



A-09

TLR3-Expressing Tumor Parenchyma and Infiltrating NK Cells promote tumor control in HCC

Valerie Chew, Charlene Tow, Caleb Huang, Emilie Bard-Chapeau, Neal G. Copeland, Nancy A. Jenkins, Achim Weber, Kiat Hon Lim, Han Chong Toh, Mathias Heikenwalder, Irene Oi-Lin Ng, Alessandra Nardin, Jean-Pierre Abastado

Tumor Immunology Lab/ Singapore Immunology Network, Agency of Science, Technology and Research (A*STAR), Singapore

Abstract

Background: Hepatocellular carcinoma (HCC) is a highly aggressive cancer that is linked to chronically dysregulated liver inflammation. However, appropriate immune responses can control HCC progression. Here we investigated the role and underlying mechanism of toll-like receptor 3 (TLR3) in HCC. Methods: Cell death, and natural killer (NK) cell activation and cytotoxicity were assessed in vitro after treatment with the TLR3 ligand poly(I:C). The effect of TLR3 on the tumor parenchyma and infiltrating immune cells was investigated in a spontaneous liver tumor mouse model and a transplanted tumor mouse model (n = 3-9 mice per group). Immunohistochemistry and quantitative polymerase chain reaction were used to analyze tumor samples from 172 HCC patients. Paired t tests and analysis of variance tests were used to calculate P values. The relationship between TLR3 expression and survival was determined by the Kaplan-Meier univariate survival analysis and a log-rank test. All statistical tests were two-sided. Results: TLR3 activation increased cell death in the TLR3⁺ SNU182 HCC cell line (30.5% vs 8.5%, P = .03) and promoted NK cell activation (32.6% vs 19.4%, P < .001) and cytotoxicity (relative 4-fold increase, P = .03) in vitro. In vivo, poly(I:C) treatment increased intratumoral chemokine expression, NK cell activation and tumor infiltration, and proliferation of tumor-infiltrating T and NK cells. Proliferation of tumor parenchyma cells was decreased. Also, expression of chemokines or treatment with poly(I:C) decreased tumor growth. TLR3 expression in patient samples correlated with NK cell activation, NK and T cell tumor infiltration, and inversely correlated with tumor parenchyma cell viability. TLR3 expression was also associated with longer survival in HCC patients (hazard ratio of survival = 2.1, 95% confidence interval = 1.3 to 3.4, P = .002). TLR3 is an important modulator of HCC progression and is a potential target for novel immunotherapy.