The Multikinase Inhibitor Sorafenib Reverses the Suppression of IL-12 and enhancement of IL-10 by PGE$_2$ in Murine Macrophages

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Conflict of Interest

**Biosante**: Under a licensing agreement between Biosante and the Johns Hopkins University, the University is entitled to milestone payments and royalty on sales of the vaccine product described in the presentation. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

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Sculpting Immunity By Cross-Talk Between Immune Cells and Macrophages

Reciprocal Cytokine Balance of Classically-Activated and Regulatory Macrophages

ERK Activation Promotes the Generation of IL-10-secreting Macrophages

PGE$_2$

Tumor Culture Supernatants

Dibutyrl cAMP

Edwards JP, unpublished data
Sorafenib: A Modulator of Macrophage Cytokine Balance?

- Multikinase inhibitor originally designed to inhibit RAF/MEK/ERK pathways
- Approved for the treatment of renal cell carcinoma and hepatocellular carcinoma
- Negatively regulates tumor growth, cell proliferation, and angiogenesis
- Conditions of strong ERK activation promote the evolution of IL-10-secreting regulatory macrophages
- Regulatory macrophage phenotype (IL-10 secretion) can be reversed by ERK inhibitors
- Regulatory macrophages and tumor-associated macrophages (TAM) are similar in their IL-10 secretion

Could sorafenib reverse the regulatory phenotype of macrophages, and restore pro-inflammatory IL-12 secretion?
Sorafenib Reverses PGE$_2$-mediated Suppression of LPS-induced IL-12 Production

Edwards JP and Emens LA, Int Immunopharm 2010
Sorafenib Reverses PGE2-mediated Suppression of LPS-induced IL-12 Production

Edwards JP and Emens LA, Int Immunopharm 2010
Sorafenib Reverses IL-12 Suppression by cAMP Analogs and Cholera Toxin

Edwards JP and Emens LA, Int Immunopharm 2010
Sorafenib Reverses IL-12 Suppression by Breast Tumor Cell Supernatants

Edwards JP and Emens LA, Int Immunopharm 2010
Sorafenib Reverses IL-10-mediated Activation of STAT-3 and Expression of SOCS-3

Edwards JP and Emens LA, Int Immunopharm 2010
Sorafenib Modulates MAPK Signaling in Macrophages

MAPK/ERK

p38/MAPK

MSK 1/2

Histone H3 Ser10 (and Ser28)

The kinases MSK1 and MSK2 act as negative regulators of Toll-like receptor signaling.

Edwards JP and Emens LA, Int Immunopharm 2010
Sorafenib Partially Inhibits AKT Activation and GSK3-β Phosphorylation

GSK3-β

Promotes Inflammatory Cytokine Production

AKT

p GSK3-β

Suppresses Inflammatory Cytokine Production

Toll-like receptor–mediated cytokine production is differentially regulated by glycogen synthase kinase 3

Edwards JP and Emens LA, Int Immunopharm 2010
Similar Downstream Effects of Sorafenib and MAPK Inhibition

Inhibitors:  
- U0126—MEK1/2  
- SB203580—p38  
- AKT IV—AKT

Edwards JP and Emens LA, Int Immunopharm 2010
Conclusions

In murine macrophages, Sorafenib
- reverses the shift in IL-10/IL-12 balance induced by PGE$_2$
- inhibits PGE$_2$-induced IL-10 secretion, indirectly preventing STAT3 activation
- inhibits p38 MAPK activation, thereby preventing MSK1 activation
- impacts the cytokine profile of macrophages by an ERK-independent mechanism

Further investigation of the impact of Sorafenib on tumor-associated macrophages, and it’s potential role in combination immunotherapy, is ongoing.
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