SUMMARY

Background
Alcoholic liver disease has a known aetiology but a complex and incompletely known pathogenesis. It is an extremely common disease with significant morbidity and mortality, but the reason why only a relatively small proportion of heavy drinkers progress to advanced disease remains elusive.

Aim
To recognize the factors responsible for the development and progression of alcoholic liver disease, in the light of current knowledge on this matter.

Methods
We performed a structured literature review identifying studies focusing on the complex pathogenetic pathway and risk factors of alcoholic liver disease.

Results
In addition to the cumulative amount of alcohol intake and alcohol consumption patterns, factors such as gender and ethnicity, genetic background, nutritional factors, energy metabolism abnormalities, oxidative stress, immunological mechanisms and hepatic co-morbid conditions play a key role in the genesis and progression of alcoholic liver injury.

Conclusions
Understanding the pathogenesis and risk factors of alcoholic liver disease should provide insight into the development of therapeutic strategies.
INTRODUCTION

Alcohol consumption is well entrenched in the social fabric of many adult populations, virtually constituting a behavioural norm. It is legal, readily available and cheap. Sustained excessive alcohol consumption is a brain-centred addictive behavioural disorder that crosses all boundaries of gender, race, age, economic strata and, in many patients, might lead to alcoholic liver disease (ALD).\textsuperscript{1–3} Heavy drinking significantly increases morbidity and mortality from infectious diseases\textsuperscript{4} and the risk of cardiovascular, brain, pancreatic, renal, cerebral and oncological diseases.

Alcoholic liver disease represents a spectrum of clinical illness and morphological changes that range from fatty liver to hepatic inflammation and necrosis (alcoholic hepatitis) to progressive fibrosis (alcoholic cirrhosis).\textsuperscript{3} Furthermore, sustained excessive alcohol intake favours the progression of other liver diseases, such as virus-related chronic hepatitis, also increasing the risk of hepatocellular carcinoma.\textsuperscript{5–7}

From the 1970s, there was a gradual decline in ALD mortality in many countries. However, in the last decade, the incidence of ALD and subsequent deaths have increased.\textsuperscript{7} Recent data showed that the mortality rate for ALD was 14.3 per 100 000 population in France\textsuperscript{8} and 7.9 per 100 000 in the United States.\textsuperscript{9}

This review aims to describe the current understanding of the pathogenesis and risk factors of ALD. Epidemiologic and experimental studies demonstrated that the degree and duration of alcohol consumption promote the genesis and progression of liver damage. However, only a minority of heavy drinkers have clinical liver disease, suggesting that other factors, constitutional and environmental, influence development and progression of ALD.

The mechanisms of alcohol hepatotoxicity are complex and multifactorial. It is likely that several primary and secondary factors interact to initiate and perpetuate alcoholic liver injury. Primary factors certainly include genetic background and its complex interrelationship with direct ethanol hepatotoxicity and alcohol-induced metabolic and immunological changes. Secondary cofactors, such as nutritional and hepatotoxic co-morbid conditions, can critically contribute to the development of liver disease.\textsuperscript{10–12}

EPIDEMIOLOGY OF ALCOHOLIC LIVER DISEASE

Alcohol consumption patterns and alcoholic liver disease

Alcoholic liver disease develops in patients consuming excessive amounts of alcohol. Alcohol dependency \textit{per se} is not always a pre-requisite for ALD development.\textsuperscript{11} In fact, some patients develop ALD and, in particular, cirrhosis, without a history of dependence. Moreover, the severity of disease does not always correlate with the amount of alcohol intake, and environmental and genetic factors likely play a crucial role in ALD development.\textsuperscript{12, 14}

Although a dose–effect relationship between alcohol intake and alcohol-induced hepatic damage has been reported, there is no set amount of alcohol consumption that could surely predict the development of ALD.\textsuperscript{2, 11, 15, 16} In fact, the majority of long-term heavy drinkers develop fatty liver, but only 10–35% develop hepatitis and only 8–20% will progress to cirrhosis\textsuperscript{11, 17–19} (Figure 1).

Daily ethanol consumption exceeding 40–80 g/day for males and 20–40 g/day for females for 10–12 years will almost certainly lead to ALD.\textsuperscript{2, 20, 21} In a large survey conducted in Northern Europe, the relative risk of ALD significantly increased above a threshold of 7–13 drinks/week for women and 14–27 drinks/week in men.\textsuperscript{2}

The Dionysos Study, a large cohort study aimed to investigate the prevalence of chronic liver disease in

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\includegraphics[width=\textwidth]{Figure1.png}
\caption{Progression of alcoholic liver disease in heavy drinkers.}
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the population of two Northern Italian communities, showed that ≥30 g/day (about 2-5 drink of wine/day) increased the risk of developing ALD in both men and women.\textsuperscript{11} Consuming alcohol with food resulted in somewhat lower risk than consuming alcohol alone.

Drinking patterns leading to high alcohol blood levels for prolonged periods increase the relative risk of ALD. Data gathered prospectively from over 30,000 subjects showed that more than 5 drinks/day increased the relative risk of developing cirrhosis by 14–20.\textsuperscript{22} However, wine drinkers were at lower risk than beer and spirit ones.

Once alcoholic hepatitis and cirrhosis develop, continuing alcohol consumption is a major predictor of poor prognosis. In clinically compensated alcoholic cirrhosis, the 5-year survival is about 90% in persistent abstainers, while lower than 70% in persistent drinkers. Once decompensated liver disease develops, the 5-year survival falls to 30% at best in patients who continue drinking.\textsuperscript{23–26}

PATHOGENESIS OF ALCOHOLIC LIVER DISEASE: THE IMPORTANCE OF THE INNATE BACKGROUND

Genetic factors

In some populations, alcohol consumption is overtly high (>50 g/day). Nevertheless, only a relatively small number of subjects develops ALD and progresses to cirrhosis.\textsuperscript{2, 11} Therefore, there must be other factors that influence ALD development and progression.

Genetic predisposition to ALD has clearly emerged. Family, twin and adoption studies have convincingly shown that genetic determinants play an important role in the development of alcohol dependence and alcohol-related disorders with heritability estimates in the range of 50–60%.\textsuperscript{57–36} The mechanisms through which genes exert this effect are complex and difficult to identify. Studies on gene polymorphism suggest that genes encoding for enzymes that metabolise both ethanol and acetaldehyde influence the predisposition to alcohol dependence, sensitivity to alcohol and ALD-cirrhosis development, even if the results are still non-conclusive.\textsuperscript{37–49} These genes include those encoding for alcohol-dehydrogenase (ADH), aldehyde-dehydrogenase (ALDH) and C2-promoter allele of the gene encoding for cytochrome CYP2E1.

Variants of ADH genotypes encoding for less active alcohol-metabolizing enzymes might facilitate liver damage by either delaying acetaldehyde formation, allowing higher alcohol intakes, or diverting alcohol metabolism through non-ADH pathways, such as the CYP2E1 and other non-oxidative pathways, which are potentially more toxic to the liver.\textsuperscript{39, 40} Similarly, ALDH gene polymorphisms have been shown to influence alcohol sensitivity in some populations (e.g. Asian) and in women, who develop ALD even consuming low amounts of alcohol.\textsuperscript{38, 44, 46} However, these findings on ADH and ALDH genotypes have been contradicted\textsuperscript{42, 47–49} or questioned.\textsuperscript{50, 51} Concerning the genetic variants of CYP2E1, a similar situation prevails. The polymorphism of CYP2E1 gene (C2-promoter allele) significantly differs among races and heavy drinkers with ALD. Alcohol consumption induces CYP2E1 and people with the C2-promoter allele exhibit a far greater ability to metabolise alcohol. This might increase free radical generation and lipid peroxidation, which promotes fatty change in the liver.\textsuperscript{40} In fact, C2 gene frequency is much higher in patients with alcoholic or non-alcoholic fatty liver than in controls.\textsuperscript{40, 41} However, the contribution of C2 gene is still subject to debate, as recent data from a large Caucasian population showed that polymorphism of CYP2E1 is not related to the risk of developing alcoholism and/or ALD.\textsuperscript{42, 47–49}

At present, the association between ALD and the polymorphism of genes encoding for ADH, ALDH and CYP2E1 is far from being defined. A recent meta-analysis\textsuperscript{50} led to the conclusion that there is not enough information to demonstrate a strong association, and more rigorous studies are still needed.

Polymorphism of the gene encoding for CD14 expressed on Kupffer cell has been implicated in the risk of ALD.\textsuperscript{52, 53} A number of studies, reviewed by Tilg and Diehl,\textsuperscript{54} have shown a correlation between endotoxin levels and alcohol-induced liver damage. Chronic ethanol exposure amplifies CD14 expression by Kupffer cell, suggesting sensitization of these cells to endotoxin,\textsuperscript{55, 56} an effect possibly linked to polymorphism in the promoter region of the CD14 gene. In fact, carriers of the T-allele of the CD14 receptor have an increase risk to develop cirrhosis.\textsuperscript{52} This has not been confirmed, as healthy subjects with TT polymorphism appeared to be protected by alcohol-induced liver function abnormalities.\textsuperscript{53}

Chronic alcohol consumption leads to free radical generation that damages DNA,\textsuperscript{57} which is repaired by the base excision-repair pathway involving DNA ligase III, DNA polymerase b and poly(ADPribose) polym-
Reduction of DNA repair represents an important risk factor for the development of ALD. A number of polymorphisms in several DNA repair genes have been discovered. The XRCC1 gene encodes the XRCC1 protein, which complexes with three DNA repair enzymes involved in the base excision-repair pathway. DNA sequencing identified five XRCC1 gene polymorphisms that might reduce DNA repair capacity. An ethnicity-dependent relationship between the XRCC1 gene polymorphism and the risk of alcoholic cirrhosis has been found by a Brazilian case-control study, suggesting that such polymorphism may impair DNA repair capacity that may be overwhelmed by excessive and prolonged alcohol intake.

Lastly, an increased risk of ALD has also been associated to polymorphisms of genes encoding for pro-inflammatory (e.g. TNF-α) and anti-inflammatory [e.g. interleukin (IL)-10] cytokines. In conclusion, alcohol sensitivity and ALD have an important heritable component. It is likely that multiple environmental and genetic factors combine to determine the risk in the individual subject. The goal of future research is to better delineate these factors.

**Gender**

Although the majority of patients with ALD are male, females appear to be more susceptible to the toxic effects of alcohol, as they have a significantly higher risk of developing cirrhosis for any given level of alcohol intake. In a large prospective study, the relative risk of developing cirrhosis during a 12-year follow-up period at an alcohol intake of 28–41 beverages (336–492 g of ethanol) per week was 7.0 for men and 17.0 for women. Thus, women seem to develop ALD after the ingestion of less than half the amount of alcohol in men.

The background for this increase sensitivity is poorly understood, but several hypotheses have been postulated. The first one is the sex difference in ethanol pharmacokinetics. Following the intake of equal amounts of alcohol, women have higher ethanol blood levels than men. This can be attributed to different reasons, including a smaller volume distribution due to lower total body water content because of a lower weight and a higher proportion of fat mass. In addition, the enhanced vulnerability of women to develop ALD has been attributed to a lower gastric ADH activity. A fraction of alcohol ingested is metabolized by gastric ADH before it enters in the blood stream. This first-pass metabolism decreases the systemic availability of alcohol. A diminished gastric ADH activity accounts for a reduced first-pass metabolism in women and is virtually abolished in alcoholic women. However, significant sex differences in gastric ADH activity were not confirmed in other studies. It should be outlined that, in addition to gender, gastric ADH activity is modulated by other factors such as genetics, age, drugs and gastric morphology. Namely, gastric ADH decreases with age, so that this gender difference is found only in younger people. Finally, compared to the liver, gastric metabolism of ethanol is quantitatively much lower.

The gender differences in ALD may also be related to estrogens, which could contribute to ethanol-induced liver injury by increasing gut permeability and portal endotoxin levels and amplifying the Kupffer cell sensitivity to endotoxin through increased expression of the endotoxin receptor CD14 and the pro-inflammatory cytokine tumour necrosis factor alfa (TNF-α). There is evidence that Kupffer cell activation by gut-derived endotoxin is critical in the development of alcohol-induced liver injury. In addition, estrogens also regulate enzymes involved in ethanol metabolism and generation and protection against oxidative stress. Finally, in an animal model, it has been suggested that higher hepatic expression of osteopontin, a matrix-cellular protein could favour hepatic neutrophil infiltration, making females more susceptible to ALD.

Taken together, these data indicate that the mechanisms that underlie the sex difference in alcohol-induced liver damage involve a variety of factors that include alcohol pharmacokinetics and metabolism, and the estrogen-dependent response to gut-derived endotoxin in the liver.

**Ethnic differences**

The prevalence of and the mortality rates for ALD substantially differ among ethnic groups. In the United States, cirrhosis rates are higher in black men than in whites, while Hispanics present the highest cirrhosis mortality. Among active drinkers, Hispanics and blacks are more likely to have a twofold increase in serum aspartate aminotransferase and gamma glutamyl-transpeptidase when compared to whites. Interestingly, no significant difference in alcohol consumption among the various ethnic groups were
found, suggesting that factors other than drinking rates are involved in setting such differences. Namely, demographic factors related to gender, age, income, education and employment as well as biological or environmental factors have been postulated to explain ethnic variations in the development of ALD. However, it is still not clear whether ethnic differences in rates of ALD are due to genetic differences, or different amounts and types of alcohol consumption or different socio-economic status and access to medical care.

PATHOGENESIS OF ALCOHOLIC LIVER DISEASE: THE MECHANISMS OF LIVER DAMAGE

Energy metabolism

The rate of ATP synthesis in liver cells exposed to ethanol is typically reduced. Chronic alcohol consumption depresses the activity of all mitochondrial complexes, except complex II, as several abnormalities in mitochondrial respiratory chain have been described in experimental models of chronic ethanol intoxication. These include: decreased activity and heme content of cytochrome oxidase, impaired electron transport and proton translocation through complex I, decreased cytochrome b content in complex III and reduced function in ATP synthase complex. As a result, the energy metabolism of liver cells can be severely impaired and this would lead to tissue damage.

Energy metabolism can also be altered by hypoxia. Chronic ethanol administration definitely enhances the oxygen uptake rate by liver cells because of the need of its metabolism, which mainly occurs in the centrilobular area of the liver lobule. In such circumstances, the liver blood flow increases, but such an increase does not match the requirements deriving from exalted ethanol metabolism. Thus, centrilobular hypoxia ensues, which can be responsible for liver injury. Centrilobular hypoxia can be further enhanced by the ethanol-induced changes in liver blood flow. In fact, ethanol infusion in a model of rat liver perfusion exerts a dose-dependent increase in portal pressure secondary to intrahepatic vasoconstriction. Such hemodynamic changes are mediated by an imbalance between nitric oxide/endothelin-1 interaction, as ethanol-induced vasoconstriction is inhibited by endothelin-1 antiserum and enhanced by nitric oxide synthase inhibitor L-NMMA. Thus, at high ethanol blood levels, hypoxia might ensue from the combination of reduced perfusion and increased oxygen demand. When blood ethanol levels subsequently decline, lobular perfusion is restored and this can lead to reperfusion injury.

Oxidative stress

Oxidative stress plays a pivotal role in the development of ALD. Oxidation of ethanol to water and carbon dioxide is mediated by three major hepatic enzyme systems: ADH in cytoplasm, microsomal ethanol oxidizing system in smooth endoplasmic reticulum of mitochondria (predominantly CYP2E1) and catalase in peroxisomal membrane. All these biochemical pathways produce acetaldehyde as their toxic by-product (Figure 2).

Alcohol leads to increased liver oxidative stress via generation of highly reactive oxygen species (ROS) and adducts. ADH generates acetaldehyde, which is subsequently oxidized to acetate by ALDH. Acetaldehyde can form hybrid-adducts with reactive residues (e.g. malondialdehyde adduct) acting on proteins or small molecules (e.g. cysteines), mediating lipid peroxidation and nucleic acid oxidation.

Further oxidations in alcohol metabolism are accompanied by an excessive reduction of nicotinamide adenine dinucleotide (NAD), with a shift in the
NADH/NAD ratio. Under normal circumstances, reduction of NAD (NAD → NADH) is finely regulated by the cell Krebs cycle. The shift caused by excessive alcohol consumption is thought to impair carbohydrate and lipid metabolism, finally causing impairment of gluconeogenesis and diversion of metabolism to ketogenesis and fatty acid synthesis. The increased amount of reducing equivalents, such as NADH, leads to their shunting into mitochondria, which induces the electron transport chain components to assume a reduced state. This facilitates the transfer of an electron to molecular oxygen to generate reactive species as superoxide anion. Mitochondrial ROS generation can also derive from the alterations produced in mitochondrial complexes I and III, which have been discussed above. In fact, such alteration can also promote superoxide anion generation within the mitochondria. Thus, mitochondria represent a main site where huge amount of ROS are generated, leading, in turn, to cell damage and necrosis. Finally, the NADH-induced inhibition of mitochondrial β-oxidation leads to accumulation of intracellular lipids, thus promoting steatosis.

Excessive alcohol consumption is also associated with the enzymatic induction of CYP2E1 pathway of alcohol metabolism. The recruitment of this pathway may indirectly contribute to ALD development by excess production of superoxide radicals via the interaction of CYP2E1 with cytochrome reductase, which leads to electron leaks in the respiratory chain and ROS production. The species produced in this cascade can interact with iron (Fenton reaction) generating even more potent hydroxyl, ferryl and perferryl radicals which perpetuate liver damage.

In conclusion, the ability of alcohol to promote oxidative stress and the role of free radicals in alcohol-induced liver damage are well known. However, additional studies are needed to further clarify the pathophysiological mechanisms involved in the major metabolic pathways, in order to provide a sufficient information to set strategies to prevent or attenuate the toxic effects of alcohol.

Immunologic mechanisms

Alcohol exposure can impair the immune response. However, the exact role of the alcohol-induced immune abnormalities in the development of ALD is not defined.

Alcohol intake increases the intestinal permeability to a variety of substances that include bacterial endotoxins, such as lipopolysaccharide. Lipopolysaccharide ‘sensitises’ Kupffer cells by binding with the CD14 receptor. This bond activates the nuclear factor kappa B (NF-κB) which, in turn, causes exaggerated transcription of pro-inflammatory cytokines such as TNF-α, IL-6 and transforming growth factor beta (TGF-β). Whereas TNF-α and IL-6 are mainly involved in cholesterol and synthesis of acute-phase proteins, TGF-β may be critically involved in fibrogenesis through the activation of hepatic stellate cells. The last scenario should be characterized by necro-inflammation, apoptosis and fibrosis, which lead to the progression of liver disease, finally culminating in cirrhosis (Figure 3).

It is likely, however, that the immune-mediated pathophysiological mechanisms leading to ALD are far more complex, and still require further investigation to be fully clarified. In fact, ethanol metabolites, such as acetaldehyde and malondialdehyde, which result from lipid peroxidation, interact, through a covalent binding, with the reactive lysine residues of proteins located on the membranes of hepatocytes. This leads to the formation of stable protein adducts which have been shown to be immunogenic (neo-antigens). These neo-antigens may induce an immune reaction with antibody production or T-cell activation or both, resulting in tissue damage, and possibly ALD. Namely, antibodies to these adducts are present in the sera of mice fed ethanol and heavy drinkers. Moreover, sera from patients with ALD can induce in vitro antibody-dependent cell-mediated cytotoxicity against hepatocytes treated with ethanol. At last, peripheral blood mononuclear T-cells from patients...
with ALD developed significantly higher responses to human serum albumin/malondialdehyde adducts with respect to those developed by T-cells from heavy drinkers without liver diseases or mild to moderate drinking controls.110

PATHOGENESIS OF ALCOHOLIC LIVER DISEASE: THE FAVOURING CONDITIONS

Nutritional factors
Nutritional deficiencies coupled with alcohol consumption can favour the development of ALD. Malnutrition is common in alcoholics,111 because chronic abusers tend to substitute their daily nutritious calories with the ‘empty’ calories provided by ethanol. Other factors contributing to malnutrition are abnormal digestion, increased skeletal and visceral protein catabolism and abnormalities in lipid metabolism.112, 113 Malnutrition per se also increases the oxidative stress by reducing the assumption and promoting the depletion of endogenous antioxidants (glutathione and vitamins A, E and C). Furthermore, patients with ALD are often deficient in folate, thiamine and pyridoxine, which enhance the likelihood of developing anaemia, altered cognitive states and night blindness.113 Protein calorie malnutrition is also frequent and predicts poor survival in ALD.114

The role of obesity as risk factor for the development of ALD is still controversial. While many observations suggest that overweight is an independent factor for the development of ALD,115–118 the Dionysos Study11 did not disclose any association between body weight or body mass index and risk of ALD.

At last, a case–control study on nutrient intake and nutritional patterns in Italian patients with alcoholic cirrhosis suggested that a diet rich in vegetables and fruits was beneficial, compared to animal and non-fruit sugar products.119

Hepatotoxic co-morbid conditions
Iron plays a role in the genesis of ALD:14, 101 chronic alcoholics exhibit a significant increase in hepatic iron concentration14 and ALD patients have an elevated hepatic iron uptake in hepatocytes and Kupffer cells.120 However, it is not known why hepatic iron accumulation occurs and how it contributes to disease progression.

The finding that iron overload does not develop in many heavy drinkers121 has raised the idea that iron overload in drinkers is genetically determined. Following heavy alcohol intake, hepatocytes may lose their ability to compensate for inborn errors in iron metabolism, resulting in iron overload and toxicity.14 The synergy between iron and alcohol is exemplified by hereditary hemochromatosis, where alcohol is known to increase the severity of liver damage and the risk of cirrhosis.122, 123 Furthermore, hepatic iron content is predictive of death in alcoholic patients.124

Up to 70% of hepatitis C virus (HCV) infected patients have a history of alcohol abuse and 30% of patients with ALD are infected by HCV.125, 126 Alcohol intake appears to accelerate the progression of chronic hepatitis C to cirrhosis.127 Although no set amount of alcohol has been established, heavy drinking (>50 g/day), age at infection and male gender are independent risk factors for development of cirrhosis in HCV patients.127 Moreover, serum HCV RNA is significantly higher in habitual than in infrequent alcohol drinkers.128, 129 Lastly, alcohol diminishes the response to interferon128 and increases the risk of hepatocellular carcinoma.130

Experimental models demonstrated that alcohol enhances HCV replicon expression at both mRNA and HCV protein levels.131, 132 The activation of the NF-κβ pathway by alcohol may be responsible for alcohol-mediated upregulation of HCV RNA expression.131, 132 As reported above, the activation of pro-inflammatory cytokines coupled with the direct dual hepatotoxic effect of both HCV and alcohol may accelerate the cyclic bouts of necrosis and fibrosis leading to cirrhosis.131 In addition, alcohol-induced activation of the endogenous opioid system may be an additional mechanism by which alcohol induces HCV expression.132

Data on interaction between alcohol and hepatitis B virus (HBV) infection are few and conflicting. While some studies suggest that HBV infection impairs the survival of patient with ALD,131, 134 a small retrospective study from Taiwan did not report different mortality rates between HBsAg positive and negative patients with alcohol dependence.135

CONCLUSION
Unhealthy alcohol consumption remains a main problem for the public health and is responsible for a high rate of morbidity, affecting various organ and systems, and mortality. The pathophysiology of ALD is quite complex, encompassing factors related to genetics, gender, ethnicity, consumption patterns and co-morbid conditions. From such a composite interplay, several
clinical manifestations ensue, ranging from a benign condition, such as steatosis, to deadly diseases, such as cirrhosis and hepatocellular carcinoma. The mechanisms leading to alcohol-induced liver damage are also complex and not completely clarified. Altered metabolic pathways, energy metabolism impairment, immune-mediated events and oxidative stress all cooperate, with a relatively prevailing importance in different settings (Figure 3). It is generally accepted that ethanol induces an altered redox state associated with free radical generation, resulting in lipid peroxidation, cell-membrane damage and depletion of mitochondrial antioxidants such as reduced GSH. Aldehydes generated by ethanol oxidizing pathways are involved in several toxic effects of alcohol by forming protein adducts which are responsible for activation of specific intracellular signalling pathways modulating collagen synthesis and inflammatory response. This latter effect is also coordinated by Kupffer cells, activated by portal vein endotoxin to release cytokines and chemokines. These changes are, in part, dependent on genetic factors including polymorphism of genes belonging to ethanol-metabolizing enzymes and to inflammatory immune response and, in part, are modulated by the presence of co-morbid conditions. Nevertheless, we are only at the beginning and much remains to be done to elucidate the mechanisms of alcohol-induced liver damage. From the better understanding of pathophysiology, it will result a more defined identification of both risk factors for the development of ALD, enabling us to set preventive strategies, and the means through which liver damage arises, thus providing the background for developing therapeutic approaches.

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