Prognosis and Chemosensitivity of Colorectal Cancer are Associated With Changes in Microtubules Composition

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Introduction

It is known that the expression of beta-tubulin isotypes is changed in cancer but there is still not enough data about such alterations in colorectal cancer (CRC) and their impact on prognosis and chemosensitivity. So the objective of this study was to reveal influence of changes in the level of betaI- and betaIII- isotypes of tubulin on CRC outcome.

Methodology

The study was performed on surgical histological material of 125 colorectal adenocarcinomas from 124 patients. Double immunofluorescence with anti-cytokeratin antibody and anti-betaI- or anti-betaIII-tubulin was performed. The level of the betaI-tubulin expression was analyzed by image analyses software: epithelial regions were automatically selected by cytokeratin channel; acquired regions of interest have been used as a mask of selection on tubulin channel; integrated density and area of regions of interest were measured. Expression value was calculated as ratio of integrated density to epithelial region's area and then normalized according to positive and negative controls.

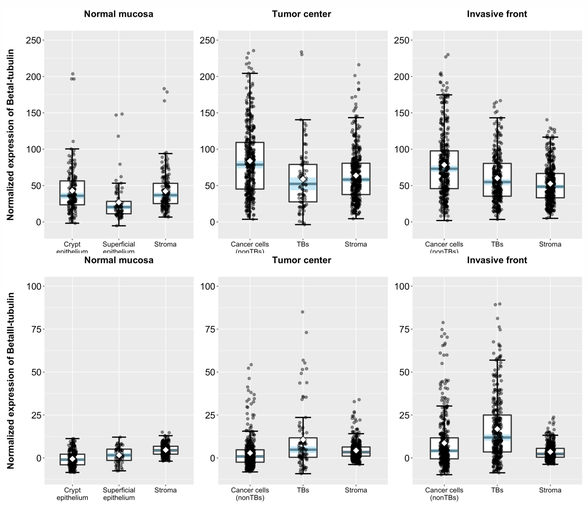

Figure 1. Normalized level of betaI- and betaIII-tubulin expression in different regions

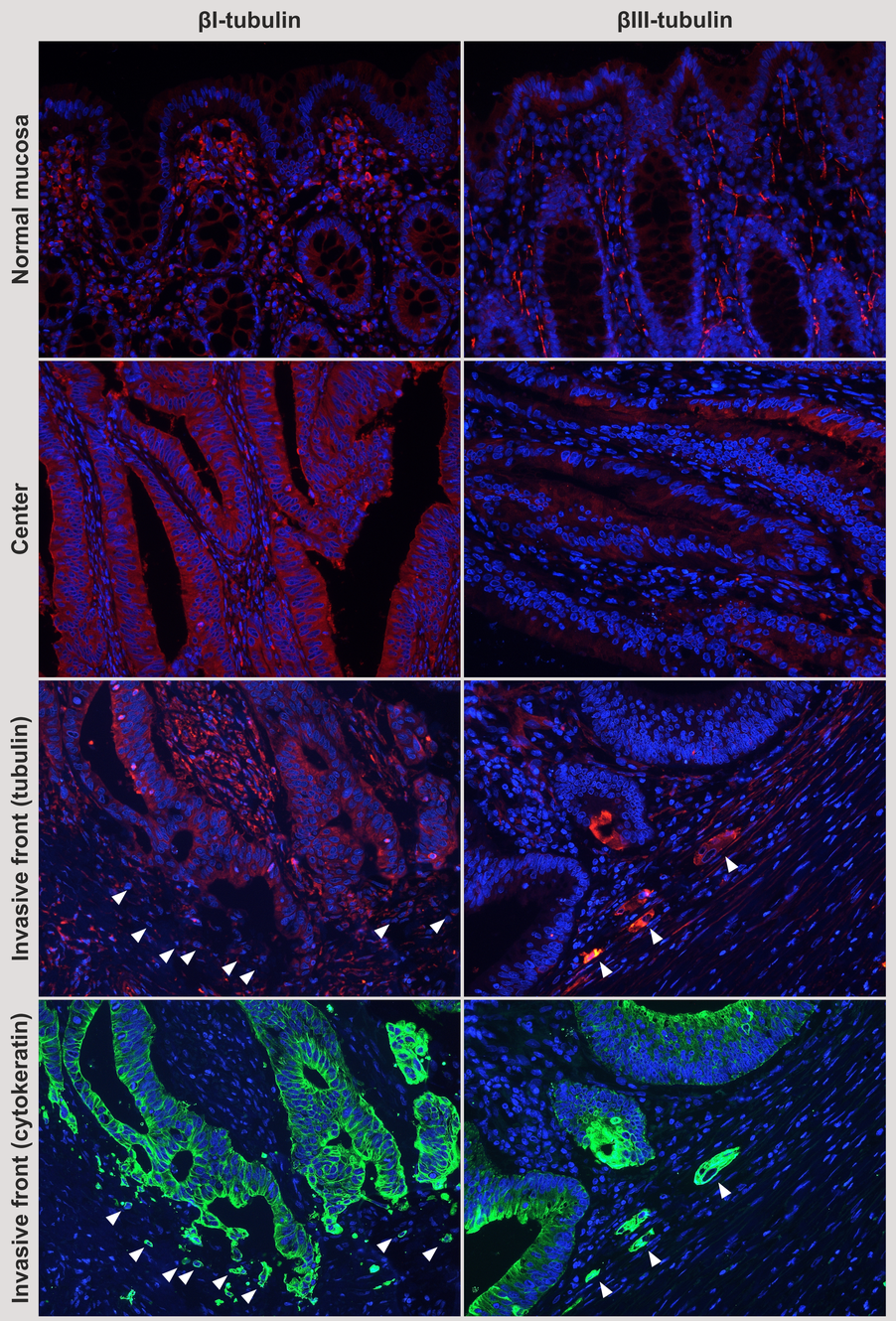

Figure 2. Immunofluorescence with antibodies to βI- and βIII-tubulin (red), cytokeratin (green), nuclei are stained with DAPI (blue), arrowheads – TBs, x200

Results

The expression of betaI-tubulin was significantly elevated in CRC (median 36.6 in normal mucosa vs. 78.8 in CRC, p=0,000). Moreover, normalized value of betaI-tubulin expression in CRC less then 85.1 and 71.5 was associated with lower disease-free (p=0,008) and cancer-specific survival (p=0,015) respectively. BetaIII-tubulin was almost absent in normal mucosa, but was present in CRC cells (median 1.6 in normal epithelium vs. 12.0 in CRC, p=0,000). Elevated normalized value of betaI-tubulin in CRC more then 12.7 and 9.7 was associated with lower disease-free (p=0,002) and cancer-specific survival (p=0,022) respectively. Moreover, increased level of betaIII-isotype in tumor budding was associated with lower disease-free survival in patients on 5-FU chemotherapy (p=0,010).

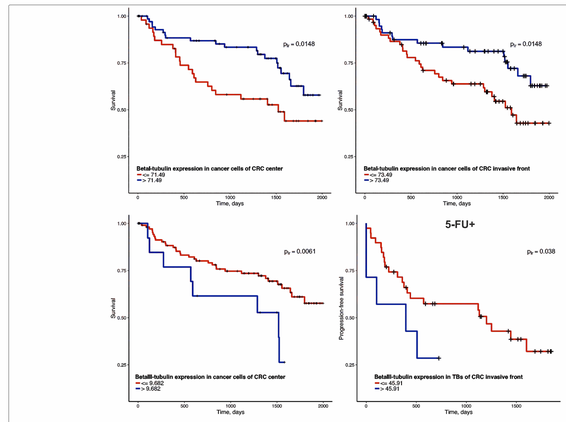

Figure 3. Tumor-specific and progression-free survival in dependence of the level of betaI- and betaIII-tubulin

Summary and Conclusions

These results demonstrate for the first time that betaI–tubulin expression is increased in CRC, but lower levels of this isotype are associated with worse survival. Expression of betaIII–tubulin is also increased in CRC, but higher levels of this molecule are associated with worse survival. Moreover, upregulation of betaIII–tubulin in the tumor budding in the invasive front could be important for determination of 5-FU resistant patients.