Tumori, 97: 350-357, 2011

A possible mechanism of impaired NK cytotoxicity in cancer patients: down-regulation of DAP10 by TGF-β1

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ABSTRACT

Aims and background. Elevated TGF-β1 secretion and down-modulation of NKG2D underlies impaired NK cytotoxicity in cancer patients. However, the molecular mechanism of immunosuppression by TGF-β1 is not yet clarified.

Methods. IL-2-activated human NK cells were cultured with TGF-β1. Protein levels of NKG2D and DAP10 were examined by FACS or immunoblot analyses. Real-time RT-PCR was performed to quantify the transcription levels. MAPK inhibitors were used to investigate intracellular signaling.

Results. TGF-β1 down-regulated total and surface NKG2D, which was partially dependent on transcriptional regulation. TGF-β1 treatment of human NK cells resulted in significant changes in both transcriptional and translational levels of DAP10. Moreover, treatment with bafilomycin A1 or folimycin restored total NKG2D levels in TGF-β1-treated NK cells. The impaired NKG2D down-modulation by TGF-β1 was not associated with activation of the MAPK signaling pathway.

Conclusions. TGF-β1 down-modulates surface NKG2D expression by controlling the transcriptional and translational levels of DAP10.

Key words: human NK cells, NKG2D, TGF-β, DAP10, tumor immunity.

Acknowledgments: This study was supported by grants of the Korea Health 21 R&D Project (A050564 & A062260) and the National R&D Program for Cancer Control, Ministry of Health & Welfare (0320020-2), Republic of Korea. The authors would like to thank Yung-Jue Bang and Sang-Gyun Kim for discussions and for proofreading of this manuscript.

The authors indicated no potential conflicts of interest.

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Received August 4, 2010;
accepted February 16, 2011.