Enhanced expression of a proto-oncogene, Pim-3, with serine/threonine kinase activity, in various types of tumors

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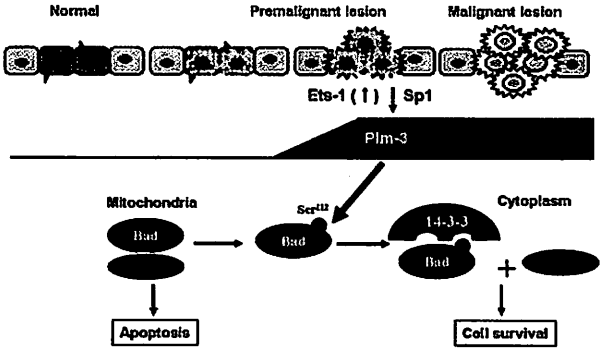
We previously observed that a member of the proto-oncogene Pim family, Pim-3, which expresses serine/threonine kinase activity, was aberrantly expressed in human and mouse hepatomas but not normal liver. Due to the unavailability of the nucleotide sequence of full-length human Pim-3 cDNA, we cloned full-length Pim-3 cDNA, consisting of 2,392 bp, which encodes a predicted open reading frame consisting of 326 amino acids.

Our subsequent studies demonstrated that Pim-3 gene expression was enhanced in malignant cells and lesions of endoderm-derived organs including pancreas, colon, and stomach, in addition to liver. The analysis on the promoter region of the human *Pim-3* gene revealed that the region up to -264 bp was essential for constitutive *Pim-3* gene expression in human pancreatic cancer cell lines, and the mutation in the Ets-1 and Sp1 binding sites reduced the reporter activities. Consistently, Ets-1 mRNA and protein were constitutively expressed together with Pim-3, in human pancreatic cancer cell lines. These observation would indicate that a transcription factor, Ets-1, can induce aberrant Pim-3 expression and subsequently prevent apoptosis in human pancreatic cancer cells, in collaboration with Sp1.

We further demonstrate that Pim-3 can phosphorylate a pro-apoptotic molecule, Bad, at its Ser^{112} but not Ser^{136} residue in human pancreatic and colon cancer cell lines. Moreover, Pim-3 overexpression can induce the expression of an anti-apoptotic molecule, Bcl-X_L. Thus, Pim-3 can inactivate Bad and maintain the expression of Bcl-X_L and eventually prevent apoptosis of human cancer cells. These observations would indicate that Pim-3 may be a good molecular target for several types of cancer, for example, pancreatic cancer, a representative intractable cancer.



References

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