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Ceramide in the prostate

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The nomenclature for the serine/threonine protein phosphatases was established by Professor Sir Philip Cohen over 30 years ago.[1] At that time protein phosphatase 1 was known to have two small inhibitory proteins (I-1 and I-2) and be regulated by sub-cellular location whereas no protein inhibitor had yet been discovered for the related multi-subunit phosphatase PP2A. That paradigm subsequently changed, and several PP2A protein inhibitors have been discovered.[2] The protein I2PP2A (SET) is considered to be oncogenic, i.e., PP2A is a tumor suppressor, and is overexpressed in many tumor cell types (ref. 3, and refs. therein). I2PP2A also has other targets besides PP2A, e.g., DNA exonucleases and modification of histone acetylation.[4] PP2A activity is known to be regulated by the bioactive lipid ceramide, and this occurs through both I2PP2A inhibition and PP2A de-repression and through ceramide actions on subunits of the PP2A enzyme complex.[5,6] In the present manuscript the authors examined the expression of I2PP2A in prostate cancer and prostate epithelial cells. They determined whether ceramide could decrease accumulation of the oncogene c-Myc through inhibition of I2PP2A and activation of PP2A. As I2PP2A is also an inhibitor of histone acetylation they determined whether ceramide could block the epigenetic action of I2PP2A.

The authors found that I2PP2A is overexpressed in prostate tumor cells and that while the expression of the PP2A catalytic subunit did not change comparing prostate epithelial cells and prostate cancer cells the tyrosine phosphorylation of the subunit was increased in tumor cells, indicative of reduced PP2A activity. Ceramide treatment killed prostate tumor cells but not normal prostate epithelial cells. Ceramide treatment disrupted the association between PP2A and I2PP2A and it blocked I2PP2A function in terms of inhibiting PP2A catalytic activity to dephosphorylate and decrease accumulation of the oncogene c-Myc. Overexpression of I2PP2A increased the c-Myc expression and ceramide treatment decreased c-Myc levels in I2PP2A-GFP expresing cells Collectively the data argued for a positive role of I2PP2A for inhibition of PP2A activity toward c-Myc.

PP2A is a well-described tumor suppressor that can reduce the activities of many pro-oncogenic signal transduction pathways. One of the initial observations of ceramide on cell signaling was inhibition of, e.g., ERK1/2 signaling, which would lead to reduced growth and a lower apoptotic threshold. The present manuscript expands upon this notion with regard to PP2A, I2PP2A, and the regulation of c-Myc. The transcription factor c-Myc can promote growth as well as regulate the cyclin kinase inhibitor p21/the cell cycle and also cause tumor cell death; these effects on tumor cell biology can be context dependent. In the present manuscript the authors went on to show that in at least one of the prostate cancer lines ceramide/I2PP2A signaling also regulated histone acetylation. Understanding how ceramide and I2PP2A regulate prostate cancer biology, tumor growth, gene expression and the apoptotic threshold in this tumor types will no doubt be the subject of a future study by these authors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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