A111 - Association of host-derived hydrogen sulfide with neutrophil phagocytosis of multidrug resistant pseudomonas aeruginosa.

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Introduction:
The role of hydrogen sulfide (H 2S) in the pathogenesis of severe bacterial infections is unclear. We investigated the role of host-produced H 2S through cystathionine-γ-lyase (Cse) in an animal infection model of multi-drug resistant (MDR) Pseudomonas (P.). aeruginosa.

Methods:
Sepsis was induced in wild-type C57Bl6 mice (n=41) and Cse knockout mice (n=41) by i.p. injection of 10^8 cfu/mice MDR P. aeruginosa. Similar experiments were repeated after cyclophosphamide induced neutropenia. Survival was recorded for 7 days. Mice were sacrificed for determination of bacterial load and myeloperoxidase (MPO) activity as a surrogate marker of myeloid cell recruitment. Cytokines were measured in serum by Legendplex inflammatory panel. Total leukocytes from mice spleens, with or without pretreatment with the H 2S donor GYY3147, were incubated with 1 x 10^4 cfu/mL MDR P. aeruginosa. Bacterial clearance was recorded.

Results:
We observed a significant decrease in survival of Cse^-/^- mice as compared to Cse^+/+ mice (12% vs. 47%; p: 0.025). This survival advantage was eliminated in neutropenic mice (17% for both groups, p: 0.873). Cse^-/^- mice had increased pathogen load in the liver (6.57 ± 0.13 vs 5.26 ± 0.50, p: 0.029) and lung (6.70 ± 0.17 vs 5.29 ± 0.55, p: 0.035). MPO activity was lower in Cse^-/^- mice in the liver (634 ± 71 vs 1029± 179, p: 0.048) and lung (7627 ± 585 vs 11121 ± 1468, p: 0.34). Cse^+/+ mice had increased serum levels of IL- 23 (121.13 ± 33.68 vs 31.41 ± 7.02 of Cse^-/-, p: 0.001); MCP-1 (4769.91 ± 908.83 vs 1940.37 ± 1062.65, p: 0.026) and GM-CSF (22.91 ± 4.66 vs 8.11 ± 1.92, p: 0.004). Phagocytic activity of leukocytes from Cse^-/^- mice was reduced compared to Cse^+/+ mice. This deficit was eliminated after GYY4137 pretreatment (Fig.).

Conclusion:
Deficiency of host-derived H 2S leads to increased susceptibility to MDR P. aeruginosa infection due to an inefficient neutrophil chemotaxis and neutrophil mediated phagocytosis.

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Image:
Effect of hydrogen sulfide on the killing of multi-drug resistant Pseudomonas aeruginosa by total leukocytes in vitro.