Cell survival regulation plays an important role in maintaining homeostasis in response to damaging factors. Neoplastic diseases are those in which failure to maintain an intact apoptotic response is associated with progression and poor response to treatment. Apoptosis is mainly regulated through growth factors and cytokines. One protein which plays a role in apoptosis is serine/threonine kinase PIM-2. PIM-2, PIM-1, and PIM-3 kinases are encoded by the protooncogenes hPIM-1, hPIM-2, and hPIM-3. The mechanism by which PIM-2 kinase promotes cell survival and inhibits apoptosis is still under investigation. The critical moment seems to be inactivation of the pro-apoptotic protein BAD and the translation inhibitor 4E-BP1. The role of hPIM-2 in the oncogenesis of solid tumors and hematological malignancies has been well documented. Over-expression of hPIM-2, at both the mRNA and protein level, was observed in human solid tumors and hematological neoplasms. Moreover, it was confirmed that inhibition of hPIM-2 expression blocked cell proliferation and increased cellular apoptosis. Studies on potential anticancer drugs which inhibit PIM-2 kinase are now being conducted (Adv Clin Exp Med 2009, 18, 4, 319–322).

Key words: hPIM-2, solid tumors, hematological malignances.

Cell survival regulation plays an important role in the maintenance of homeostasis, but the response to damage is deregulated in various disorders. Neoplastic diseases are those in which failure to maintain an intact apoptotic response is associated with progression and poor response to treatment. Apoptosis is mainly regulated by growth factors and cytokines. They act through their cognate receptors, activating signaling pathways often composed of protein kinase cascades, including the Jak/Stat, PI3-kinase/Akt, and MAP kinases and IKK/NFκB. Thus with the phosphorylation of specific substrates, survival activity can be maintained in many ways by spanning the reg-
ulation of transcription through the direct modification of apoptotic effectors [1]. There are a large number of growth factors and cytokines which regulate hematopoietic cell growth and survival by modulating intracellular signaling cascades, in which oncogenic kinases are important effectors. Among the signaling intermediates implicated in cell survival and growth factor-mediated apoptotic resistance is the serine/threonine kinase PIM-2 [2].

The Human PIM Protooncogene Family

The human PIM gene family consists of three members: hPIM-1, hPIM-2, and hPIM-3. These genes encode related kinases which show substantial homology, but differ in tissue expression [3, 4]. The hPIM-2 gene encodes a cytoplasmic serine/threonine kinase whose expression is regulated by hematopoietic cytokines, mainly interleukin-3 (IL-3). Like PIM-1 kinase, there are multiple isoforms of PIM-2 protein (three in the mouse, two in humans) [3, 5]. The mechanisms by which PIM-2 kinase acts to promote cell survival and inhibit apoptosis have not been fully characterized. Fox et al. suggested that at least one PIM-2 target is common to many apoptotic pathways [2]. The critical moment seems to be the phosphorylation and inactivation of the pro-apoptotic protein BAD, which belongs to the BH3 protein family. Yan et al. showed that PIM-2 kinase phosphorylates BAD protein on serine 112 (p-Ser112BAD) and reverses BAD-induced cell death [6]. These results were confirmed by McDonald et al. [7]. The next substrate for PIM-2 kinase is the translation inhibitor 4E-BP1, a protein which belongs to the PI3K/AKT/m-TOR signaling pathway. 4E-BP1 is a common site of phosphorylation by PIM-2 and AKT kinases on serine 65 (p-Ser65-4E-BP1), which enhanced anti-apoptotic effect [7, 8]. Other targets for PIM-2 worth examining are the pro-apoptotic proteins BIM and Puma and p53 tumor-suppressor protein [1]. The survival signaling pathways regulated by PIM-2 and AKT are presented in Figure 1 (according to E. White) [1].

hPIM-2’s Role in Oncogenesis

Constitutive PIM-2 expression results in resistance to various apoptotic stimuli and promotes cell survival in the absence of growth factor stimulation. These data suggest that PIM-2 participates in oncogenic transformation by regulating cell survival [2]. Previous studies identified PIM-2 as a frequent site of proviral insertion in experimental murine lymphomas [3]. A further study revealed that co-expression of the PIM-2 and c-Myc genes induced lymphomas in double-transgenic animals in vivo [9]. Synergism of PIM-1/PIM-2 kinases and c-Myc was also observed in human colon cancer cell lines, a human leukemia cell line (K562), a human lung cancer cell line (H1299), and a prostate cancer cell line (DU-145) [10]. Hammerman et al. confirmed that PIM-1/PIM-2 and the PI3K/AKT/m-TOR signaling pathway are important for survival hematopoietic cells and that coexpression of PIM-2/Act-1 leads to lymphomas in double-transgenic mice [11]. Increased expression of hPIM-2 was observed in human solid tumor lines (G361, A549, SW480) and hematopoietic cell lines (HLA60, K562, RAJ) [3]. Dai et al. demonstrated over-expression of hPIM-2 in prostate cancer (PCa) cells; moreover, increased nuclear level of PIM-2 in PCa was associated with many established prognostic factors, higher proliferation, and reduced apoptosis [12]. Dai et al. indicated that antisense oligodeoxynucleotides (ASODN) targeting hPIM-2 proliferation of the human prostate cancer cell line DU-145 can efficiently suppress target gene expression and inhibit the growth of these cells [13]. Increased expression of PIM-2 (both mRNA and protein) was observed by Gong et al. in human hepatocellular carcinoma cells (HepG2), and after PIM-2 knockdown the cancer cells lost survival ability in IL-3 starvation medium [14]. Zang et al. presented specific and efficient silencing of hPIM-2 gene expression by the siRNA (small-interference RNA) method in the human colon cancer cell line SW480 [15].

In hematological malignances, over-expression of hPIM-2 was found in chronic lymphocytic leukemia (CLL), follicular non-Hodgkin’s lym-
increased levels of PIM−2 mRNA in patients with 
[18]. The present authors’ own data found 
siRNA (small interfering RNA) targeting PIM−2 
cell death upon expression of the highly specific 
and the cells were sensitive to knockdown of PIM−2 
levels of PIM−1 and PIM−2 mRNA were detected 
−ITD (Fms−like tyrosine kinase 3/internal tandem 
duplication) and BCR/ABL. Interestingly, high 
transformed by the protein tyrosine kinases FLT3− 
ried out by Adam et al. on hematopoietic cells 
−expression in acute leukemia. The first studies 
published by Amson et al. revealed that the related 
gene for PIM−1 was up−regulated in acute 
myeloid leukemia [17]. The latest study was car− 
ed gene for PIM−1 was up−regulated in acute 
expression in acute leukemia cell lines (HLA60, 
K562, REH), there are few data on hPIM family 
expression in acute leukemia. The first studies 

References


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