clearly associated to a rapid induction of a broad-range neutralizing antibodies in the early phase of infection, while inability to eradicate the virus was characterized by low neutralizing antibody titers at the same time points [4]. Collectively, these data indicate that production of a broad-range neutralizing humoral response can be crucial for viral clearance, in line with findings in HIV infection, in which neutralizing antibodies act in concert with cell-mediated responses for the control of infection [5].

Several well-characterized human monoclonal antibodies (mAb) endowed with broad-range neutralizing activity at very low concentrations and recognizing the AR3 epitope have been described and are available today [6,7]. Each of these molecules is a potential new tool for prevention and treatment of HCV infection. Indeed, prophylaxis with a single mAb or with a mixture of synergic mAbs, can protect from infection; however, this should be tested in the experimental chimpanzee model of HCV infection. Moreover definition of conserved B-cell epitopes able to elicit protective immunity can be a key element for the design of more effective vaccines.

Conserved regions, such as the one identified by Law et al., are particularly attractive as their mutation can be detrimental to the HCV life cycle. Passive administration of human monoclonal antibodies directed against these conserved epitopes would force the virus to mutate in functionally important regions, and this may represent a novel therapeutic approach in those patients who did not respond to current treatments. Antiviral compounds targeting crucial viral proteins have been demonstrated to be effective in inducing a modification of the viral replication capacity as well as the pathogenic potential of rapidly evolving RNA viruses [8]. Human mAbs directed against conserved HCV epitopes with broad-range neutralization activity are promising antiviral compounds that, through their unique mechanism of action, could be useful in preventing and treating HCV infection.

References

The relationship between liver and heart diseases has been historically a matter of debate. Cardiac hyperdynamic abnormalities, characterized by increased baseline cardiac output and mean arterial pressure, were first reported in 1953 by Kowalski & Abelmann in patients with cirrhosis [1]. Today, the complex hemodynamic alterations present in cirrhotic patients are classified as “cirrhotic cardiomyopathy”, and are recognized to play a role in the pathogenesis of the hepatorenal syndrome and in the mortality associated with TIPS insertion or liver transplantation. However, both old and modern clinicians would certainly agree that when the liver is damaged as in cirrhosis, the principal clinical problem is the liver and not the heart.

With the appearance on the clinical scenario of non-alcoholic fatty liver disease (NAFLD), and with the rapid recognition that NAFLD is the commonest hepatic disorder in the developed world affecting up to a third of individuals and the increasing number of heart disease, the relationship between liver and the heart has been revisited. It is becoming increasingly evident that the so-called “metabolic syndrome” (MS) represents the main link between liver and heart diseases [2]. Subjects with MS are in fact considered at risk of cardiovascular and coronary heart disease, although the clinical usefulness of this syndrome is still debated [3,4].

Recent studies have stressed the importance of fatty liver as an independent predictor of some cardiovascular outcomes [2,5]. Other studies have shown that subjects with abnormal liver enzymes, mainly ALT, are at risk of developing hypertension and diabetes. In addition, NAFLD has been associated with surrogate cardiovascular outcomes such as endothelial dysfunction, abnormal vascular reactivity, increased carotid intimal thickness and the number of carotid plaques [5,6]. Recently, in a prospective study, Ekstedt and colleagues have shown that the 14-year risk of cardiovascular mortality is doubled in tertiary care patients with biopsy-proven NAFLD as compared to a reference population [7].

Cardiac lipotoxicity is a well-described phenomenon associated with insulin resistance, and is generally attributed to an excess production of free fatty acids [8]. Perseghin and colleagues have recently shown that individuals with an increased amount of fat in the liver have also an increased amount of epicardial fat [9]. Despite alterations in cardiac metabolism detected by phosphorous magnetic resonance spectroscopy, these subjects had a normal morphology and function of the heart.

In the general population of the Hoorn Study, Schindhelm and colleagues reported that elevated serum ALT activity significantly increased the 10-year risk of coronary heart disease, even after adjustment for alcohol intake and for the component of MS. They concluded that in the general population, ALT is a predictor of 10-year cardiovascular mortality independently of traditional cardiovascular risk factors, such as systolic blood pressure, HbA1c, LDL-cholesterol and BMI [10]. As acknowledged by the Authors, the study has several limitations: (1) a highly selected population (Caucasians aged 50–75 years); (2) the lack of information on non-fatal disease; (3) the use of ALT as a surrogate marker of NAFLD in place of more reliable imaging or histological procedures; and (4) the lack of exclusion of ALT elevations due to hepatotropic viruses and drugs. Despite these shortcomings the message of the study is clearly important. An additional problem to be considered is that not all the patients with fatty liver do show increased ALT level as recently demonstrated in the general population of the Dionysos Study where 50% of subjects with steatosis detected by ultrasonography had normal levels of ALT [11]. Taking ALT as the only surrogate marker of NAFLD, instead of performing hepatic ultrasound to find out if steatosis was present, probably underestimates the predictive value of ALT, questioning the validity of the message.

Collectively, the paper by Schindhelm and colleagues [10] challenges the assumption that ALT is only a marker of liver disease, and strongly suggests that elevation of ALT and NAFLD are associated with increased risk of cardiovascular disease, and are independent predictors of cardiovascular mortality. Further studies are needed to confirm these findings and to evaluate the possibility that NAFLD may or may not be an early marker (or mediator) of atherosclerosis, and possibly unravel
what is the trigger for lipotoxicity in the liver or in the heart. In the meantime, there is a clear take-home message for the practising physician: perform an evaluation of common cardiovascular risk factors in patients with elevated ALT or NALFD [6].

References


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