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Cynomolgus monkeys are successfully and persistently infected with HEV-3 after long-term immunosuppressive therapy

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Epidemiological studies found that hepatitis E virus genotype 3 (HEV-3) infection has been associated with chronic hepatitis and cirrhosis in immunocompromised patients. Our study aimed to investigate the relationship between the host immunosuppressive status and the occurrence of HEV-related chronic hepatitis. Here we describe a successful experimental study, using cynomolgus monkeys previously treated with tacrolimus, a potent calcineurin inhibitor immunosuppressant, and infected with a Brazilian HEV-3 strain isolated from a naturally infected pig HEV infected monkeys were followed up for 160 days post infection by clinical signs; virological, biochemical and haematological parameters; tacrolimus blood levels; and liver histopathology. Immunosuppression was confirmed by clinical and laboratorial findings, such as: moderate weight loss, alopecia, and herpes virus opportunistic infection. In this study, chronic HEV infection was characterized by the mild increase of liver enzymes serum levels, persistent RNAemia, viral faecal shedding, and liver histopathology. Three out of four immunosuppressed monkeys showed recurrent HEV RNA detection in liver samples, evident hepatocellular ballooning degeneration, mild to severe macro and microvesicular steatosis (zone 1), scattered hepatocellular apoptosis, and lobular focal inflammation. At 69 dpi, liver biopsies of all infected monkeys revealed evident ballooning degeneration (zone 3), discrete hepatocellular apoptosis, and at most mild portal and intra-acinar focal inflammation. At 160 dpi, the three chronically HEV infected monkeys showed microscopic features (piecemeal necrosis) corresponding to chronic hepatitis in absence of fibrosis and cirrhosis in liver parenchyma. Within 4-months after infection, cynomolgus monkeys' tacrolimus-immunosuppressed and infected with a Brazilian swine HEV-3 strain induced more severe hepatic lesions progressed to chronic hepatitis without liver fibrosis, similarly as shown in tacrolimus-immunosuppressed SOT recipients. The cause and effect relationship between HEV infection and tacrolimus treatment was confirmed in this experiment.

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