AB030. Characterization of the interactions between hepatic stellate cells and tumor cells during uveal melanoma metastatic progression

Léo Piquet[1,2,3], William Pelletier[1], Peter Gerges[1], Julie Bérubé[1,2], Solange Landreville[1,2,3]

[1]Centre de recherche du CHU de Québec-Université Laval, Hôpital du Saint-Sacrement, Québec, QC, Canada; [2]Centre de recherche en organogénèse expérimentale de l'Université Laval/LOEX, Québec, QC, Canada; [3]Département d'ophtalmologie et d'ORL-CCF, Faculté de médecine, Université Laval, Québec, QC, Canada

Background: Uveal melanoma (UM) is the most common primary eye tumor in adults, and the most frequent site of malignant transformation of the melanocytes after the skin. It spreads to the liver in half of the cases, and the death rate following the report of metastasis is 92% at 2 years. Hepatic tropism of UM cannot simply be explained by the blood circulatory system organization, and illustrates the "seed and soil" hypothesis that describes an interaction between tumor cells (seed) and a specific microenvironment (soil). We decided to focus our study on the synergic interaction between UM cells and hepatic stellate cells (HSC), whose role has been previously described in the metastatic progression of colon and pancreatic cancers. Furthermore, HSC have been found surrounding UM liver metastasis, and the UM secretome contains activating cytokines of hepatic stromal cells. Our hypothesis is that HSC provide a specific microenvironment in the liver enhancing the growth of UM cells and increasing their therapeutic resistance. Using an *in vitro* 3D model and an original xenograft mouse model, we aim to decipher the mechanisms of UM metastatic progression, in order to elaborate new therapeutic strategies.

Methods: First, using an agar coating, spheroids were generated with UM cells and were allowed to grow for 72 h. These tumor spheroids were then embedded in Matrigel and the HSC conditioned medium was used to evaluate the impact of the HSC secretome on UM invasion. Next, an original *in vivo* xenograft mouse model was generated, in which metastatic UM cells were injected alone or with human HSC in the spleen of immunodeficient mice. This model allows us to evaluate in 3–6 weeks the metastatic potential of each cell population, and thus to determine the cooperation between HSC and UM cells in the liver.

Results: The HSC conditioned medium increased the invasion of UM spheroids compared to non-conditioned medium in our *in vitro* model. In addition, UM cells inoculated in the mouse spleen alone or with human HSC were able to metastasize to the liver, and the host HSC were also recruited by UM metastases.

Conclusions: Our preliminary results strongly suggest that the secretome of HSC provides a permissive microenvironment for UM metastatic progression. We now have to confirm these results by characterizing the secretome of HSC, in order to identify cytokines or growth factors that increase the invasion of the liver by UM. Our models can be used to test the efficacy of new therapeutic strategies targeting the UM microenvironment.

Keywords: Uveal melanoma (UM); hepatic stelllate cells-interaction; metastasis

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