Modeling hemolytic-uremic syndrome: In-depth characterization of distinct murine models reflecting different features of human disease.

Dennhardt S, Pirschel W, Wissuwa B, Daniel C, Gunzer F, Lindig S, Medyukhina A, Kiehntopf M, Rudolph WW, Zipfel PF, Gunzer M, Figge MT, Amman K, Coldewey S (2018) Modeling hemolytic-uremic syndrome: In-depth characterization of distinct murine models reflecting different features of human disease. *Front Immunol* 9, 1459.

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Abstract

Diarrhea-positive hemolytic-uremic syndrome (HUS) is a renal disorder that results from infections with Shiga toxin (Stx) producing Escherichia coli. The aim of this study was to establish well-defined refined murine models of HUS that can serve as preclinical tools to elucidate molecular mechanisms of disease development. C57BL/6J mice were subjected to different doses of Stx2 purified from an E. coli O157:H7 patient isolate. Animals received 300 ng/kg Stx2 and were sacrificed on day 3 to establish an acute model with fast disease progression. Alternatively, mice

received 25 ng/kg Stx2 on days 0, 3, and 6 and were sacrificed on day 7 to establish a subacute model with moderate disease progression. Indicated by a rise in hematocrit, we observed dehydration despite volume substitution in both models, which was less pronounced in mice that underwent the 7 day regime. Compared with sham-treated animals, mice subjected to Stx2 developed profound weight loss, kidney dysfunction (elevation of plasma urea, creatinine, NGAL), kidney injury (tubular injury, loss of endothelial cells), thrombotic microangiopathy (arteriolar microthrombi) and hemolysis (elevation of plasma bilirubin, LDH, free hemoglobin). The degree of complement activation (C3c-deposition), immune cell invasion (macrophages, T lymphocytes), apoptosis and proliferation were significantly increased in kidneys of mice subjected to the 7 day but not in kidneys of mice subjected to the 3 day regime. However, glomerular and kidney volume remained mainly unchanged, as assessed by 3D analysis of whole mount kidneys using CD31 staining with light sheet fluorescence microscopy. Gene expression analysis of kidneys revealed a total of only 91 overlapping genes altered in both Stx2 models. In conclusion, we have developed two refined mouse models with different disease progression, both leading to hemolysis, thrombotic microangiopathy, and acute kidney dysfunction and damage as key clinical features of human HUS. While intrarenal changes (apoptosis, proliferation, complement deposition, immune cell invasion) mainly contribute to the pathophysiology of the subacute model, prerenal pathomechanisms (hypovolemia) play a predominant role in the acute model. Both models allow the further study of the pathomechanisms of most aspects of human HUS and the testing of distinct novel treatment strategies.

Beteiligte Forschungseinheiten

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doi: 10.3389/fimmu.2018.01459

PMID: 29988557