B-21

Transcriptomic profiling of the BCL-2 pathway in Neuroendocrine Neoplasms (NENs)

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BACKGROUND

BCL-2 is an anti-apoptotic protein associated with resistance to tumor cell death and is a histopathologic marker of neuroendocrine differentiation. We characterized the transcriptomic profile of *BCL2* expression in NENs and its association with site, immune infiltration, and overall survival (OS).

METHODS

Next-generation sequencing of both DNA (592-gene panel or whole exome) and RNA (whole transcriptome) was performed on NENs of pancreatic (P-NENs, N = 230), small bowel (SB-NENs, N = 149), colorectal (CR-NENs, N = 136), and lung (L-NENs; N = 121) origin at Caris Life Sciences (Phoenix, AZ). Comparisons were perfomed against non-NENs; Colorectal Carcinoma (N = 15,422), Non-small cell lung cancer (N = 21,565), Pancreatic cancer (N= 5,484) and Small Bowel Cancer (N = 470). *BCL2*- or *MKI67* -High (H) and -Low (L) cohorts were defined based on the top and bottom quartile expression (transcripts/million [TPM]) of these genes, respectively. Gene expression profiles were analyzed for a transcriptomic signature predictive of response to immunotherapy (T-cell inflamed score). Mann-Whitney U and $\chi 2$ tests were applied with p-values adjusted for multiple comparisons ($p < 0.05$). OS data was obtained from insurance claims, and Kaplan-Meier estimates were calculated.

RESULTS

NENs had significantly higher expression of *BCL2 (TPM)* compared to non-NEN counterparts (CR-NENs 4.22 vs 1.55; L-NEN 4.14 vs 1.90 P-NEN 1.90 vs 1.52; $p < 0.01$ all) except for SB-NENs (1.82 vs 1.53, $p = 0.07$). *BCL2* expression (TPM) was significantly higher in *MKI67*-H vs -L tumors (CR-NEN 5.7 vs 1.9; L-NENs: 6.9 vs 2.2; P-NENs: 2.7 vs 1.4 all $p < 0.05$), except in SB-NENs (2.5 vs 1.6, $p = 0.074$). In P-NENs, there was a higher prevalence of *RB1* mutations in BCL2-H vs -L (40 vs 4.9%, $p < 0.005$). BCL2-H tumors were more frequently T-cell inflamed across all investigated NENs (CR-NENs: 29 vs 8%, L-NENs: 37 vs 3%, P-NENs: 31 vs 3%, SB-NEN: 32 vs 5%, all $p < 0.05$). *BCL2*-H was associated with decreased OS as compared to *BCL2*-L in all tumor types (CR-NENs: HR 1.58, $p = 0.14$; L-NENs: HR 1.75, $p = 0.188$; P-NENs: HR 1.94, $p = 0.047$; SB-NENs: HR 1.059, $p = 0.902$).

CONCLUSIONS

NENs have increased expression of *BCL2* vs. non-NENs of the same site. *BCL2*-H co-related with high *MKI67* expression. *BCL2*-H tumors were more inflamed/immunogenic and there was a trend towards worsening OS compared to *BCL2*-L within each type of NEN. The *BCL*-2 pathway is of interest for therapeutic investigation in aggressive NENs.

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