



IRAK1 functional genetic variant affects severity of septic shock

Submitted by Emmanuel Lemoine on Fri, 07/18/2014 - 09:44

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Type de publication Article de revue

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Editeur Lippincott, Williams & Wilkins

Type Article scientifique dans une revue à comité de lecture

Année 2010

Langue Anglais

Date 2010/12

Numéro 12

Pagination 2287 - 2294

Volume 38

Titre de la revue Critical Care Medicine

ISSN 0090-3493

Résumé en anglais

Objectives: Excessive inflammation is closely related to severity and outcome of sepsis. Because interleukin-1-receptor-associated kinase 1 is a key signaling protein in the activation of NF- κ B during infection, we aimed to evaluate the effect of functionally relevant haplotypes of IRAK1 on severity, development of acute lung injury, and mortality in septic shock. Design: Prospective, observational, cohort study. Setting: Three medical intensive care units in three French university hospitals. Patients: Eight hundred forty-three Caucasian patients with septic shock and 800 sex-matched Caucasian control subjects were enrolled. Interventions: Patients were genotyped for the IRAK1-1595C/T polymorphism, which tagged the IRAK1 functional haplotype. Measurements and Main Results: No significant differences in IRAK1 genotypes were seen between patients and control subjects. Among the septic shock group, the IRAK1 variant haplotype was significantly associated with the need for prolonged mechanical ventilation ($p = .02$). In a prespecified subgroup, this genetic risk was most severe in the youngest patients (age <65 yrs, $p = .005$). Furthermore, in the more severe subgroup of patients, a higher mortality rate was found in patients carrying the IRAK-1 variant haplotype as compared with the wild type ($p = .02$) (odds ratio, 2.1; 95% confidence interval, 1.1-4.8). Conclusions: The IRAK1 variant haplotype is associated with prolonged ventilation in septic shock. In the future, the IRAK1-1595C/T polymorphism might be included in scores such as PIRO (predisposition, insult, response, and organ dysfunction) to adapt preventive and therapeutic interventions in the intensive care unit.

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DOI 10.1097/CCM.0b013e3181f9f9c7 [15]

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