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Deep Insight Section

Intracellular tyrosine phosphatases and kinases in lymphoma

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Tyrosine phosphorylation and dephosphorylation

Tyrosine phosphorylation is a key mechanism for signal transduction and for the regulation of many cellular processes (Mustelin et al., 2005; Tonks, 2006). The protein tyrosine kinases (PTKs) phosphorylate at tyrosine residues and the protein tyrosine phosphatases (PTPs) dephosphorylate. The human PTP genes are divided into several families: Class I cysteine-based PTPs, class II cysteine-based PTPs, class III cysteine-based PTPs and Asp-based PTPs (Andersen et al., 2004; Mustelin et al., 2005). The class I cysteine-based family constitute the largest family of PTPs, and is further classified into 38 classical PTPs and 61 VH1-like "dual-specific" protein phosphatases (DSPs) (Alonso et al., 2004). Of the 38 classical PTPS, 17 are non-receptor intracellular PTPs and 21 are receptor-like transmembrane PTPs. All the classical PTPs are strictly tyrosine-specific (pTyr). In contrast, the VH1-like DSPs are much more diverse and are divided into several subgroups: PTPs specific for mitogen-activated protein (MAP)-kinases (MKPs), atypical DSPs including VHR, VHY, VHX and VHZ, slingshots, PRLs, CDC14s, PTENs and myotubularins (Alonso et al., 2004).

PTPs have a catalytic domain with an intrinsic substrate preference, and most have non-catalytic amino- or carboxy terminal extensions domains that interact with other molecules or targets (Mustelin et al., 2005). The non-catalytic regions can also participate in regulation of phosphatase activity by intramolecular folding mechanisms (Mustelin et al., 2005). It has been long appreciated that PTPs have capacity to function as inhibitors by phosphotyrosine (pTyr)-dependent signaling, but also to act as positive regulators in promoting signaling (Mustelin et al., 1999; Gjörloff Wingren et al., 2000; Andersen et al., 2004; Mustelin et al., 2005; Tonks, 2006). Lymphocytes express 50-60 of the total 107 PTP genes. The most well-studied PTPs in lymphocytes are presented in Table 1 (12 non-receptor intracellular PTPs, PTEN and the class II cysteine-based PTP LMW-PTP).

Lymphoma and leukemia

Tumors of the immune system are classified as either leukemia or lymphoma. Leukemias often proliferate as single cells in the blood or lymph while lymphomas tend to proliferate as solid tumors within lymphoid tissues. Historically, the lymphomas have been classified as either Hodgkin's lymphoma (HL) or non-Hodgkin's lymphoma (NHL), the latter diagnosis being the most common and comprising many different subtypes originating from B-cells, T-cells or natural killer (NK) cells. About 85 % of the NHLs are of B-cell origin and these B-cell lymphomas can be divided into around 15 types according to the World Health Organization (WHO) lymphoma classification (Jaffe et al., 2001; Swerdlow et al., 2008). The various subtypes can have very different clinical behaviours and requirements for treatment strategies, due to the differentiation stage of the B-cell they originated from.

Gene	Protein	Chromosome location	References
PTPN1	PTP1B	20q13.1-13.2	Brown-Shimer et al., 1992; Forsell et al., 2000
PTPN2	TCPTP	18p11.3-11.2	Sakaguchi et al., 1992
PTPN3	PTPH1	9q31	Itoh et al., 1993
PTPN4	PTP-MEG1	2q14.2	Gu et al., 1991
PTPN5	STEP	11p15.1	Lombroso et al., 1991
PTPN6	SHP1 (PTP1C, SH-PTP1, HCP)	12p12-13	Plutzky et al., 1992
PTPN7	HePTP (LCPTP)	1q32.1	Zanke et al., 1992; Zanke et al., 1994; Adachi et al., 1994
PTPN9	PTP-MEG2	15q23	Gu et al., 1991
PTPN11	SHP2 (SH-PTP2, Syp, PTP1D, PTP2C, SH-PTP3)	12q24.1	Dechert et al., 1995; Isobe et al., 1994
PTPN12	PTP-PEST	7q11.23	Takekawa et al., 1992; Charest et al., 1995
PTPN13	PTP-BAS	4q21.3	Inazawa et al., 1996; Maagdenberg et al., 1996
PTPN22	LYP (PEP)	1p13.3-p13.1	Cohen et al., 1999
PTEN	PTEN (MMAC1, TEP1)	10q23.3	Li et al., 1997; Steck et al., 1997
ACP1	LMPTP (low Mr PTP, LMWPTP, BHPTP)	2p25	Hopkinson et al., 1963

Table 1. Commonly studied PTP genes in the human genome.

As the different stages of B-cell development and maturation are characterized by the structure of the BCR and of the expression of certain differentiation markers, and since the malignant B-cell is said to be "frozen" at the particular stage it developed from, this can be used to determine the cellular origin of the B-cell lymphoma. Diffuse large B-cell lymphoma (DLBCL) is together with B-cell chronic lymphocytic leukemia (CLL), mantle cell lymphoma and follicular lymphoma the most common B-cell lymphomas in adults. DLBCLs exhibit marked biological heterogeneity and variable clinical presentation and clinical course. DLBCL and Burkitt lymphoma (BL) account for the majority of aggressive lymphomas in adults and children. Conversely, BL is genetically relatively homogeneous but associated with variable clinicopathological features (de Leval and Hasserjian, 2009). Gene expression profiling is a powerful tool to uncover complex molecular networks in cancer and, specifically, in malignant lymphomas. Within DLBCL, germinal center B-cell-like (GCB) DLBCL, strongly resembles normal germinal center B-cells and has a good prognosis following chemotherapy, whereas activated B-cell-like (ABC) DLBCL resembles mitogenically activated blood B cells and has a poor outcome (Shipp et al., 2002; Rosenwald et al., 2002). Gene expression profiling furthermore allows the molecular separation of BL from DLBCL and reveals a Burkitt-specific signature which is also expressed by a subset of tumors that are currently classified as DLBCL.

B-cells are especially vulnerable for transforming events during the rearrangements of their BCR, hence the over representation of B-cell lymphomas derived from the GC compartment where somatic hypermutation takes place. Many B-cell leukemias and lymphomas involve an oncogene (mutated and proliferation-enhancing version of a normal gene) that has developed from the corresponding proto-oncogene (normal version of the oncogene) translocated into the Ig-genes. As a consequence, the oncogene is controlled by the Ig-locus and this result in a deregulated, constantly expressed oncogene, contributing to the lymphoma pathogenesis.

Protein tyrosine kinases

PTKs of the SRC (from "neoplastic transformation of cell by avian sarcoma virus is mediated by a single viral gene (src)", one of the most extensively studied retroviral oncogenes), SYK (Spleen tyrosine kinase), TEC (Tec protein tyrosine kinase) and CSK (c-terminal src tyrosine kinase) families are crucial for antigen-receptor induced lymphocyte activation (Ku et al., 1994; Sato et al., 1994; Coussens et al., 1985). LCK (lymphocyte-specific protein tyrosine kinase) (Marth et al., 1985), and the proto-oncogene protein tyrosine kinases FYN (FYN binding protein, FYB-120/130) (Alland et al., 1994; Resh, 1998) and YES (Semba et al., 1985)

Gene	Protein	Chromosome location	References
CSK family			
CSK	CYL	15q23-q24	Sondhi et al., 1998
SRC-A family			
FGR	SRC2	1p36.2-p36.1	Abram et al., 2000; Schwartzberg, 1998; Thomas and Brugge, 1997
FYN	SLK, SYN	6q21	
SRC		20q12-q13	
YES1		18p11.31-p11.21	
SRC-B family			
BLK		8p23-p22	Dymecki et al., 1990; Ziegler et al., 1987; Marth et al., 1986; Yamanashi et al., 1987
HCK	JTK9, HCTK	20q11-q12	
LCK		1p35-p34.3	
LYN		8q13	
TEC family			
BMX	ETK, PSCTK2	Xp22.2	Schaeffer et al., 2000; Rawlings and Witte, 1995
BTK	ATK, PSCTK1, AGMX1, IMD1	Xq21.33-q22	
ITK	EMT, PSCTK2	5q31-q32	
TEC	PSCTK4	4p12	
TXK	PSCTK5, BTKL	4p12	
SYK family			
SYK		9q22	Turner et al., 2000; Chu et al., 1998
ZAP70	SRK, STD	2q12	

Table 2. Commonly studied PTK genes in the human genome.

are expressed in T cells, and LYN (tyrosine protein kinase Lyn) (Yamanashi et al., 1987), FYN and BLK (B lymphocyte kinase) (Dymecki et al., 1990) in B cells. The most well-studied PTKs in lymphocytes are presented in Table 2.

In haematopoietic cells, SRC kinases such as LCK, FYN and LYN are the first protein tyrosine kinases that are activated after stimulation through the immunoreceptors. They phosphorylate ITAMs (immunoreceptor tyrosine-based activation motifs) that are present in the signal transducing subunits of the immunoreceptors, thereby providing binding sites for SRC homology 2 (SH2)-domain containing molecules, such as SYK (Mustelin et al., 2005). The SYK-family kinases, SYK and ZAP70 (ζ-chain-associated protein kinase of 70 kDa) function downstream of the SRC-family kinases to amplify the signal and are focal points for the assembly of signalling complexes (Chan et al., 1991; Bradshaw, 2010; Wang et al., 2010). Many PTKs, such as the SRC-family and SYK-family PTKs found in B and T cells, are tightly controlled by PTPs.

ZAP70 plays a critical role in the events involved in initiating T cell responses by the antigen receptor (Wang et al., 2010). The importance of functional ZAP70 has been revealed by observations of both Zap70 deficient humans and mice. ZAP70 deficient patients have no functional T cells in their peripheral blood and suffer from severe combined immunodeficiency (SCID) (Wang et al., 2010). Apart from the critical role in T cells, ZAP70 is also expressed in some populations of activated B cells and in B cell CLL (B-CLL) (Chen et al., 2007; Gobessi et al., 2007; Chen et al., 2008). B-CLL causes accumulation of monoclonal CD5+ B cells in the blood, bone marrow, lymph nodes and spleen. Several different prognostic factors have been proposed for patients with B-CLL. In around 50% of patients with B-CLL, the immunoglobulin heavy-chain variable-region (IgVH) genes have undergone somatic mutations which can be identified by sequencing these genes. It has been shown that patients whose B-CLL cells express mutated Ig genes have a better prognosis than patients whose B-CLL cells express unmutated Ig genes (100% germline Ig identity) (Hallek et al., 2008). It has been shown that ZAP-70 is the most promising candidate marker to replace the need for IgVH studying for mutational status with a high predictive value (Chen, 2002). The role of ZAP70 in a B cell disease is unclear. B cells normally express PTK Syk instead of ZAP70. Syk and ZAP70 function downstream of Src-family kinases, which are PTKs such as Lck, Fyn and Lyn and the first tyrosine kinases to be activated after stimulation through the immunoreceptors (Mustelin et al., 2005). The phosphorylation of their targets provide binding sites for Syk and Zap70. As B-CLL cells are characterized by lower surface expression of IgM and CD79b than normal B lymphocytes, it is conceivable that association between ZAP-70 and CD79b may facilitate the recruitment of a Src kinase such as Lyn to the BCR complex, resulting in Lyn-mediated

phosphorylation of the limiting numbers of ITAMs of CD79b following BCR ligation. Regardless of how ZAP-70 promotes BCR signaling in B-CLL, it is clear that its expression is associated with a worse prognosis. Expression of ZAP-70 is now being used clinically for prognostication.

Protein tyrosine phosphatases

PTPN6 or SHP-1 (SH2-domain-containing phosphatase-1) is a cytosolic key regulatory PTP that controls intracellular phosphotyrosine levels predominantly in hematopoietic cells of all lineages, but is also expressed at lower levels in epithelial cells (Lorenz, 2009). The human SHP-1 gene is located on chromosome 12p13 (Plutzky et al., 1992; Matsushita et al., 1999). It consists of 17 exons and spans approximately 17 kb of DNA with a transcription size of 2,4-2,6 kb (Wu et al., 2003). The SHP-1 gene encodes two forms of SHP-1 protein, with differences in the N-terminal, but with negligible activity as a result. Two different and mutually exclusive tissue-specific promoters regulate expression of the two forms of SHP-1 protein. Promoter 1 is active in all cells of non-hematopoietic origin, whereas promoter 2 is active exclusively in cells of hematopoietic lineage (Wu et al., 2003). Structurally, both SHP-1 and SHP-2 are composed of a central catalytic domain containing a specific PTP signature motif, two SH2 domains at their N-termini and a C-terminus (Poole and Jones, 2005). The SH2 domains are important for localization and activity regulation (Lorenz, 2009). The N-terminal SH2 domain is intramolecularly associated with the PTP domain, thereby repressing its activity. The repression is released when the SH2 domains are engaged, leading to activation of the phosphatase. Two tyrosines in the C-termini of SHP-1 (Y536 and Y564) and SHP-2 (Y542 and Y580) have been shown to become phosphorylated upon various stimuli which further influence the function and activities. Importantly, SHP-1 has also been proposed to have a role as a tumour-suppressor in lymphoma and leukaemia since decreased levels of both SHP-1 protein and mRNA have been observed in these malignancies (Wu et al., 2003). Moreover, SHP1 may be involved in the clinical evolution of myelodysplastic syndrome (MDS) (Mena-Duran, 2005). The role of SHP-1 in acute lymphoblastic leukaemia (ALL) has also been investigated, revealing that both SHP-1 and the tumor suppressor PTEN showed a significant difference in expression compared to nonmalignant controls (Gauffin et al., 2009). Studies also show that activated proliferation of B-cell lymphomas/leukemias with SHP1 gene silencing by aberrant CpG methylation (Koyama et al., 2003; Sato et al., 2010).

SHP-1 has been proposed as a candidate tumor suppressor gene since a decreased expression level of SHP-1 has been reported in several different types of haematological malignancies (Wu et al., 2003). Several mechanisms have been suggested for low expression level of SHP-1 protein and also SHP-1 mRNA in these malignancies: methylation of the promoter region of the SHP-1 gene or the post-transcriptional block of SHP-1 and also mutation of the SHP-1 gene.

Taken together, SHP-1 protein has a central role in normal cell growth by regulating the activity of protein tyrosine kinases. Since the negative regulatory function of SHP-1 and its central role in many hematological malignancies has been suggested, it has been of great interest to find which molecules or substrates interact with SHP-1 protein. In this context, several different putative substrates for SHP-1 have been proposed. For instance, ZAP-70 and Syk have been proposed as potential substrates for SHP-1 in intact cells (Brockdorff et al., 1999).

Several other PTPs have been identified as the products of tumor suppressor genes (Tonks, 2006). One of the most studied is the PTP tumor suppressor, PTEN, a dual-specificity phosphatase, which is selective for dephosphorylating the critical phosphothreonine and phosphotyrosine residues. PTEN is short for "Phosphatase and tensin homologue deleted on chromosome 10", also referred to as "mutated in multiple advanced cancers" (MMAC1), and was discovered in 1997 (Li et al., 1997; Steck et al., 1997). PTEN is frequently inactivated in somatic cancers and is ranked the second most mutated tumour suppressor gene after p53 (Di Cristofano and Pandolfi, 2000; Georgescu, 2010). Loss of PTEN is seen in over half of all glioblastomata and in a high portion of breast and prostate cancer, in lymphomas and many other common malignancies (Tautz et al., 2009).

SHP-2, which is encoded by the PTPN11 gene was the first PTP with proven oncogenic function (Östman et al., 2006; Tonks, 2006).

Gain-of-function mutations in SHP-2, initially identified as Noonan syndrome, facilitate activation of the PTP (Tartaglia et al., 2001). SHP-2 normally facilitates Ras activation by regulating the activity of Src-family PTKs, or the level of Sprouty proteins (Östman et al., 2006). Activating somatic mutations in the gene PTPN11 have been associated with increased risk of certain sporadic childhood malignancies, such as juvenile myelomonocytic leukemia (JMML) and acute myeloid leukemia (AML), which induce hypersensitivity to granulocyte-macrophage colony-stimulating factor (GM-CSF) in hematopoietic progenitor cells (Östman et al., 2006).

Upon transplantation into lethally-irradiated mice, bone marrow expressing leukemia-associated SHP-2 mutants give rise to a fatal invasive myeloproliferative disease that is associated with hyperactivation of the mitogen-activated protein kinase (MAPK) Erk and other signalling pathways (Mohi et al., 2005). The LEOPARD syndrome shares clinical features with the Noonan syndrome, but is instead associated with mutations that act as dominant negatives and interfere

with Erk MAPK activation (Kontaridis et al., 2006).
Except for SHP-2, one more intracellular PTPs has been shown to have positive regulatory function, namely low molecular weight protein tyrosine phosphatases (LMW-PTP) (Mustelin et al., 2005). LMW-PTP dephosphorylates the negative regulatory site Y292 of PTK Zap70, which results in a slower down-modulation of cell surface T cell receptor (TCR) (Bottini et al., 2002a). Acid phosphatase locus 1 (ACP1) is a polymorphic gene located on chromosome 2 showing three common codominant alleles: ACP1A, ACP1B and ACP1C (Hopkinson et al., 1963; Bottini et al., 1995). The corresponding 6 genotypes are associated with different enzymatic activities (Spencer et al., 1964). The ACPs, or LMW-PTPs, are a group of tyrosine phosphatases expressed in certain tissue including glandular cells of different tissue as well as lymphocytes, breast, colon, brain, gastric ventricle and prostate. LMW-PTP has been characterized as tyrosine, but not a serine or threonine phosphatase (Malentacchi et al., 2005). In humans, LMW-PTP is expressed by a single copy gene located on chromosome 2. The primary transcript shows a complex pattern of alternative splicing which leads to the production of four different mRNAs. The role of LMW-PTP in cell proliferation seems to be important and is carried out by dephosphorylation leading to inactivation of tyrosine kinases such as the insulin-receptor, platelet-derived growth factor-receptor (PDGF-R), the ephrin receptor and docking proteins such as β-catenin having both adhesion and transcription activity (Chiarugi et al., 2002; Chiarugi et al., 2004). The enzyme interacts with several receptors and proteins and is involved in the regulation of Jak/STAT, which is one of the signaling pathways that is often dysregulated in leukemias. Moreover, the JAK-gene is linked to some hematopoietic malignancies. Inhibition of LMW-PTP results in a partly increased and prolonged phosphorylation of JAK/STAT as well as a decrease in apoptosis. Oxidation of the enzyme also leads to anti-apoptotic effects. Over-expression of LMW-PTP has been shown to counteract malign transformation and signaling of tyrosine kinase oncogenes. Moreover, over-expression of LMW-PTP is also associated with several cancer forms (Bottini et al., 2002b; Alho et al., 2008).
Hematopoietic phosphatase (HePTP), PTPN7, is the only pTyr-specific PTP known to dephosphorylate MAPKs in hematopoietic cells (Saxena et al., 1999; Sergienko et al., 2012). HePTP is a 38-kDa enzyme, consisting of the C-terminal catalytic PTP domain and a short (45 residues) N-terminal extension, which contains the kinase interaction motif (KIM, residues 15-31) (Zanke et al., 1992; Zanke et al., 1994; Adachi et al., 1994). The first indication of a role of HePTP in cell proliferation or differentiation came from the finding that the HePTP gene is located on the long arm of chromosome 1, which is often found in extra copies (trisomy) in bone marrow cells from patients with MDS, which is characterized by reduced hematopoiesis and increased risk of acute leukemia. Indeed, amplification and overexpression of HePTP is also reported in cases of acute myeloid leukemia (AML) (Saxena et al., 1999). HePTP is down-regulated in pediatric lymphoma compared to control lymphoid cells (Fridberg et al., 2008). Loss of HePTP might indicate increased cell proliferation and/or survival of lymphoma cells.
T-cell phosphatase (TC-PTP), PTPN2, (Mosinger et al., 1992) is described as a phosphatase for both JAKs and STATs, which are important signaling proteins downstream of cytokine receptors (Kleppe et al., 2011). TC-PTP has been shown to be a tumor suppressor gene in T-cell malignancies (Kleppe, 2010; Kleppe, 2011). Moreover, TC-PTP was identified as a physiological regulator of STAT6 phosphorylation in ABC-like DLBCLs, which may contribute to the different biological characteristics of these DLBCL tumors (Lu et al., 2007).

Summary and conclusion

Many PTKs have already been discovered as drug targets and the treatment of many human diseases. Also PTPs will be found to be involved in human diseases and will be used as drug targets to treat these diseases in the future. However, there is a great need to investigate interactions between factors which are likely of pathogenic importance to develop new therapeutics for patients with lymphoma and/or leukemia. Moreover, establishing laboratory tests which are sufficiently sensitive and specific to be prognostic for these patients might influence management decisions for determining the best course of treatment.

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