

POSTER PRESENTATION

Open Access

Synergistic induction of cancer-related immunosuppression by β 2-adrenergic stress mediators and P38MAPK inflammatory pathway

Ravikumar Muthuswamy^{1*}, Frank Jenkins², Dana Bovbjerg³, Pawel Kalinski^{1,4}From Society for Immunotherapy of Cancer 28th Annual Meeting
National Harbor, MD, USA. 8-10 November 2013

Background

Psychological stress has been implicated in promoting cancer recurrence and progression, but the magnitude of this effect and underlying mechanism remain unclear. In attempt to address this controversy, we have evaluated the impact of stress on molecular and cellular components of cancer Immune-surveillance and tested the hypothesis that the impact of stress in promoting tumor-associated immune suppression is context-dependent.

Materials and methods

Modulatory impact of epinephrine (EPI) was tested *ex vivo*, in cultured myeloid cells, CD4+ or CD8+ T cells or while tumor tissue explant cultures. Celecoxib (COX-2 inhibitor) was used to assess whether EPI mediated generation of MDSC/Treg involves COX-2 induction. In order to delineate the specific signaling pathway involved in EPI mediated induction of suppressive markers in MDSC, Treg and tumor explant cultures, selective inhibitors of PKA(H89), PKB(MK2206) and p38 MAPK (PH797804) were used.

Results

Epinephrine showed strong synergy with TNF α and IL1mediators of tumor-associated inflammation, in the induction of high levels of mediators of tumor-associated immune suppression (COX-2, IDO) and Treg-attracting chemokine, CCL22. Epinephrine-driven immunosuppressive events were highly dependent on the availability of TNF α or IL1-dirven inflammation. Macrophages cultured in presence of TNF α + EPI suppressed CD3/CD28 stimulated proliferation of naïve CD8+ T cells. CD4+

T cells showed up regulation of suppressive mediator, IL-10, reduced proliferation and reduced IFN γ expression when stimulated in presence of epinephrine. Suppressive effects of EPI were antagonized by celecoxib, and blocked by the combination of propranolol (β 2-adrenergic antagonist) and celecoxib (COX-2 blocker) or by inhibitors of PKA and p38 MAPK pathways.

Conclusions

Current demonstration that immunosuppressive effects of stress mediators are context-dependent and require the component of p38MAPK-mediated inflammation helps to explain current controversy regarding the link between psychological stress and cancer recurrence/progression. That interplay between stress, inflammation and COX-2/PGE2 system in the development of tumor-associated immunosuppression suggests the possibility of new combination immunotherapies of cancer, involving β 2-adrenergic antagonists, COX2 blockers and/or or p38MAPK inhibitors.

Authors' details

¹Surgery, University of Pittsburgh, Pittsburgh, PA, USA. ²Pathology, University of Pittsburgh, Pittsburgh, PA, USA. ³Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA. ⁴Immunology, University of Pittsburgh, Pittsburgh, PA, USA.

Published: 7 November 2013

doi:10.1186/2051-1426-1-S1-P191

Cite this article as: Muthuswamy et al: Synergistic induction of cancer-related immunosuppression by β 2-adrenergic stress mediators and P38MAPK inflammatory pathway. *Journal for ImmunoTherapy of Cancer* 2013 **1**(Suppl 1):P191.

¹Surgery, University of Pittsburgh, Pittsburgh, PA, USA
Full list of author information is available at the end of the article