Intravital High Resolution Optical Molecular Imaging of Early Events of Tumorigenesis and Metastasis in GFP-Met Transgenic Mice

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Aberrant HGF/SF-Met signaling is important in the pathogenesis of many types of human tumors and is often associated with poor clinical outcome. To follow primary events of tumorigenesis and metastasis, we generated transgenic mice expressing functionally active green fluorescent protein (GFP)-Met chimeric receptor. In parallel we developed high resolution optical molecular imaging methods to allow intravital analysis at single cell resolution. Intravital Image analysis of GFP-Met mice showed enhanced fluorescence in cells of sebaceous glands. Within several months, male mice spontaneously developed sebaceous gland tumors that were metastatic to the lung, kidney, and liver. Using intravital molecular imaging, we observe proliferating single cells in sebaceous glands preceding tumor formation. These cells showed high GFP-Met levels relative to adjacent normal tissue. We also observed single cells spreading from the tumor mass. These cells expressed high GFP-Met levels of and appeared to be single cell precursors of metastases.

We have developed a novel, real time imaging modality, for *intravital* imaging at single cell resolution. Using this modality we can follow and quantitatively evaluate functional activity and localization of a member of the tyrosine kinase growth factor receptor family, Met, in pre-cancerous lesions and possibly pre-metastatic cells, in live animals. This technology should be valuable for pre-clinical evaluation of therapeutic strategies targeting oncogenes as the Met receptor.