Abstract: Introduction: The significance of loss of SOCS3, a negative regulator of signaling pathways including those of STAT3 and NF-κB, was examined in mantle cell lymphoma (MCL).

Methods: The protein expression and gene methylation status of SOCS3 were detected using immunohistochemistry/Western blots and methylation-specific PCR, respectively. To evaluate its functional importance, SOCS3 was restored in two SOCS3-negative MCL cell lines using a lentiviral vector.

Results: Loss of SOCS3 protein expression was found in 3/4 MCL cell lines and 18/33 (54.5%) tumors. SOCS3 was found consistently methylated in cell lines (3/4) and tumors (7/7) negative for SOCS3, and was unmethylated in all SOCS3-positive cell line (1/1) and tumors (5/5) examined. Treatment of all 3 SOCS3-negative cell lines with 2′-deoxy-5-azacytidine restored SOCS3 expression. SOCS3 is biologically important in MCL, as lentiviral transfer of SOCS3 in SOCS3-negative cell lines increased their apoptotic activity, downregulated NF-κB-p65, cyclin D1, Bcl-2 and Bcl-xL, and substantially dampened IL-10-induced STAT3 activation. In our cohort (n=33), patients who were ≤ 69 years of age at diagnosis and carried SOCS3-negative tumors showed a trend toward a worse outcome (p=0.1, log-rank).

Conclusion: Loss of SOCS3, a frequent finding in MCL, contributes to the abnormal activation of the STAT3 and NF-κB pathways in these tumors.