Retroviral insertional mutagenesis and characterization of the frequently activated PIM kinases

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Chapter II

An introduction to the *Pim* family of proto-oncogenes

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General *Pim* features

The *PIM* proto-oncogenes belong to a distinct family of serine/threonine kinases (Figure 1). The first member of this family, *Pim1*, was identified as a target for proviral activation in Moloney murine leukemia virus (M-MuLV) induced T cell lymphomas (Cuypers *et al.*, 1984). In the mouse, *Pim1*

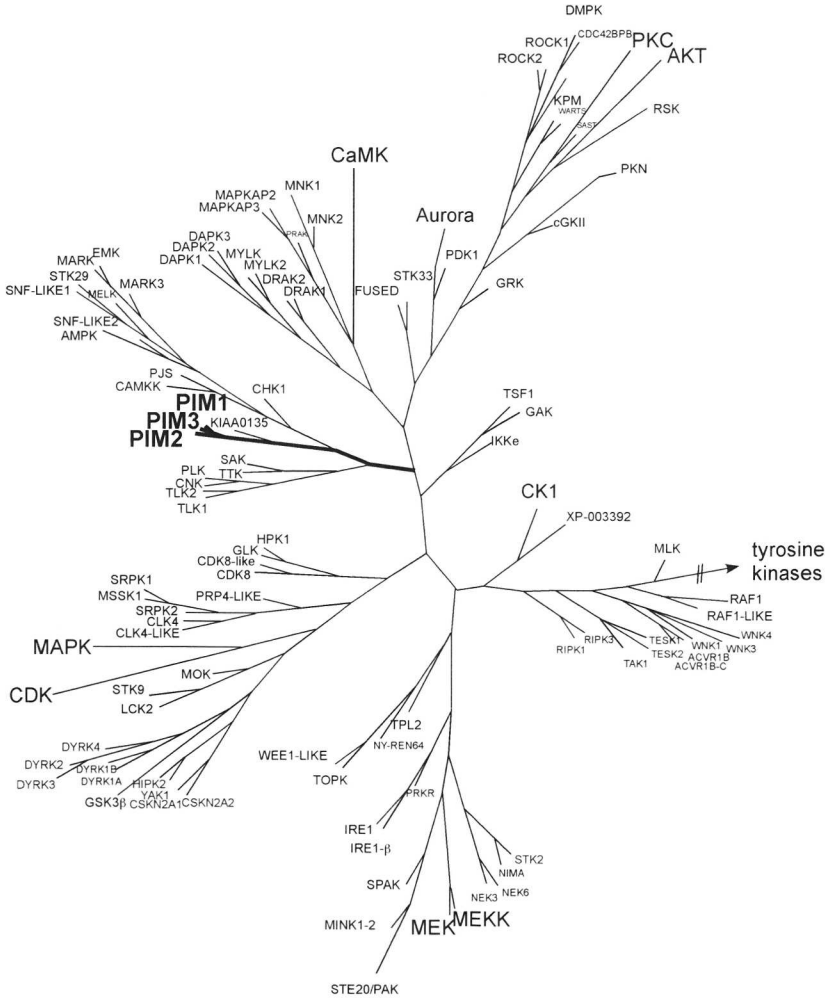

Figure 1. Phylogenetic tree of mammalian serine/threonine kinases.

encodes two proteins, a 33 kD and a 44 kD protein, which is initiated from an upstream CTG codon (Saris *et al.*, 1991). In human, *PIM1* encodes a 34 kD protein (Domen *et al.*, 1987; Meeker *et al.*, 1987; Zakut-Houri *et al.*, 1987). The half-life of mouse and human *PIM1* mRNA as well as the protein is very short (Saris *et al.*, 1991). *Pim1* mRNA is labile due to the presence of five copies of an ATTTA destabilization motif in the 3'UTR (Saris *et al.*, 1991). The Pim family of kinases contains besides *Pim1* two very homologous *Pim2* and *Pim3* genes (Allen and Berns, 1996; Baytel *et al.*, 1998; Feldman *et al.*, 1998; van der Lugt *et al.*, 1995). PIM3 shares 71% and PIM2 61% of the amino acids with PIM1 (Figure 2). *Pim2* has similar properties as *Pim1*; the mRNA and protein is labile, and its transcription can be initiated from an upstream CTG codon (van der Lugt *et al.*, 1995).

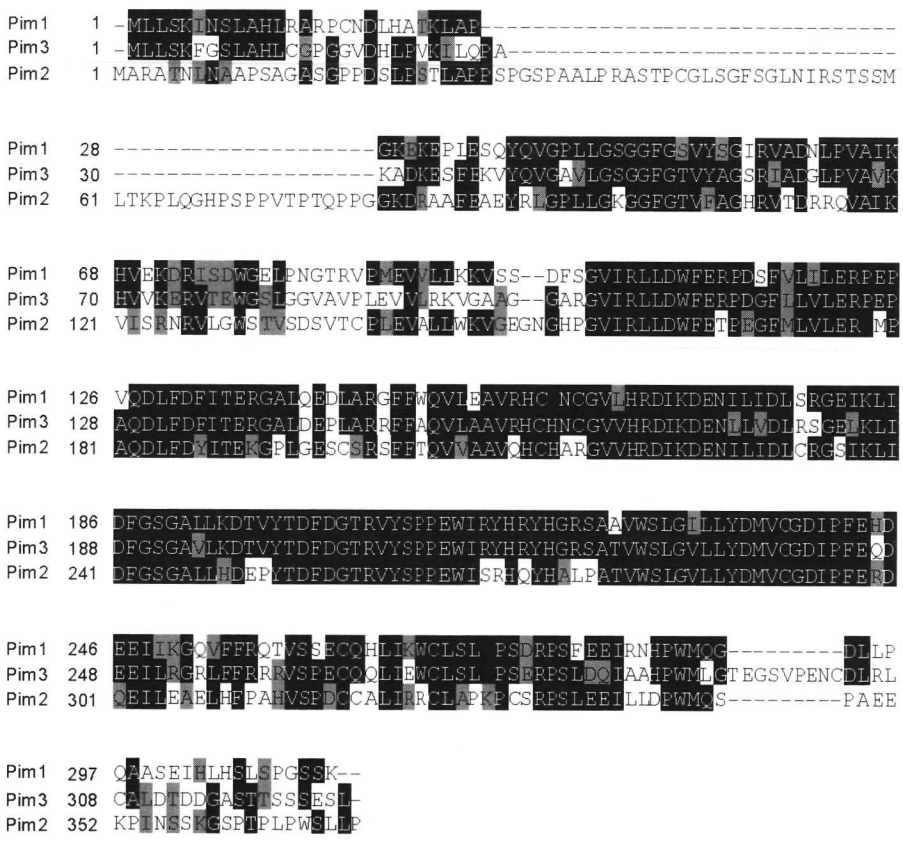

Figure 2. Alignment of the mouse PIM1, PIM2 and PIM3 proteins.

The *Pim* genes are rather ubiquitously expressed and the encoded proteins reside in both the nucleus and cytoplasm of the cell. The highest *Pim1* mRNA

levels are found in thymus and testis (Selten *et al.*, 1985), *Pim2* in brain and thymus (Allen *et al.*, 1997), and *Pim3* in mammary gland (this thesis) and kidney (Feldman *et al.*, 1998). During mouse development either *Pim1* and *Pim3* or *Pim2* and *Pim3* are co-expressed (Eichmann *et al.*, 2000). The expression of *Pim1, Pim2*, and likely also *Pim3*, is regulated by a range of cytokines and growth factors: IL-2 (Allen *et al.*, 1997; Dautry *et al.*, 1988), IL-3 (Allen *et al.*, 1997; Domen *et al.*, 1993b; Lilly *et al.*, 1992), GM-CSF and G-CSF (Lilly *et al.*, 1992), IL-4 (Allen *et al.*, 1997), IL-5 (Temple *et al.*, 2001), IL-6 (Lilly *et al.*, 1992), IL-7 (Allen *et al.*, 1997; Domen *et al.*, 1993a), IL-9 (Allen *et al.*, 1997), , IL-12, IL-15, IFNα (Matikainen *et al.*, 1999), IFNγ (Allen *et al.*, 1997; Yip-Schneider *et al.*, 1995), erytropoietin (Miura *et al.*, 1994), (Nagata and Todokoro, 1995), prolactin (Borg *et al.*, 1999; Buckley *et al.*, 1995), ConA (Allen *et al.*, 1997), and LPS (Allen *et al.*, 1997). The majority of these factors transduce their signal through the JAK/STAT pathway. Together with the presence of Stat-binding elements in the promoter of mouse *Pim1*, this implies an important role for the JAK/STAT cascade in regulating expression of the *Pim* genes. Although this notion is generally accepted, the direct involvement of STAT and expression of *Pim* has only been demonstrated for STAT3 in relation to IL-6 (Shirogane *et al.*, 1999). The strong and early induction of the *Pim* genes in response to distinctive cytokines would predict an important function for PIMs in cytokine signaling. Cytokine signaling induces either proliferation or differentiation and blocks apoptosis. Hirano and colleagues demonstrated that simultaneous expression of *Pim1* and *c-Myc* abrogates the requirement for STAT3 to mediate cell cycle progression and prevent apoptosis. In addition, ectopic expression of *Pim1* overrules the cytokine-dependent survival of a murine pre-B cell line, possibly via a BCL2-dependent pathway, illustrating the crucial role for PIM in cytokine signaling (Lilly *et al.*, 1999).

Pim and tumorigenesis

The role of *Pim1* in mouse lymphomagenesis has been well documented. *Pim1* transgenic mice, expressing *Pim1* under the control of the immunoglobulin Eμ enhancer, are highly predisposed to lymphomas (van Lohuizen *et al.*, 1989). Carcinogenic agents such as ENU (Breuer *et al.*, 1989; Breuer *et al.*, 1991), heterocyclic amines (Sorensen, 1996, 1997) and leukemia viruses (van Lohuizen, 1989; Allen, 1998), but also X-ray (van der Houven van Oordt *et al.*, 1998) and exposure to electro-magnetic fields cause an accelerated onset of tumor formation in these mice (McCormick *et al.*, 1998; Repacholi *et al.*, 1997). An even more dramatic acceleration of tumor formation is seen in *Pim1* and *c-Myc*, N-*Myc* or L-*Myc* double transgenic mice that die as a result of pre-B cell leukemia (Moroy *et al.*, 1991; Verbeek *et al.*, 1991). This observation illustrates that PIM1is a very efficient collaborator of MYC in lymphomagenesis. Similar experiments with *Pim2* transgenic mice have shown that *Pim2* is an equally potent oncogene as *Pim1* (Allen *et al.*, 1997). In human tumors, levels of *PIM1* are high in some acute myeloid and lymphoid leukemias (Amson *et al.*, 1989; Nagarajan *et al.*, 1986); Allen, personal communication), but the enhanced expression is not the result of translocations or amplifications involving the *PIM1* locus. In addition,

expression of PIM1 appears to be a marker for prostate carcinomas as metastatic tumors lose expression of PIM1, which is relatively high in the primary tumors (Dhanasekaran *et al.*, 2001).

PIM signaling targets

In contrast to the role of PIM1 in mouse lymphomagenesis, the signaling pathways in which PIM1 plays a decisive role remain largely unknown. The generation of *Pim1*-deficient mice, which are apparently normal (Laird *et al.*, 1993; te Riele *et al.*, 1990), initially, only underscored the role of *Pim1* in interleukin signaling ((Domen *et al.*, 1993a; Domen *et al.*, 1993b). *Pim1*-deficient bone marrow cells exhibit a reduced proliferation in response to IL-3 or IL-7. It was shown by the group of Kuhl that besides the role PIM1 in the hematopoietic system, PIM1 might act in the establishment of long-term memory, since *Pim1*-deficient hippocampal granule cell neurons lack consolidation of enduring long-term potentation (LTP) (Konietzko *et al.*, 1999).

A decennia after its cloning, the first substrate of PIM1, protein P100, was identified (Leverson *et al.*, 1998). P100 can bind to the transcription factor c-MYB and upon phosphorylation of P100 by PIM1, the c-MYB mediated transactivation is enhanced. Shortly after P100, two other substrates of PIM1, were discovered, the cell cycle phosphatase CDC25a (Mochizuki *et al.*, 1999) and a heterochromatin binding protein HPγ (Koike *et al.*, 2000). The PIM1-mediated phosphorylation of CDC25a and HPγ alters these coactivator proteins' phosphatase and repressor activity, respectively *in vitro*. Other PIM targets that were reported on are SOCS (Chen *et al.*, 2002; Losman *et al.*, 1999), NFATc (Rainio *et al.*, 2002), TFAF2/SNX6 (Ishibashi *et al.*, 2001) and PAP1 (Maita *et al.*, 2000). Phosphorylation of SOCS1 stabilizes the protein resulting in suppression of cytokine signaling. TFAF2/SNX6 is supposed to be translocated into the nucleus upon phosphorylation by PIM, whereas phosphorylation of the transcription factor NFATc has been reported to increase its transactivation potential. Future experiments might teach us whether these proteins indeed are the PIM1 targets that provide the link between PIM and lymphomagenesis.

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