Cysteinyl leukotriene receptors promote melanoma progression and metastasis

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Background: Cysteinyl leukotrienes (cys-LTs; LTC4, LTD4, LTE4) are pro-inflammatory mediators mainly produced by hematopoietic cells, which enhance inflammation through their receptors, CysLT1R and CysLT2R. They are crucial in causing chronic asthma in humans. The link between inflammation and cancer has sparked interest in the role of cys-LTs in cancer progression and metastasis. Yet, the precise molecular mechanisms through which these inflammatory mediators regulate tumor proliferation and metastasis are still unexplored. A thorough investigation of these molecular mechanisms, and identification of the specific receptor/s responsible, can aid in understanding their therapeutic potential in various cancers like melanoma. Since the inhibitors of these receptors are already FDA approved for asthma treatment, we aim to repurpose these drugs to treat melanoma progression, thereby achieving maximum efficacy with minimal side effects.

Objectives: To determine the mechanistic aspects of how CysLTRs regulate melanoma tumor initiation, progression, and metastasis.

Methods: Protein expression by western blotting and ELISA, transcript expression by qPCR, viability and proliferation by XTT and BrDU, migration using trans-well assay, tumor growth and metastasis examined through in vivo experiments.

Results: B16F10 melanoma cells express high CysLT1R compared to CysLT2R. Further, cys-LTs mediated the activation of major signaling proteins such as ERK and p38 that are important for melanoma survival and proliferation. Moreover, treatment with CysLTR antagonists significantly reduced melanoma cell proliferation, survival, and migration *in vitro*. Accordingly, we observed a significant reduction in the melanoma tumor volume *in vivo* in both *Cysltr1-/-* and *Cysltr2-/-* mice compared to the WT mice. Interestingly, angiogenesis was significantly reduced in *Cysltr2-/-* mice but not in *Cysltr1-/-*.

Conclusion: Therefore, we speculate that while both receptors play a crucial role in tumor proliferation in vivo, CysLT2R is the main driver of angiogenesis and metastasis. Therefore, targeting both these receptors using their specific antagonists can offer effective therapy for melanoma progression.

