Melanoma MetAlert mice: a platform for in vivo imaging and targeting of pre-metastatic niches

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Introduction: Melanoma is a paradigm of cancers with a high potential for colonization of lymph nodes, a process usually preceded by neo-lymphangiogenesis. However, removal of sentinel lymph nodes does not necessarily increase patient survival. Therefore, a key pending question in the field the specific contribution of tumor-induced lymphangiogenesis to the generation of visceral metastases, and if case, what mechanisms are involved. Moreover, anticancer agents able to blunt melanoma-associated lymphangiogenesis and metastasis in a sustained manner and without secondary effects to the normal vasculature have yet to be identified. In particular, the characterization and targeting of pre-metastatic niches has been hampered by the scarcity of physiologically relevant models for live imaging of tumor-associated neolymphangiogenesis.

Materials and methods: We have generated the melanoma-"lymphoreporter" mouse models that allow for whole-body visualization of melanoma initiation and progression in vivo by non invasive methods. These animals are derived from a knock-in system whereby bioluminescence is coupled to the endogenous activation of the Vegfr3 gene, a key lymphatic marker. These Vegfr3-reporters were exploited for gene discovery and drug testing using melanoma cell lines and patient derived xenografts, as well as in genetic backgrounds engineered to recapitulate alterations in BRAF and PTEN characteristic of human melanomas.

Results: We demonstrated that the Vegfr3-Luc models represent a novel "MetAlert" platform since they allow for the visualization of lymphovascular niches at very early stages of the disease (before tumor cells actually colonized distal sites). Moreover, these MetAlert animals guided in the visualization of metastatic relapse after surgical excision of primary melanomas. Analysis of the melanoma secretome combined with histopathological studies in patient biopsies identified the MIDKINE growth factor as a systemic inducer of lymphovascular pre-metastatic niches and a new prognostic factor in melanoma. Moreover, pharmacological studies in the MetAlert mice used identified a novel class of anti-melanoma agents able to synergize with immunomodulatory agents actively pursued in the clinic.

Conclusions: Vegfr3-Luc Lymphoreporter models represent a versatile platform for gene discovery and pharmacological analyses of (pre)metastatic niches. While our studies have focused in melanoma, our MetAlert animal models can be used in other cancer types, were we expect that they would contribute as well to in vivo visualization and targeting of early, intermediate and late stages of tumor progression