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Stromal macrophages closely interact with infiltrating tumor cells in the tumor microenvironment of colorectal cancer

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Background. Tumor loaded macrophages are found in the circulation of colorectal cancer (CRC) patients with possible value as a diagnostic biomarker. Here, we investigate the interaction of CD68+ macrophages (CD68M) with infiltrating tumor cells (tumor buds) in the tumor microenvironment and explore associations of tumor loaded CD68+/PanCK+ macrophages with clinicopathological features.
Methods. PanCK+ tumor buds, stromal (s) and cytokeratin (CK) loaded CD68M were quantified in a multi-punch TMA of 205 CRC patients by immunohistochemical double stain. Tumor buds, sCD68M infiltration, tumorbud/CD68M contact and tumor loaded CD68M were assessed for clinical relevance.
Results. Consistent with published data, presence of tumor buds correlated with more advanced T-Stage (p=0.0041), N-Stage (p=0.003), higher tumor grade (p<0.0001), frequent lymphatic invasion (p=0.0086), venous invasion (p=0.0159), BRAF-mutation (p=0.006) and a poor 5-year survival outcome (p=0.0496). In contrast, sCD68M infiltration predicted long term overall survival (p=0.0242) independently of pT, pN and adjuvant therapy. Further, sCD68M infiltration predicted smaller tumor diameter (p=0.0052) and absence of distant metastasis. sCD68M infiltration was more frequent in adjuvantly treated patients (p=0.0436) and mismatch repair-deficient CRC (p=0.0047). Tumor bud/CD68M contact was found in aggressive cancers with high grade budding (p<0.0001) advanced T-Stage (p=0.0041), N-Stage (p=0.001) and lymphatic invasion (p<0.0001) and was related to poor disease free survival outcome (p=0.0039). CD68M loaded with PanCK+ tumor cell fragments were frequent in the tumor microenvironment (97.6% of cases). No correlation of tumor-loaded CD68M with clinicopathological features was identified.
Conclusions. Interaction between infiltrating tumor cells and macrophages is common in the microenvironment of CRC leading to the generation of tumor loaded sCD68+/CK+ macrophages. The prognostic effect of sCD68M infiltration may be context dependent as a close interaction with tumor buds was observed in aggressive tumors. These preliminary data require careful interpretation as both pro- and anti-tumoral effects of tumor-associated macrophages have been described.

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Colorectal cancer patients in two Austrian regions are differentiated by their microRNA expression profiles

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Background. When comparing colorectal cancer mortality rates in Austria, a dramatic difference in distribution between the east and the west of the country is conspicuous. With mortality culminating in Lower Austria, Vorarlberg has an approximately 25% lower rate. In colorectal cancer as well as in other cancer types, microRNAs present a class of tumour biomarkers due to their often dysregulated expression profiles already in early stages of malignant tumourigenesis. In all types of tissue, microRNAs regulate gene expression at the posttranscriptional level. The aim of this study was to compare microRNA expression profiles of untreated, primary colorectal tumours (pT2) of patients from Lower Austria and Vorarlberg for identification of differentially expressed microRNAs. This would serve as a first explanatory approach for the differing mortality rates and for the characterisation of patients at high risk for recurrence and/or metastasis.
Methods. Formalin-fixed paraffin embedded tissue samples of untreated, non-metastasised patients with primary colorectal tumours (pT2) were matched regarding sex, age, tumour location and differentiation (n=90). microRNA microarray analysis was performed using isolated total RNA (n=44, Exiqon). RT-qPCR was performed to validate the results obtained from microarray profiling.
Results. Microarray analysis revealed a subset of 101 microRNAs whose expression differ significantly (p<0.05) between patients of Lower Austria and Vorarlberg. Among these microRNAs, expression of miR-4668-5p and miR-4491 was highly upregulated, whereas miR-3182 was strongly downregulated when comparing patient profiles of Vorarlberg with those of Lower Austria (≥2-fold change). Additional to those three microRNAs, miR-4695-3p and miR-4301 as well as miR-4511 were differentially expressed in the populations studied (down- and upregulated in patients from Vorarlberg compared to patients from Lower Austria, respectively), although with slightly lower difference. The validation of the microRNA analysis with a total of 90 samples confirmed the highly significant differential expression of miR-4695-3p.
Conclusions. We assume that differential microRNA expression may distinguish patients of both Austrian regions on a molecular biological level, which may offer an explanation for the divergent mortality. This investigation might be a very first starting point for the identification of patients at high risk with a focus on regional differences within one country.

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