Author's Accepted Manuscript

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PII: S0014-4827(18)30678-5
DOI: https://doi.org/10.1016/j.yexcr.2018.08.014
Reference: YEXCR11165

To appear in: *Experimental Cell Research*

Received date: 2 June 2018
Accepted date: 8 August 2018

Cite this article as: Sai Han, Ying Wang, Xuejiao Shi, Liju Zong, Lu Liu, Juan Zhang, Qiuhong Qian, Jing Jin, Yana Ma, Baoxia Cui, Xingsheng Yang, Beihua Kong and Youzhong Zhang, Negative roles of B7-H3 and B7-H4 in the microenvironment of cervical cancer, *Experimental Cell Research,* https://doi.org/10.1016/j.yexcr.2018.08.014

Negative roles of B7-H3 and B7-H4 in the microenvironment of cervical cancer

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Abstract:

Although persistent human papilloma virus (HPV) infection exerts a crucial influence on cervical carcinogenesis, other factors are also involved in its development, such as intraepithelial lesions and cervical cancer. B7-H3 and B7-H4, which have been reported to be co-regulatory ligands in the B7 family, had been found to be overexpressed in cervical cancer and correlated with adverse clinicopathological features and poor prognosis in our previous studies. In this study, we sought to explore the effects of B7-H3 and B7-H4 on the cervical microenvironment. Among several immune cytokines, interleukin-10 (IL-10) and transforming growth factor (TGF) β1 stand out as important immunosuppressive factors. Our studies found that IL-10 expression increased with pathological change levels and significantly correlated with cervical cancer differentiation ($P<0.05$). TGF-β1 correlated with lymph node metastasis (LNM) ($P<0.01$). Expression of B7-H3 and B7-H4 positively correlated with the expression of IL-10 and TGF-β1. After co-culture, we found that overexpression of B7-H3 and B7-H4 in cervical cancer cell lines resulted in activation of the cell cycle and decreased apoptosis of U-937 cells. In addition, the contents of IL-10 and TGF-β1, as well as their protein expression levels, increased in co-culture supernatants in U-937 cells, suggesting regulation by the p-JAK2/STAT3 pathway. The in vivo results demonstrated that with the increasing expression of B7-H3/B7-H4, the expression of IL-10 and TGF-β1 also increased significantly. Overall, the expression of B7-H3 and B7-H4 favored an immunosuppressive microenvironment by promoting the production of IL-10 and TGF-β1, thereby resulting in progression of cervical carcinogenesis.

Keywords: cervical cancer; B7-H3; B7-H4; IL-10, TGF-β1; co-culture