**Modulation by PCSK9 of the immune recognition of colorectal cancer liver metastasis**

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**Background:** Colorectal cancer liver metastasis (mCRC) are refractory to immunotherapies though effective against other metastatic solid cancers. The proprotein convertase subtilisin/kexin type 9 (PCSK9), discovered by Dr. M. Chrétien's team in 2003, causes the internalization of the LDL receptor on hepatocytes, but could also internalizes the major histocompatibility complex class 1 (MHC-I) from the surface of cancer cells preventing tumor recognition by T lymphocytes. Our goal is to assess whether PCSK9 contributes to immune evasion of liver metastasis.

**Methods:**
**1) Prognostic value of PCSK9.** Correlations between the oncological outcomes of a cohort of 250 patients following mCRC resection and the quantity of PCSK9 at **a)** intra-tumoral levels (immunohistochemistry on tissues and RNA sequencing), **b)** plasmatic levels (ELISA).
**2) In vitro impact of PCSK9 on MHC-I.** Assess the ability of different cancer lines to secrete PCSK9, the co-localization of PCSK9 and MHC-I (PLA) and the modulation of MHC-I (FACS) by the blockage of PCSK9 or the addition of a PCSK9 recombinant protein.

**Results:** In RNAseq analysis of 52 resected mCRC, PCSK9 expression was lower in metastasis classified as immune-reactive compared to non-immune reactive metastasis. Unlike melanoma, cancer lines of the gastrointestinal tract secrete PCSK9. Although proximity ligation assays show a co-localization of PCSK9 with the MHC-I on cancer cell lines, the MHC-I does not seem downregulated by different PCSK9 concentrations. High plasmatic PCSK9 may be associated with poorer survival in patients with resected mCRC. We have developed an immunohistochemical labeling technique for PCSK9 on mCRCs.

**Conclusions:** Our data so far support that PCSK9, produced by both liver and mCRC cells, is associated with lower immunological reactivity in the tumor microenvironment and poorer patient survival. As anti-PCSK9 is clinically approved, we will test in a pilot clinical study whether it can stimulate intra-tumoral immune reactivity when administered before resection of mCRC.