and varied number of DAMPs have been identified (Table 15.21.1). Two contrasting types of cell death are the programmed death termed apoptosis in which there is nuclear degradation and sequestration of cellular contents within plasma membrane blebs, and the unexpected and unregu-lated cell death termed necrosis in which cellular contents are ii: Damage-associated molecular patterns (damps) i: Dying cell Sensing immune cell vi: Immune- mediated injury v: Sterile inflammatory response Healthy cell iv: Inflammatory cytokines iii: DAMP receptor Fig. 15.21.1 Pathological cell death results in the production and release of DAMPs which activate specific receptors on immune cells and initiate release of inflammatory cytokines. This results in a sterile inflammatory response that exacerbates tissue injury. Table 15.21.1 Molecules associated with damage, their receptors, and potential therapies Molecule Receptor Therapy ATP P2X7 Receptor antagonists, Apyrase Cytochrome c Unknown γ-Tocotrienol Defensins CCR6, TLR4 Antagonists and antibodies HMGB1 TLR4, RAGE Neutralizing antibodies HSP TLR4, CD14, CD91 Anti-HSP antibodies Hyaluronic acid TLR2, TLR4 Antagonists Hyaluronidase Mitochondrial DNA TLR9, NLRP3 TLR9 antagonists DNAses Nuclear DNA TLR9 TLR9 antagonists DNAses N-formylated peptides FPR and FPRL1 Antibodies NFPs in combination with TFAM RAGE and TLR9 TLR9 antagonists S100 proteins RAGE Blocking antibodies Uric acid Nonreceptor Xanthine oxidase inhibitor HSP, heat shock protein; RAGE, receptor for advanced glycation endproducts; TFAM, mitochondrial transcription factor.

 relatively intact and extravasate due to disruption of the plasma membrane. In addition to physical retention of DAMPs in apop- totic plasma

membrane blebs, several active processes such as deg- radation of nucleic acids and inactivation of high mobility group box (HMGB)-1 by oxidation limit DAMP activity during apop- tosis. Immunologically silent cell death by apoptosis is dependent on the removal of apoptotic bodies by phagocytosis. In its absence, apoptotic bodies undergo secondary necrosis and lose their integ- rity with spillage of their contents including DAMPs into the extra- cellular environment. Tissue injury is frequently a combination of apoptosis and necrosis. Many DAMPs activate pattern recognition receptors (PRRs), of which TLRs are the best characterized. The function of these re- ceptors is best studied on immune cells, but they are expressed very broadly in the liver with important functions on parenchymal cells. Among the immune cells, Kupffer cells and infiltrating monocytes are key players in this inflammatory response. The inflammasome is a cytosolic multiprotein complex that is vital for the activation of caspase-1 and initiation of many inflammatory responses. Full activation of the inflammasome machinery requires two distinct signals (Fig. 15.21.2). The first signal results in transcriptional upregulation of many molecules, including inflammasome com- ponents and (importantly) the procytokines pro-IL-1β and pro- IL-18. This is provided by TLRs and other receptors with the MyD88 signalling domain via a NF-κB pathway. In the absence of additional signals, the pro-IL-1β produced is inactive and re- mains inside the cell. A diverse range of signals can provide signal 2, including ATP via the P2X7 receptor, and reactive oxygen spe- cies. This results in caspase-1 activation, which in turn activates by cleavage of the inflammatory procytokines pro-IL-1β and pro- IL-18 and results in their secretion from the cell. Identification of the important role of the inflammasome has also identified down- stream pathways such as IL1-R as key therapeutic targets in sterile liver inflammation. Pathophysiology of cirrhosis The processes resulting in liver injury described in the previous section are diverse, yet after chronic liver injury there develops a common phenotype of fibrosis and cirrhosis. Liver cirrhosis is de- fined histologically by regenerative hepatocyte nodules surrounded by fibrous bands of matrix. Traditionally, cirrhosis was also con- sidered to be irreversible, but fortunately the regenerative capaci- ties of the liver can extend to remodelling liver tissue even after the development of some types of cirrhosis. This has become evi- dent with increasing numbers of patients receiving treatment for HCV, and after weight loss in patients with NASH. It is uncertain at what point cirrhosis becomes irreversible, but irreversibility be- comes more likely as the scar thickens, becomes more acellular, and is chemically cross-linked, all of which are associated with long-standing cirrhosis. Cirrhosis likely has a number of stages, but it is unclear how these can be identified and classified. The successes in demonstrating fibrosis regression, even in patients with cirrhosis, indicate that the liver has the capacity to regress scar, increasing optimism that this can be manipulated therapeutically. Understanding of the development of liver fibrosis was greatly advanced by the isolation and characterization of hepatic stellate cells (HSCs). This allowed for identification of their activation, a transdifferentiation process which converts them from vitamin A-storing cells to proliferative myofibroblasts, resulting in their acquisition of a range of functions. Primary among these is the deposition of extracellular matrix, including collagen, during par-enchymal liver diseases. HSC activation unfolds progressively in sequential stages. The ‘initiation’ phase refers to early events that render the quiescent stellate cell responsive to a range of growth factors. Rapid induction of β-platelet-derived growth factor re- ceptor, development of a contractile and fibrogenic phenotype, and modulation of growth factor signalling are the cardinal features of this response. Signal-1 Transcription NLRP ASC Pro-caspase-1 Signal-2 Active caspase-1 Pro-IL-1β IL-1β IL-1β Nucleus TLR Ligand ATP P2X7 Fig. 15.21.2 Inflammasome activation requires a two-signal process. Signal 1 results in transcriptional upregulation of procytokines and inflammasome components. Signal 2 results in assembly of the inflammasome, cleavage of caspase-1, and

activation and secretion of cytokines.

section 15 Gastroenterological disorders 3046 Initiation and progression of for HSC activation The key event in HSC activation is injury to hepatocytes or bil- iary epithelium, subsequent to which many of the factors that are known to activate immune cells can also activate HSC. These include many DAMPs, reactive oxygen species, and hedgehog ligands. The changes initiated by HSC activation can then further provide signals to maintain HSC activation, for example, the enhanced density of the extracellular matrix leads to increasing matrix stiffness, which is a significant stimulus to stellate cell activation in part through in- tegrin signalling. After initiation of activation, HSCs can then re- spond to a number of cytokines and growth factors to which they were previously inert. These signals combine to enhance HSC prolif- eration, contractility, fibrogenesis, matrix remodelling, and increase proinflammatory signalling. Despite significant overlap there are disease-specific pathways of fibrogenesis, but details of the sequence of activation of these pathways is not yet known. Resolution of liver fibrosis Reduction in the number of activated HSCs is critical to the re- versibility of fibrosis, and activated HSCs are known to be removed by at least three processes: apoptosis, senescence, and reversion to an inactivated phenotype. The apoptosis of activated stellate cells has been documented in a rodent experimental fibrosis model, and surprisingly is a feature even during ongoing fibrosis. With removal of the injury insult, the degree of apoptosis increases. Cellular sen- escence is a genetically controlled programme preventing cell div- ision once cells exceed a finite proliferative capacity, and can also occur as a regulated process in response to the loss of proliferative signals. HSCs undergo senescence and then accumulate in experi- mental hepatic fibrosis. Senescent HSCs are also targeted by NK cells for clearance in vivo, thereby linking senescence to HSC apop- tosis. There is also evidence of reversion of activated stellate cells to a more inactivated state in rodent models of fibrosis. Although these reverted HSCs lose many of the features of activation, they have an enhanced capacity to reactivate upon re-exposure to fibrogenic stimuli. The relative contribution of each of these pathways of re- duction of HSC number is unclear, but reversion is thought to be the dominant one. Immune regulation of liver fibrosis The innate and adaptive immune responses are central to the de- velopment of liver injury in many types of chronic liver diseases, and they also significantly modify the development of fibrosis (Fig. 15.21.3). Among the innate cell population, liver macrophages have been most thoroughly investigated and have key functions in fibrogenesis and fibrinolysis. Resident liver macrophages (Kupffer cells) are present at birth and are self-renewing. After injury, they ini- tiate a fibrotic response via recruitment of additional innate immune cells, including large numbers of inflammatory blood monocytes. The infiltrating monocytes undergo a phenotypic change such that they resemble Kupffer cells and have the capacity to produce a wide range of cytokines, many of which have potent proinflammatory or direct profibrotic actions on activated HSCs, such as TNFα and IL-1β, and transforming growth factor (TGF)-β1 and PDGF-BB, re- spectively. They also express a range of chemokines, for example, C- C motif ligands, which recruit myofibroblasts and other leucocytes. Due to their important role in fibrosis these ligands are great can- didates for antifibrotic therapy, indeed several strategies that try to block TGFβ1 activity have demonstrated efficacy in rodent models of liver fibrosis. These include a fully humanized anti-TGFβ1 anti- body, soluble TGFβ1 receptors, blocking peptides, and small mol- ecules to block downstream receptor-like kinase activity. Similarly, inhibition of several chemokines and their receptors have demon- strated antifibrotic efficacy, although these mediators affect different cell types and are involved in many process including angiogenesis, cellular proliferation, and differentiation, and their inhibition may have

significant off-target effects. When liver injury stops, liver macrophage populations that have been vital for fibrogenesis undergo a major phenotypic switch, with enhanced production of the extracellular metalloproteinase Activation Proliferation Apoptosis Profibrogenic macrophage (Ly6Chi) Proresolution macrophage (Ly6Clow) Phenotype switch Quiescent Activated Myofibroblast Apoptotic myofibroblast Natural killer cells TGFβ IL-1β Galectin 3 PDGF TRAIL MMP9 Th2/Th17 Th1 IL-13 (TGFβ) IL-4 IL-17 IFN-γ IL-12 HSC HSC Platelets TRAIL Granzyme Perforin Fig. 15.21.3 HSCs undergo activation, proliferation, and apoptosis. Many immune-mediated factors regulate the transition between these stages.

15.21 Pathobiology of chronic liver disease 3047 enzymes to degrade the excess extracellular matrix and release of proapoptotic ligands which can induce activated HSC apop- tosis. For established fibrosis, enabling this phenotypic switch and enhancing the number of proresolution macrophages is an attractive antifibrotic approach. The relative balance of the T-helper (Th)-1 and Th2 T-cell pheno- type is also an important determinant of fibrosis for innate immune and T cells. The classically proinflammatory Th1 cytokines IFN-γ and IL-12 are typically antifibrotic/fibrolytic, whereas the Th2 cyto- kines IL-4 and IL-13 are profibrogenic. Macrophages show analo- gous M1 and M2 polarization, which is induced by similar cytokines to those responsible for Th1 versus Th2 polarization. However, there are several subtypes of M2 macrophages, with some of them possibly exhibiting antifibrotic effects, complicating simple Th1/M1 versus Th2/M2 polarizing approaches using cytokine blockade. Skewing towards Th1 and M1 is more attractive than general inhibition of the Th2/M2 pathway, although this may enhance classical inflammation and tissue destruction. The two related innate immune cell populations, NK and NKT cells, have opposite effects. NK cells can limit fibrosis by inducing cell cycle arrest and apoptosis of activated HSC. Conversely, deple- tion and adoptive transfer experiments suggest that NKT cells can promote fibrogenesis, but the mechanism of their profibrotic action is not well characterized. Clinical manifestations of cirrhosis Most cirrhosis is subclinical or affects the quality of life with nonspecific symptoms such as malaise, fatigue, insomnia, and re- duced concentration that are not easily attributed to liver disease. Characteristic symptoms develop after cirrhosis has advanced to a significant degree, but there is great variability in their presenta- tion. The development of jaundice (which also occurs in acute liver injury) is the clearest indicator of liver disease and occurs when hepatocyte excretory function is severely compromised. This is vis- ible as a yellow dislocation of the skin, conjunctiva, and mucous membranes. There is a poor correlation between serum conjugated hyperbilirubinaemia and jaundice. Spider angiomas may be visible as small reddish spots, typically on the face and upper trunk, which on closer examination are a conflu- ence of dilated vessels that are fed by a single arteriole. They are due to reduced degradation of oestradiol by the cirrhotic liver. Palmar erythema is also due to this hormonal imbalance and is identified by a relative increase in erythema of the thenar and hypothenar prom- inences, compared to the central palm. On abdominal examination, percussion may reveal a reduced area of liver dullness, although this is very variable. In lean patients, the liver edge may be felt to be hard, but it is usually not tender. The development of severe portal hypertension is associated with a number of physical findings. Splenomegaly is very common but usually not clinically detectable. The development of ascites is a marker of decompensation in cirrhosis and is clinically evident as a shifting dullness on percussion or the presence of a fluid thrill. Clinical examination, however, has poor sensitivity for mild ascites, with reliable detection only when the volume is greater than 1 to 2 litres. With long-standing, severe portal hypertension, prominent veins may been seen radiating from the umbilicus (caput medusa). Diagnosis There is a significant need for diagnostic tools for cirrhosis because

pathognomonic signs are only present very late in disease. This ques- tion typically arises when the diagnosis of a liver disease has been made (e.g. HCV infection, NASH, etc.). The definitive, although still imperfect, test is the liver biopsy. The definition of cirrhosis is histo- logical, and if the tissue sample size is adequate, this is the current gold standard. Its two weak points are the very small sampling size, and the fact that doing the test is very invasive. To overcome these limitations, several noninvasive tests have been developed. These can be broadly categorized as serological or radiological. In general, these noninvasive tests have high sensitivity and specificity to dis- tinguish between normal and cirrhotic livers, but poor accuracy to differentiate between moderate and severe fibrosis. The serological markers utilize surrogates for hepatic function, or turnover of the extracellular matrix. Most have a high accuracy to distinguish between normal and cirrhotic livers, and approxi- mately 80% accuracy for distinguishing mild from moderate fi- brosis. The established radiological tests such as ultrasonography, CT, and MRI have low sensitivity, but in the presence of certain features (an enlarged caudate lobe, inhomogeneous hepatic tex- ture or surface, splenomegaly, or collateral vessels) the specificity is high. Ultrasonography is the most widely used test and can provide valuable information about gross hepatic architecture, atrophy and hypertrophy of hepatic lobes, and thrombosis in the portal system. A technique that quantifies the degree of stiffness of the liver based on the velocity of an elastic wave via an intercostally placed transmitter has been a valuable addition in assessing the degree of liver fibrosis. The velocity of a pressure wave is determined by pulse ultrasonography and correlates with liver stiffness. This test is fre- quently limited, especially in NASH patients, by morbid obesity, ascites, and small intercostal spaces, but has a higher degree of sen- sitivity and specificity for quantifying fibrosis than serological tests. Prognosis There have been many attempts at developing prognostic scoring systems and one of the earliest scoring systems—the Child–Pugh– Turcotte (CPT)—provides fairly good prognostic information and is widely used because of its simplicity (encephalopathy, ascites, bili- rubin, albumin, and INR). It classifies cirrhotic patients into three stages, with 1-year survival for stage A approximately 100%, stage B 80%, and stage C 45%. The more objective Model for End-Stage Liver Disease (MELD) system (creatinine, bilirubin, INR) provides prognostic information over 3 months and is used for prioritizing for liver transplantation. Both scores are affected by medical interven- tions: CPT by management of encephalopathy and ascites, MELD by changes in creatinine, and both by infusion of albumin. The ability to treat the underlying condition clearly has the greatest impact on the prognosis of a cirrhotic patient. The other factor which is significantly associated with prognosis is obesity. In many industrially developed countries, the prevalence of obesity is around 25% and is even higher in patients with liver dis- ease. The presence of obesity is associated with faster progression to cirrhosis in HCV infection and NASH, and is also associated with a

 greater likelihood of developing HCC, even in some precirrhotic pa- tients. Importantly, in a prospectively followed, well-defined cohort, obesity had a deleterious effect on the evolution of compensated cirrhosis of all aetiologies, independent of portal pressure and liver function, with clinical decompensation occurring in 43% and 31% of obese and overweight patients, respectively, compared with 15% of patients with normal body mass index after a median follow-up of 59 months. The ability of weight loss to delay the development of de- compensation in obese patients has not been proven, but it has been shown that weight loss in patients with NASH can reverse all the histological features, including fibrosis and cirrhosis in some cases. It is particularly encouraging that the weight does not need to return to the ideal, and a loss of approximately 10% is sufficient to see histo- logical improvement. Future developments One of the most active areas is the development of antifibrotic therapeutics. Approaches to antifibrotics

range across a wide area of biology, from agents that limit the original injury to those that directly limit the deposition or increase the removal of fibrotic scar tissue. It is known that the extracellular matrix undergoes remodelling even after the development of cirrhosis, and the im- provement in cirrhosis after loss of liver injury by treatment of HCV or weight loss in NASH has demonstrated that cirrhosis is a dynamic state that is amenable to improvement. The great expansion in our understanding of the biology of fibrogenesis has greatly enriched the field of antifibrotic therapeutics and many antifibrotic approaches are being pursued (Table 15.21.2). These are also of much interest in other areas, and two drugs have been approved for idiopathic pulmonary fibrosis. The major limitation to progress in relation to liver fibrosis, however, is the problem of identification of valid end-points for clinical trials: disease progres- sion occurs relatively slowly, repeated sampling by liver biopsy is not practicable, and there is no consensus on noninvasive surro- gates for liver biopsy. FURTHER READING Arulanandan A, Loomba R (2015). Non-invasive testing for NASH and NASH with advanced fibrosis: are we there yet? Curr Hepatol Rep, 14, 109–18. Mehal WZ (2014). The inflammasome in liver injury and non- alcoholic fatty liver disease. Dig Dis, 32, 507–15. Mehal WZ, Schuppan D (2015). Antifibrotic therapies in the liver. Semin Liver Dis, 35, 184–98. Tsochatzis EA, Bosch J, Burroughs AK (2014). Liver cirrhosis. Lancet, 383, 1749–61. Table 15.21.2 Strategies for antifibrotic drugs Reduce HSC proliferation Immunosuppressants HMG-CoA-reductase inhibitors Angiogenesis inhibitors PDG-β receptor antagonism Reduce HSC activation Inhibitors of phosphodiesterase Cytokine regulators: IFN-α, TGFβ modulators, integrin αvβ6 antagonists PPARα, PPARγ agonists Farnesoid X receptor antagonists Histone deacetylase inhibitors

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