Expression of Class III beta-tubulin (TUBB3) in 3580 colorectal cancers (CRCs) and correlation with clinicopathological and molecular features

1Joanne Xi, 2Sandeep Reddy, 3Wafik S. El-Deiry
1Caris Life Sciences, Phoenix, AZ 2Fox Chase Cancer Center, Philadelphia, PA

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Background: Class III beta-tubulin plays a crucial role in intracellular transport, mitosis and mitosis. High expression of TUBB3 has been shown to associate with poor prognosis and taxane resistance in various cancer types. CRC is known to be generally resistant to taxane therapy. We investigated expression of TUBB3 in 3580 CRCs and made correlations with clinicopathological and molecular parameters.

Methods: 3580 CRC samples were evaluated by tumor profiling (Caris Life Sciences, Phoenix, AZ). Tests included Sanger or next generation sequencing (NGS), protein expression by immunohistochemistry (IHC) and gene amplification by in situ hybridization (ISH). TUBB3 expression was evaluated by immunohistochemistry (Ab: PQG, Covance) and expression higher than 2+, 30% was scored as positive.

Results: TUBB3 positive expression was observed in 37% (1320/3580) of the complete CRC cohort, specifically 27% in mucinous histology (164/617) and 37% in signet ring histology (207/571). While the expression was not associated with average patient age (59 years old) or gender (53% vs. 50% male), TUBB3 was more frequently expressed in tumors that originated from the left colon (370/1035 or 36%) than from the right colon (235/790 or 30%, p=0.003). In the 1847 tumors taken from metastatic sites, 40% (746/1907) overexpressed TUBB3 while in 1629 CRCs taken from primary tumors, only 34% (547) overexpressed TUBB3 (p<0.0001). Interestingly, in tumors that overexpressed TUBB3, 65% also overexpressed cMET (828/1275) and 53% also overexpressed TLE4 (43/1209). This compared to 50% cMET expression (1096/2207, p=0.0001) and 23% TLE3 expression (157/2225, p=0.0001) in tumors that were negative for TUBB3. Microtubule instability detected by fragment analysis was more prevalent in the TUBB3negative cohort than the TUBB3positive cohort (7.4% vs 77/1046 vs. 2.9% or 165/5388, p<0.0001). Mutations in APC (52% vs. 56%, p=0.0003) and KRAS (5% vs. 46%, p<0.0001) were more frequent in TUBB3positive tumors, while GNAS (2% vs. 5%, p<0.0001) and SMAD4 (10.1% vs. 14.6%, p<0.00001) mutations were significantly more frequent in tumors that were negative for TUBB3 expression.

Conclusions: High expression of TUBB3 was found in 37% of CRCs, and was significantly associated with tumors that originated from the left colon and with tumors taken from metastatic sites. Distinct biomarker features detected by IHC and sequencing suggest that TUBB3 expression may carry therapeutic importance which warrants further investigation in clinical trials.

Results:

1. Patient characteristics

2. TUBB3 staining details in the complete cohort of 3580 colorectal tumors. The staining results on the Y axis include the staining intensity (1+, 2+ or 3+ and staining percentage (0%-100%). Red: positive results using the threshold of 2+, 30%: green: negative results.

3. TUBB3 expression is higher in tumors originating from the left colon.

4. TUBB3 expression is higher in metastases vs. primary tumors


6. Molecular profile comparison of TUBB3 positive and negative CRC tumors tested by IHC and ISH. A star indicates the differences are statistically significant (p<0.05) by Chi-square test.

7. Molecular profile comparison of TUBB3 positive and negative CRC tumors tested by sequencing. A star indicates the differences are statistically significant (p<0.05) by Chi-square test.

Conclusions:

• Immunohistochemical staining of TUBB3 reveals overexpression in 37% of 3580 CRC tumors, with significantly higher prevalence in tumors originating from the left colon and tumors taken from metastatic sites.

• There are histological differences of TUBB3 expression in colorectal cancer, with the highest expression in mucinous cell tumors and the lowest seen in signet ring tumors.

• Distinct biomarker features detected by IHC and sequencing suggest that TUBB3 expression may carry therapeutic importance which warrants further investigation in clinical trials.

• TUBB3 expression serves as a potential resistance mechanism for taxane resistance and should be considered together with other molecular features including chromosomal instability and expression of multigene resistance proteins when selecting for a small subgroup of taxane responders in clinical trials.

References:

