**Development of Targeted Therapies for Liver Metastases: Is Heterogeneity a Major Issue?**

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Targeted cancer therapies are nowadays gaining importance in the effort to provide a more specific tool for patient treatment. Extracellular and membrane cancer protein biomarkers are ideal targets as they bear the potential to be accessible to systemically administered compounds. However, focusing on one biomarker assumes its relative homogenous distribution within the lesion. In the frame of the current work we have explored the heterogeneity of the accessible proteome of liver metastasis from colorectal carcinoma (CRC). Accordingly, we have *ex-vivo* biotinylated accessible proteins from several CRC-liver metastases and divided the specimen in 4 zones: normal, peri-tumoral, tumor-rim and center. The proteins were affinity purified and analyzed for each zone separately using nano-UPLC-MSe proteomics technique. In total over 1500 unique proteins were statistically divided into six patterns of expression. Approximately 1/3 was expressed solely in one of the 4 zones. A further 1/3 was found in all zones. Remaining proteins were present in 2 or 3 regions studied. Interestingly, significant differences were notable between normal tissue collected far away and the one sampled in the peri-tumoral zone. Finally, using IHC and more individual samples we have validated several novel and known proteins for their heterogeneous distribution.

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