

A nice scenario for generation of autoantibodies against CYP2E1 in ALD patients, here offered as a paradigmatic model, has been outlined [249] that involves the following steps:

a) the alkylation of the cytochrome by hydroxyethyl-radicals (HERs) during ethanol metabolism in chronic patients;

b) CYP2E1-HERs may up-regulate an autoimmune response as a consequence of phagocytosis of irreversibly injured hepatocytes by APCs (possibly including also HSCs); however, one should also remind that hepatocytes themselves may present antigens since under stimulation by pro-inflammatory cytokines they have been reported to express class II antigens of MHC and CD-80 [350]; then professional APCs, HSCs or hepatocytes may present these oxidized epitopes to CD4+ T lymphocytes;

c) oxidative stress may favour the activation of quiescent CD4+ T lymphocytes to autoreactive cells that, in turn, can lead to both the expansion of B lymphocytes producing IgG also recognizing native CYP2E1 as well as to the generation of autoreactive CD8+ cells; in this connection, it has been proposed that oxidative stress in liver steatosis (then a condition common to ALD and NAFLD but also often found in HCV patients) may promote the apoptosis of liver regulatory T cells [351] and that oxidative stress - mediated immune response may be sustained also by the characteristic predominance of a Th1 response in relation to steatosis [249]; still related to the prevalence of Th1 cytokine pattern, it should be stressed again that an additional role may be also played by changes in the levels of adipokines like adiponectin and leptin, that have been proposed to modulate both inflammatory and immune response;

d) since CYP2E1 has been reported to be also expressed at the level of hepatocyte plasma membrane, the final step here is then represented by immune-mediated hepatocyte death that can involve both CYP2E1-autoreactive CD8+ T lymphocytes as well as to an antibody - dependent cell cytotoxicity (ADCC).