ePoster: 632P

Differential transcriptomic profiling of BCL2-related genes in primary tumor (PT) and metastatic sites (MS) of prostate cancer (PCa)

Benedito A. Carneiro[1], Jun Yin[2], Luke Soliman[1], Andre De Souza[1], Dragan Golijanin[3], Anthony Mega[1], Pedro C. Barata[4], Shuchi Gulati[5], Shuanzeng Wei[6], Daniel M. Geynisman[7], Daniel Magee[2], W. Michael Korn[2], Inas Abuali[5], Elisabeth I. Heath[8], Charles Ryan[9], Paul Bertone[1], Wafik S. El-Deiry[1]

[1]Hematology/Oncology Division, Cancer Center at Brown University, Lifespan Cancer Institute, Providence, USA, [2]Caris Life Science, AZ, USA, [3]Department of Urology, Brown University, Providence, [4]Internal Medicine department, Tulane University, USA, [5]Division of Hematology Oncology, University of Cincinnati Cancer Center, USA, [6]Pathology, FOX Chase Cancer Center, USA, [7]Medical Oncology Department, Fox Chase Cancer Center, [8]Oncology, Karmanos Cancer Institute, USA, [9]Division of Hematology, Oncology and Transplantation, University of Minnesota, USA

BACKGROUND

- BCL2-related anti-apoptotic (BCL-2, BCL-XL, MCL-1, BCL2A1, BCL2L10) and pro-apoptotic proteins (BAX, BAD, BID, BAK-1) regulate cellular sensitivity to apoptosis stimuli [1].
- Overexpression of *BCL2* and resistance to apoptosis have been implicated in the development of androgen-independent PCa and disease progression, which has clinical relevance given several therapeutic strategies targeting this pathway [2,3].
- This project aimed to characterize the transcriptomic profile of *BCL2*-related genes and investigate distinct sensitivity to apoptosis between primary prostate tumors (PT) and metastatic sites (MS).

METHODS

A total of 2185 PCa specimens (1258 PT; 927 MS) underwent comprehensive molecular profiling (Caris Life Sciences). Analyses included next-generation sequencing of DNA and RNA (592 Gene Panel, NextSeq, WES, NovaSEQ). MS: lymph node (LN; 273), bone (B; 46), liver (Li; 147), lung (Lu; 174). Gene Set Enrichment Analysis (GSEA) were assessed by mRNA (transcripts per million; TPM) analysis. Fisher's exact and Dunnett's tests after ANOVA were used for multigroup comparison. Neuroendocrine PCa (NEPC) and androgen receptor (AR) signaling scores were calculated as previously described[4]. The results in the table represent statistically significant differences in mRNA expression between PT and MS (adjusted $P < 0.05$).

RESULTS

- Median age of patients (pts): 68 years old (61-74)
- Gleason score available in 978 PT specimens: 47% had grade group 5.
- In comparison to PT, the mRNA expression of anti-apoptotic *BCL2* was decreased in LN, Li, Lu and B while pro-apoptotic genes *BID* and *BAK1* were upregulated (Table 1).
- *MCL1* was downregulated in Li and B. Expression of pro-apoptotic *BAX* was higher in Li and B, and *BAD* was increased in LN (Table 1).

Table 1. mRNA expression level (mean TPM) of *BCL2* family genes, with red box indicating significant comparison between mRNA levels of MS with respect to PT

genes	Prostate	Lymph node	Lung	Liver	Bone
BCL2	4.3	3.2	2.6	2.6	3.0
BCL2L1*	26.0	22.6	27.9	24.4	24.4
MCL1	17.1	16.2	16.3	16.0	16.0
BCL2A1	3.0	3.2	5.7	3.1	3.7
BCL2L10	32.0	1.5	1.5	32.0	36.8
BAX	14.9	16.0	30.7	32.7	37.3
BAD	7.5	9.2	10.6	12.1	8.6
BID	3.7	4.3	4.9	4.9	4.0
BAK1	24.3	4.3	16.0	12.1	18.4

*The *BCL2L1* gene encodes the BCL-xL protein

- MS showed upregulation of G2M checkpoint, E2F pathways and higher rates of *TP53* mutations (37%, 55%, 40% for LN, Li and B vs 32% PT).
- Increased frequency of *TP53* mutations and decreased expression of *CCDN1* (Li, B) suggest a mechanism for *BCL2* downregulation specific to these MS.

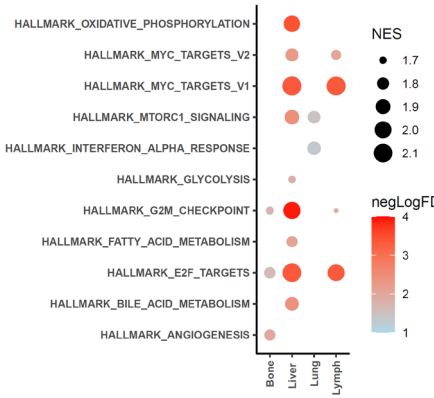


Figure 1. Differential pathway enrichment in metastatic site with respect to primary site

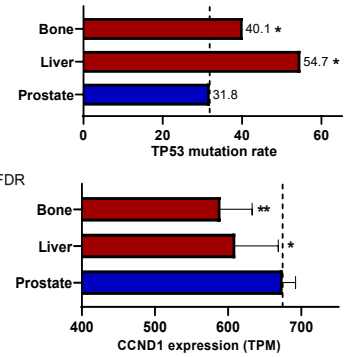
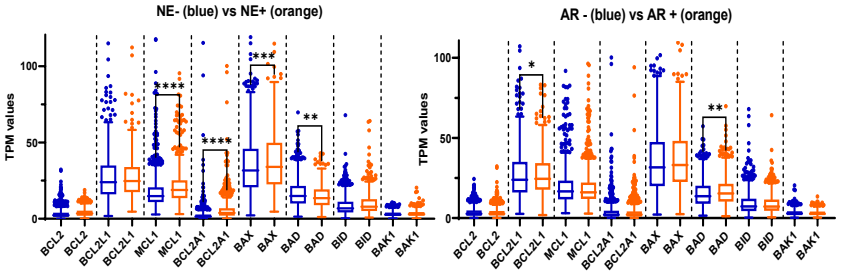


Figure 2. *TP53* mutational status and mean of *CCND1* mRNA expression levels in primary, liver and Bone

- Tumors enriched for NEPC scores displayed significant higher levels of *MCL1*, *BCL2A1, BAX* but lower mRNA expression levels of *BAD*
- AR signaling scores did not have a significant impact on the expression of most *BCL2* family members



CONCLUSIONS

- Metastatic sites of PCa exhibit downregulation of anti-apoptotic *BCL2* family members and increased expression of pro-apoptotic genes compared to PT.
- In contrast to evidence that metastatic PCa displays *BCL2* overexpression and resistance to apoptosis, our results suggest that MS are primed to apoptosis with site-specific expression profile of *BCL2*-related genes. Further studies are needed to elucidate the role of cell cycle (G2M, *CCND1* expression, E2F pathway) and apoptosis regulation by *TP53* in this site-specific variation.
- Higher NEPC scores were associated with increased mRNA expression of *MCL1*, *BLC2A1* and *BAX* suggesting a distinctive profile of *BCL2* genes in neuroendocrine PCa that warrants further investigation.

REFERENCES

1) Ashkenazi A et al. Nat Rev Drug Discov. 2017 Apr;16(4):273-284. PMID: 28209992
2) Pilling AB et al. Prostate. 2019 Aug;79(11):1347-1359. PMID: 31228231
3) Carneiro BA, El-Deiry WS. Nat Rev Clin Oncol. 2020 Jul;17(7):395-417. PMID: 32203277.
4) Beltran H et al. Nat Med . 2016 Mar;22(3):298-305. PMID: 26855148

Benedito_Carneiro@brown.edu

No conflicts of interest to declare.