Toll-like Receptor 3 suppression as an escape mechanism to apoptosis associated with poor prognosis in hepatocarcinoma

AUTHORS (Times New Roman, font12, Upper-case letters, Italic)
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Purpose:
Toll-like receptor 3 (TLR3) detects dsRNA and triggers not only inflammation but also apoptosis in human epithelial cancer cells. As low level of TLR3 has been associated with poor prognosis in hepatocarcinoma (HCC), we explored the role of TLR3-triggered apoptosis in HCC development.

Experimental Design: (Times New Roman, font12)
RT-qPCR, Western Blot, comparative genomic hybridization and immunohistochemistry were used to analyze human and mouse HCC cell lines, primary human hepatocytes (PHH) and primary hepatoma cells. Functional analyses were performed after lentiviral restoration of TLR3 in hepatoma cells. The role of TLR3-triggered apoptosis in hepatocarcinogenesis was analyzed in vitro with PHH and in vivo with SV40 T-antigen transgenic mice. Correlation between TLR3 expression and survival was tested by Kaplan–Meier univariate analysis. Validations were performed with EBI and TCGA online data.

Results: (Times New Roman, font12)
Low levels of TLR3 mRNA in tumor vs. non-tumor matched tissue was observed in 20 % (26/126) of primary HCC and was predictive of recurrence-free disease after surgical resection in both univariate (hazard ratio [HR], 1.79; 95% confidence interval [CI]: 1.04 - 3.06; P = 0.03) and multivariate analyses (HR= 1.73; CI: 1.01 – 2.97; P = 0.04). Immunohistochemistry confirmed the frequent suppression of TLR3 in human and mouse primary hepatoma cells. Genetic and transcriptional mechanisms contributed to TLR3 suppression. Re-expression of TLR3 restored inflammatory response, sensitized hepatoma cells to TLR3-triggered apoptosis, and restrained the transformation of normal hepatocytes in vitro and in transgenic mice in vivo.
Conclusion: (Times New Roman, font12)

Low TLR3 mRNA is predictive of poor prognosis in HCC and protects transforming hepatocytes from TLR3-triggered apoptosis.