Summary

Notch-1 receptor is a highly conserved transmembrane protein that determines differentiation, proliferation and survival during embryogenesis. Upon ligand activation, the receptor is cleaved by metalloproteases, and then its intracellular domain translocates to the nucleus, and induces subsequent activation of target gene transcription. Involvement of Notch signaling in several cancers is well known, but its role in melanoma remains poorly characterized.

In our work, we studied the role of the Notch-1 receptor and the Notch signaling in the progression of melanoma. Here we show that the Notch-1 receptor is expressed in human melanoma malignum tissue specimens, and that the Notch1 pathway is activated in human melanoma. We have showed that blocking Notch signaling suppressed the proliferation of primary melanoma cell lines. We have demonstrated that constitutive activation of the Notch1 intracellular domain enhanced the primary melanoma cell growth both in vitro and in vivo, as well as enhanced their anchorage independent growth, yet had little effect on metastatic melanoma cells. We have found that activation of Notch1 signaling enabled primary melanoma cells to gain metastatic capability. Notch1 activation increases tumor cell adhesion, up-regulates N-cadherin and Mel-CAM expression, as well as FAK phosphorylation. Notch1 activation also enhances tumor cell survival when cultured as three-dimensional spheroids. Furthermore, the oncogenic effect of Notch1 on primary melanoma cells was mediated by β-catenin, which was up regulated following Notch1 activation. Inhibiting β-catenin expression reversed Notch1-enhanced tumor growth and metastasis.

We conclude that the Notch-1 signaling is an active mechanism in the pathogenesis of melanoma. Our data therefore suggest a β-catenin–dependent, stage-specific role for Notch1 signaling in promoting the progression of primary melanoma. This is the first study to show the oncogenic role of Notch-1 in human melanoma malignum.