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Accessibility
EGFR-mediated tumor immunoescape
The imbalance between phosphorylated STAT1 and phosphorylated STAT3

Fernando Concha-Benavente1, Raghvendra M Srivastava2, Soldano Ferrone3, and Robert L Ferris1,2,4,*

1Department of Immunology; University of Pittsburgh; Pittsburgh, PA USA; 2Department of Otolaryngology; University of Pittsburgh; Pittsburgh, PA USA; 3Department of Surgery; Massachusetts General Hospital; Harvard Medical School; Boston, MA USA; 4Cancer Immunology Program; University of Pittsburgh Cancer Institute; Pittsburgh, PA USA

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Abbreviations: APM, antigen-processing machinery; CCR5, chemokine (C-C motif) receptor 5; CTL, cytotoxic T lymphocyte; CXCR3, chemokine (C-X-C motif) receptor 3; DC, dendritic cell; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; IFNγ, interferon γ; IL, interleukin; MAPK, mitogen-activated protein kinase; PSMB9, proteasome (prosome, macropain) subunit, β type, 9; PTPN11, protein tyrosine phosphatase, non-receptor type 11; STAT, signal transducer and activator of transcription; TAA, tumor-associated antigen; TAP, transporter of antigen processing, ATP-binding cassette, sub-family B (MDR/TAP); TGFβ1, transforming growth factor β1; VEGF, vascular endothelial growth factor

The epidermal growth factor receptor (EGFR) supports the escape of malignant cells from immunosurveillance by inhibiting the activation of signal transducer and activator of transcription 1 (STAT1) while promoting that of STAT3. We have recently demonstrated that protein tyrosine phosphatase, non-receptor type 11 (PTPN11, best known as SHP2), a phosphatase that operates downstream of EGFR, is responsible for the dephosphorylation of active STAT1 and for the inhibition of the antigen-processing machinery (APM), hence favoring tumor immunoescape. Thus, EGFR signaling may skew the tumor microenvironment to suppress cellular immune responses.

Compelling evidence from clinical trials testing multiple immunotherapeutic interventions demonstrates that the immune system has the potential to inhibit oncogenesis and tumor progression. Thus, to generate neoplastic lesions, malignant cells must evolve strategies that allow them to evade recognition and elimination by tumor-infiltrating cytotoxic T lymphocytes (CTLs). These escape mechanisms are multiple, influencing most, if not all, the steps that underpin a productive immune response, from the presentation of tumor-associated antigens (TAA) to the susceptibility of cancer cells to lysis. The mechanisms of immunoescape related to the effector phase of cellular immunity have been extensively described. Conversely, how malignant cells avoid the elicitation of cellular immune responses has been investigated to a limited extent, in spite of an increasing body of data showing that target cells have a major impact on the clinical response to T cell-based immunotherapy. Here, we will comment on immunoescape mechanisms stemming from defects in the signal transduction and activator of transcription (STAT) signaling pathway, emphasizing our recent results in models of head and neck squamous cell carcinoma (HNSCC).

We selected HNSCC for our studies since it employs several of the immunoescape mechanisms generally harnessed by malignant cells. Moreover, the etiology of HNSCC encompasses chemical carcinogenesis as well as viral carcinogenesis, hence providing a broad working model. One common mechanism whereby cancer cells evade immune recognition is the downregulation of MHC class I antigen-processing machinery (APM) components such as transporter of antigen processing 1, ATP-binding cassette, sub-family B (MDR/TAP) (TAP1), TAP2 and proteasome (prosome, macropain) subunit, β type, 9 (PSMB9, best known as LMP2), which results in limited TAA presentation.1 These defects are clinically relevant since they are often associated with poor disease outcome among patients affected by a variety of neoplasms. Furthermore, they have a negative impact on T cell-based as well as on antibody-based immunotherapy, at least in settings in which TAA-targeting antibodies trigger or enhance TAA-specific T-cell immune responses.

In HNSCC cells, the downregulation of the APM is mediated (at least in part) by the epidermal growth factor receptor (EGFR)-induced activation of protein tyrosine phosphatase, non-receptor type 11 (PTPN11, best known as SHP2), which dephosphorylates (hence inactivating) signal transducer and activator of
transcription 1 (STAT1). Interestingly, this phenomenon can be counteracted by interferon gamma (IFNγ) treatment as well as by the inhibition of SHP2, which is actually overexpressed by HNSCC cells. We have recently shown that the depletion of SHP2 favors STAT1 activation, in turn promoting the expression of APM components, MHC class-I restricted TAA presentation and activation of TAA-specific CTLs. In addition, the SHP2-mediated suppression of STAT1 signaling inhibits the production of Th1 cytokines by HNSCC cells, since SHP2 inhibition stimulated the secretion of interleukin (IL)-12p70 as well as of IFNγ-dependent chemokine (C-X-C motif) receptor 3 (CXCR3)- and chemokine (C-C motif) receptor 5 (CCR5)-binding chemokines. Interestingly, the activation of SHP2 by EGFR promotes mitogen-activated protein kinase (MAPK) signaling by increasing the half-life of GTP-bound RAS.

Furthermore, it has recently been shown that the inhibition of v-raf murine sarcoma viral oncogene homolog B (BRAF) enhances the IFNγ-mediated upregulation of MHC class I molecules by melanoma cells. Hence, the upregulation of the MHC class I APM observed upon the depletion of SHP2 may be due to increased STAT1 activation as well as to the downregulation of MAPK signaling.

Remarkably, EGFR overexpression, which is frequent in HNSCC cells, not only reduces the level of phosphorylated STAT1 upon the activation of SHP2 but also stimulates the phosphorylation of STAT3, hence promoting the survival, proliferation and dissemination of cancer cells (Fig. 1). As a matter of fact, HNSCC cells also escape immunosurveillance by promoting the establishment of a tumor microenvironment rich in immunosuppressive lymphoid and myeloid cells. Such an immunosuppressive infiltrate forms in response to tumor-derived soluble factors including IL-6, IL-10, transforming growth factor β1 (TGFβ1) and vascular endothelial growth factor (VEGF).

**Figure 1.** Signaling pathways involved in EGFR-mediated immunoescape. Interferon γ (IFNγ) promotes the phosphorylation of signal transducer and activator of transcription 1 (STAT1), favoring the upregulation of multiple components of the MHC class I antigen-processing machinery and hence antigen presentation. Conversely, the activation of protein tyrosine phosphatase, non-receptor type 11 (PTPN11, best known as SHP2) by epidermal growth factor receptor (EGFR) results in STAT1 dephosphorylation as well as in the activation mitogen-activated protein kinase (MAPK) signaling, ultimately inhibiting MHC class I-restricted antigen presentation. Similar to the interleukin-6 receptor (IL-6R), EGFR also promotes STAT3 phosphorylation, stimulating the secretion of immunosuppressive cytokines, such as interleukin-10 (IL-10), transforming growth factor β1 (TGFβ1) and vascular endothelial growth factor (VEGF).


References


Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.