論 文 要 旨

Establishment of disseminated intravascular coagulation (DIC) model by a single iv administration of Escherichia coli-derived lipopolysaccharide (LPS) to cynomolgus monkeys and evaluation of its pathophysiological status.

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We prepared a DIC model by administrating LPS to cynomolgus monkeys, and investigated its potential for evaluations of new medicines for DIC therapy. Peripheral blood mononuclear cells (PBMC) collected from cynomolgus monkeys were incubated with LPS (8 types), and TNF-α levels in the media were measured. LPS from Escherichia coli (K-235) was most appropriate in terms of larger increases and smaller variation in TNF-α levels. PBMC from rats, cynomolgus monkeys or humans were incubated with LPS (K-235), and the TNF-α response to LPS was investigated. The response was comparable between cynomolgus monkeys and humans but small in rats. In an in vivo experiment, LPS (K-235) was administered once intravenously to cynomolgus monkeys with or without recombinant human thrombomodulin (rhTM) to investigate any changes in coagulation and fibrinolysis biomarkers and the suppressive effect of rhTM. The liver, kidney, and lung were examined histopathologically. Almost all of the changes resembled the pathophysiological status of human DIC and were suppressed by co-administration of rhTM. The DIC model resembling human DIC was established by LPS (K-235) treatment in cynomolgus monkeys, and therapeutic effect of rhTM was noted, suggesting that this model is useful in evaluations of the efficacy of new medicines for DIC therapy.