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BCL2L12: A highly complex gene locus with possible clinical utility in breast cancer

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Introduction: Apoptosis is a fine tuned and genetically regulated form of cell death, the malfunction of which is among the major hallmarks in malignant transformation of the mammary gland. Among the recently identified members of the *BCL2* family of apoptosis-related genes is *BCL2L12*, which is subjected to alternative splicing, resulting thus in the generation of 13 alternatively spliced variants. Lately, the largest splice variant *BCL2L12 v.1* has been studied in various malignancies, revealing its dynamics as a tumor biomarker. The aim of this study was the quantification of *BCL2L12* splice variants 1 and 2 (v.1 and v.2) expression at the mRNA level and the assessment of their biomarker potential in breast cancer (BC).

Methods: Total RNA was extracted from 40 pairs of frozen pulverized BC and normal tissues, and was reverse transcribed into first strand cDNA. A sensitive qRT-PCR methodology was developed for the molecular analysis of both *BCL2L12* transcript variants *BCL2L12 v.1* and *v.2*, utilising the SYBR Green I chemistry and the comparative C_T (2ddCT) method was used for the relative quantification analysis. Finally, the associations of *BCL2L12* variants expression with various clinopathological parameters were evaluated by statistical analysis.

Results: *BCL2L12 v.1* and *v.2* mRNA levels transcript variants were found to be significantly ($p = 0.003$, $p = 0.009$) higher in malignant compared to their matched non-cancerous breast tissues. Moreover, *BCL2L12 v.1* demonstrated increased expression in premenopausal women ($p = 0.026$) as well as in those with early TNM stage tumors ($p = 0.039$). Interestingly, significant *BCL2L12 v.1* upregulation ($p = 0.044$) was observed in triple negative BC. Moreover, increased *BCL2L12 v.2* expression levels were associated with advanced tumor grade ($p = 0.022$) and ER-negativity ($p = 0.01$).

Conclusion: Our preliminary results indicate a possible involvement of *BCL2L12 v.1* and *v.2* in BC progression and suggest their potential as biomarker in this malignancy.

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