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Letter to the Editor

KIR gene haplotype A is associated with hospital mortality in patients with sepsis

Dear Editor,

Natural killer (NK) cell activity represents a potential prognostic marker in sepsis, although its pathophysiological role is complex and remains poorly understood [1]. NK cell function is regulated by a set of activating and inhibitory cell surface receptors named killer immunoglobulin-like receptors (KIR). The number and type of KIR genes show considerable variability among individuals, but haplotypes fall within two broad types. Haplotype A is defined by the predominance of inhibitory genes and a single activating gene, whereas haplotype B can show multiple stimulatory genes in combination with inhibitory ones. Haplotype B has been recently associated with better clinical outcomes in diseases including myelodysplastic syndromes [2], acute myeloid leukemia after hematopoietic stem cell transplantation [3], and type 1 diabetes [4]. We have previously reported a reduced frequency of two activating KIR genes, 2DS1 and 3DS1, in patients with sepsis compared with critical patients with no sepsis [5]. Here we report a follow-up analysis of the impact of KIR gene haplotypes on clinical outcomes in the same patient cohort.

Patients and methods were described previously [5]. The study was approved by the institutional Research Ethics Committee (CAEE 10555212.6.0000.5327, protocol number 13-0038). To determine KIR haplotypes, DNA was genotyped using the polymerase chain reaction method with sequence-specific oligonucleotide (PCR-SSO kit, One Lambda® Inc., Woodland Hills, USA) for 16 KIR genes (2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 3DL1, 3DL2, 3DL3, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 2DP1, 3DP1 and 3DS1). Haplotype A was identified by the presence of a single activating gene KIR2DS4 combined with inhibitory genes. The presence of more than one activating gene defined haplotype B. Comparison of the KIR haplotype between groups was done with Pearson chi-square. To evaluate the influence of individual genotypes on outcomes, Cox multivariate logistic regression analysis was used. Kaplan–Meier survival analysis was performed for survival curves. A $p \leq .05$ after correction was considered to indicate a statistically significant difference.

Forty-three different KIR gene combinations were found [5]. Haplotype A was identified in 28.41%, and haplotype B in 71.59% samples. Haplotype A was identified in 29.38% septic patients and 8.33% controls, whereas haplotype B was identified in 70.62% septic patients and 91.67% controls (non-significant). Haplotype B was significantly associated with increased hospital survival ($p = .035$) and was more frequent in ICU survivors compared to non-survivors, although this latter comparison fell just short of significance ($p = .055$). Logistic regression revealed that haplotype A was associated with a hospital mortality risk of about 50% (HR = 1.501; IC 95%: 1.036–2.175; $p = .032$, adjusted for APACHE II; Fig. 1A). Among patients with sepsis, haplotype A was associated with a hospital mortality risk of about 56% (HR = 1.556; IC 95%: 1.057–2.28; $p = .025$, adjusted for APACHE II; Fig. 1B).

In conclusion, KIR haplotype A may be a marker of higher probability of hospital mortality in septic patients. These early findings, if confirmed by larger studies, might have implications for the development of therapies based on NK cell function in sepsis.

These findings might implicate on NK cell-based therapies in sepsis.

Compliance with ethical standards

The study was approved by the Institutional Research Ethics Committee (CAEE 10555212.6.0000.5327, protocol number 13-0038) and was conducted in accordance with the Declaration of Helsinki; confidentiality was observed for all samples. All subjects or their sur-

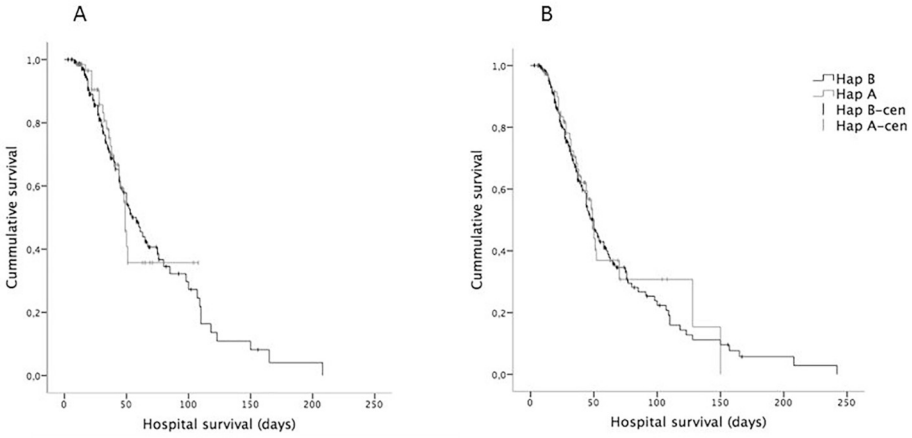

Fig. 1. Survival curves for A critical care patients population with and without sepsis ($n = 271$) and B septic patients ($n = 211$). Lines in grey represent haplotype A; lines in black represent haplotype B. In critical care patients, logistic regression adjusted for APACHE II shows a significant association between haplotype A and hospital mortality (HR = 1.501; IC 95%: 1.036–2.175; $p = .032$). In patients with sepsis, haplotype A was associated with higher hospital mortality (HR = 1.556; IC 95%: 1.057–2.28; $p = .025$).

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rogates received detailed explanations and provided written consent prior to inclusion in this investigation.

Conflicts of interest

The authors declare no competing interests.

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