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The Role of Polymorphisms in Co-Signalling Molecules' Genes in Susceptibility to B-Cell Chronic Lymphocytic Leukaemia

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1. Introduction

Chronic lymphocytic leukaemia (CLL) is associated with several humoural and cellular immune abnormalities (Scrivener *et al*, 2003; Stevenson & Caligaris-Cappio, 2004) that could lead to an inadequate anti-tumour response. The immune surveillance of tumour cells depends on the recognition of antigens presented in the context of human leukocyte receptor HLA class I molecules by cytotoxic T lymphocytes (CTLs), via their T-cell receptors (TCRs) (Rosenberg, 2001). However, antigen alone is insufficient to drive the activation of naïve T-cells (Lafferty *et al*, 1978), and the two-signal model of T-cell activation was proposed. According to this model, the effective activation of naïve T cells requires second, antigen independent, co-stimulatory signal provided by the interaction between a co-stimulatory receptor and its ligand on an antigen-presenting cell (Jenkins *et al*, 1990; Schwartz *et al*, 1989). The lack of co-stimulation results in T-cell tolerance and anergy. Over the past several years, a large number of molecules have been identified that function as second signals following TCR engagement, and many have been revealed to be negative co-stimulatory molecules, which dampen T-cell activation and regulate immune tolerance. Some have been shown to be upregulated in the tumour microenvironment and have become potential targets for augmenting anti-tumour immunity (Sharpe, 2009).

Polymorphisms in genes can influence the level of protein expression (Anjos *et al*, 2002; Kouki *et al*, 2000; Wang *et al*, 2002b; Oki *et al*, 2011). Therefore, genetic variation in genes encoding co-signalling molecules may also alter the antitumour response and influence cancer susceptibility, particularly susceptibility to CLL.

Here we focus on polymorphisms in genes encoding co-signalling molecules that belong to the best-characterized B7/CD28 family, which plays a crucial role in T-cell activation.

2. Co-signalling molecules – Overview

2.1 Cluster of differentiation 28 (CD28)

CD28 is the primary co-stimulatory molecule constitutively expressed on the majority of T cells (95% of $CD4^+$ T cells and approximately 50% of $CD8^+$ T cells). Upon interaction with its

ligands CD80 (B7.1) and CD86 (B7.2), CD28 transduces a signal that enhances the activation and proliferation of T cells and IL-2 production (Frauwirth & Thompson, 2002; Carreno & Collins, 2002). In addition, a higher level of secretion of other cytokines such as IFN-γ, GM-CSF, IL-4, IL-8 and IL-13, can be observed after CD28 ligation. Moreover, CD28 signalling promotes cell survival via Bcl-x_L transcriptions and prevents anergy (Boise *et al*, 1995). It has been shown that mice deficient in CD28 or both of its ligands (B7.1 and B7.2) have severely impaired $CD4^+$ T cell proliferation (Shahinian *et al*, 1993; Borriello *et al*, 1997) and lymphokine secretion after stimulation with concanavalin A (Con A) or superantigen (Mittrucker *et al*, 1996). Furthermore, CD28-deficient mice exhibit lower levels of certain isotypes of immunoglobulins, and germinal centres are not formed in response to immunisation (Ferguson *et al*, 1996). The requirement for CD28 for the co-stimulation of $CD8^+$ T cells is more controversial; it was postulated that $CD8^+$ T cells are less CD28 dependent than $CD4^+$ cells (Green *et al*, 1995).

The *CD28* is located on the q33 region of chromosome 2. The gene encoding *CD28* consist of four exons, of which exon 1 encodes the leader peptide, exon 2 the ligand binding domain, exon 3 the transmembrane segment, and exon 4 the cytoplasmic tail. Within the gene encoding the CD28 molecule several polymorphic sites have been identified. Three of these sites are non-synonymous gene polymorphisms: the *CD28c.73G>A* (rs3181099) single nucleotide polymorphism (SNP) in exon 1, which leads to change from Gly 25 to Arg; the *CD28c.224G>A* (rs35290181) SNP in exon 2 which changes Ser 75 to Asn, and the *CD28c.272G>A* (rs75899942) SNP that is also in the second exon, which changes Gly91 to Asp. Moreover, 4 synonymous SNP were found, all in the third exon.

It has been reported that variations in non-coding regions can regulate gene expression by altering the motif of functional DNA binding sites, thereby affecting their affinity to transcription factors.

In the intronic region of *CD28* gene eleven SNPs have been described, but CD28c.*17+3T>C* (rs3116496) is the best studied in the context of susceptibility to autoimmune and neoplastic disease. This polymorphism is located near the splice receptor site and might influence the mRNA splicing efficiency and thus the expression of the CD28 molecule (Ahmed *et al*, 2001). Another widely investigated SNP in the *CD28* gene is *CD28 -372G>A* (rs35593994), which is situated in the promoter (Teutsch *et al*, 2004). The potential functional effect of this SNP remains to be elucidated, but a search for transcription factor binding sites suggested that the *CD28-372G>A* [A] allele differs from the *CD28-372G>A* [G] allele by the presence of a binding site for the CCAAT enhancer-binding protein and the lack of a binding site for growth factor independence 1 (Teutsch *et al*, 2004). Only one microsatellite polymorphism was described in the *CD28* gene and in comparison with many other microsatellites, it presented a low degree of polymorphism. The most common allele occurred at frequencies higher than 0.8, and the gene diversity is close to 0.3 (Pincerati *et al*, 2010).

2.2 Inducible co-stimulator (ICOS)

The second co-stimulatory molecule is ICOS, which appears on T lymphocytes rapidly upon activation (Hutloff *et al*, 1999) and on unpolarised as well as Th1, Th2, Th17, and Treg subpopulations of $CD4^+$ cells (McAdam *et al*, 2000; Tan *et al*, 2008; Nakae *et al*, 2007; Akiba *et al*, 2005; Burmeister *et al*, 2008). This co-stimulatory molecule binds the B7-related protein

B7RP-1 (Yoshinaga *et al*, 1999). Like CD28, ICOS provides a signal for T-cell activation and differentiation, and in one model, animals lacking this molecule had a reduced $CD4^+$ T-cell response (Dong *et al*, 2003).

While CD28 and ICOS have overlapping functions in early T-cell activation, ICOS augments the T-cell effector function, in particular the production of IL-4, IL-5, IL-10, IFN-α, and IFN- γ (Beier *et al*, 2000), but not IL-2 (Hutloff *et al*, 1999). In addition, ICOS is important for the generation of chemokine receptor 5 $(CXCR5)^+$ follicular helper T cells (T_{FH}), a unique T-cell subset that regulates germinal centre formation and humoural immunity (Nurieva *et al*, 2008).

ICOS knockout mice have reduced $CD4^+$ T-cell responses, an increased risk of experimental autoimmune encephalomyelitis (Dong *et al*, 2001), and defects in immunoglobulin class switching and germinal centre formation (McAdam *et al*, 2001).

In human, the homozygous loss of the *ICOS* gene is the cause of the ICOS deficiency (ICOSD) form of common variable immunodeficiency (CVID). ICOSD patients suffer from recurrent bacterial infections of the respiratory and digestive tracts, which are characteristic of humoural immunodeficiency, but do not have other complicating features, such as splenomegaly, autoimmune phenomena, or sarcoid-like granulomas, or clinical signs of overt T-cell immunodeficiency (Grimbacher *et al*, 2003). A severe disturbance of T cell-dependent B-cell maturation occurs in the secondary lymphoid tissue; B cells exhibit a naive IgD^+/IgM^+ phenotype, and the numbers of IgM memory and switched memory B cells are substantially reduced in individuals with ICOSD (Grimbacher *et al*, 2003).

The *ICOS* gene also located in the 2q33 region contains five exons. Exons 1-4 are parallel to those of *CD28*, while exon 5 encodes an additional fragment of the cytoplasmic tail. In the *ICOS* gene, two microsatellites in the fourth intron and 31 single-nucleotide polymorphisms (SNPs) (http://www.hapmap.org) have been found. None of the described *ICOS* SNPs leads to changes in the amino acid sequence, although a few have been demonstrated to be functional variants (Kaartinen *et al*, 2007; Haimila *et al*, 2009; Castelli *et al*, 2007; Shilling *et al*, 2005).

The *ICOSc.1624C>T* (rs10932037) polymorphism has been shown to influence the ICOS mRNA level (Kaartinen *et al*, 2007). The authors described that activated $CD4^+$ T cells from *ICOSc.1624C>T* [CC] homozygous people had higher actual levels of ICOS mRNA than cells from [TC] heterozygous people 1 h and 3 h after activation, following which this difference disappeared.

The *ICOSc.1624C>T (rs10932037)*, *ICOSc.1624C>T*(rs10932037), and *ICOSc.2373G>C* (rs10183087) SNPs, which are located in the 3′ untranslated region (UTR) of the *ICOS* gene, influence the functions of the *ICOS* gene (Castelli *et al*, 2007). Three major haplotypes, which were associated with different levels of expression of ICOS in $CD3^+$ cells and IL-10 secretion have been identified. The AA genotype, characterised by presence of *ICOSc.1624C>T*[CC], *ICOSc.602A>C*[AA], and *ICOSc.2373G>C*[GG] was shown to be associated with the lowest percentage of CD3+ activated cells expressing ICOS and the highest levels of IL-10 secretion.

The *ICOSISV1+173T>C* (rs10932029) polymorphism, which is located close to the *CTLA-4* gene, has been reported to affect the expression of the CTLA-4 isoforms (Kaartinen *et al*, 2007; Brown *et al*, 2007).

Two microsatellite polymorphisms have been described in the fourth intron of the *ICOS* gene. The first is a GT repeats at position 1554, the location of an Sp1 binding site, and the second, a T repeats, is at a position near the splice donor site (Ihara *et al*, 2001).

2.3 Cytotoxic T lymphocyte- associated antigen-4 (CTLA-4)

CTLA-4 has been well established as negative regulator of T-cell function (Walunas *et al*, 1994; Walunas *et al*, 1996). CTLA-4 is rapidly expressed on T cells following activation and is highly up-regulated by CD28 engagement. CTLA-4 shares the B7 ligands with CD28.

CTLA-4 binding with its ligands antagonises early T-cell activation, leading to decreased IL-2 production, the inhibition of cell-cycle progression, decreased cyclin expression, and the modulation of TCR signalling (Luhder *et al*, 2000). CTLA-4-deficient mice develop a severe lymphoproliferative disease and die within 3-4 weeks (Tivol *et al*, 1995; Waterhouse *et al*, 1995). CTLA-4 is also important in the function of regulatory cells, which suppress effector T-cell activation and function (Tang *et al*, 2004; Tai *et al*, 2005).

Many mechanistic models have been postulated for the function of CTLA-4. These models include competition with the co-stimulatory CD28 molecule by more effectively binding their common ligands, the inhibition of downstream TCR signalling by the phosphates SH2 domain, the inhibition of lipid-raft and microcluster formation, and the negative regulation of the immune response by extrinsic components such as TGF-β and the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) (Rudd *et al*, 2009).

The *CTLA-4* gene is located between *CD28* and *ICOS* genes. It is similar to *CD28* gene and consists of four exons, of which exon 1 encodes the leader peptide, exon 2 the ligand binding domain, exon 3 the transmembrane segment, and exon 4 the cytoplasmic tail. The functional significance of the polymorphisms in the *CTLA-4* gene have been widely explored and described. The most studied is the *CTLA-4c.49A>G* (rs231775) transition. This non-synonymous SNP causes an amino acid change from threonine to alanine. It influences T-cell activation and could have a role in antitumour immunity. The presence of the [AA] genotype as opposed to the [GG] genotype has been shown to be associated with significantly lower levels of activation of T lymphocytes and lower proliferation. The protein product encoded by the *CTLA-4c.49A>G*[AA] genotype, CTLA-4^{17}Thr, had a higher capacity to bind B7.1 and a stronger inhibitory effect on T-cell activation compared with CTLA-4^{17}Ala (Sun *et al*, 2008). It was also postulated that the *CTLA-4c.49A>G* polymorphism in the leader sequence of the protein alters the inhibitory function of the molecule by influencing the rate of endocytosis or surface trafficking (Kouki *et al*, 2000) and the glycosylation of CTLA-4 (Anjos *et al*, 2002).

The *CTLA-4*g.319C>T (rs5742909) SNP located in the promoter region also has documented functional significance. The *CTLA-4*g.319C>T[T] allele has been associated with a higher promoter activity (Wang *et al*, 2002b), probably due to the creation of a lymphoid enhancer factor-1 (LEF1) binding site in the *CTLA-4* promoter (Chistiakov *et al*, 2006). This allele has also been associated with significantly increased mRNA and surface expression of CTLA-4 in stimulated and non-stimulated cells (Ligers *et al*, 2001; Anjos *et al*, 2002).

The *CTLA-4g.1661A>C* (rs4553808) SNP, also located in the promoter, appears to be involved in the transcription-associated binding activity of nuclear factor (NF-1) and C/EBPβ and might cause abnormal alternative spicing and affect the expression of CTLA-4 (Wang *et al*, 2008).

The *CTLA-4*g.*6230G>A (CT60) (rs3087243) polymorphism situated in the 3′ UTR was shown to be associated with variations in the mRNA level of soluble CTLA-4, an isoform lacking the transmembrane domain, that is generated by the alternative splicing of the primary transcript (Ueda *et al*, 2003). Our recent results indicate that the CT60 polymorphism together with the Jo31 SNP (*CTLA-4*g.10223G>T, rs11571302, also located in the 3′ region) is associated with the levels of membrane and cytoplasmic CTLA-4 in $CD4^+$ T lymphocytes from multiple sclerosis patients (Karabon *et al*, 2009) and with the altered levels of soluble CTLA-4 in the serum of Graves' disease patients (Daroszewski *et al*, 2009).

Another widely investigated genetic marker situated in the 3′ UTR region of *CTLA-4* gene is a microsatellite polymorphism *CTLA-4*g.*642AT(8_33). The number of dinucleotide (AT) repeats at position 642 in the 3′UTR region has been shown to be associated with the stability of the mRNA transcripts (Wang *et al*, 2002a).

2.4 Programmed death-1 (PD-1)

Similar to CTLA-4, PD-1 has been described as a negative regulator of T- and B-cell function. PD-1 is an inducible molecule expressed on activated T- and B-cells (Greenwald *et al*, 2005). In reactive lymph nodes, PD-1 was mainly expressed in follicular T cells (Dorfman *et al*, 2006). PD-1 binding limits T-cell functions, including T-cell proliferation, apoptosis and interferon-γ production (Freeman *et al*, 2000).

Knockout PD-1 mice develop different autoimmune diseases depending on the genetic background: BALBc mice develop autoimmune cardiomyopathy (Nishimura *et al*, 2001); C57BL mice develop progressive arthritis and lupus-like glomerulonephritis (Nishimura *et al*, 1999); and NOD mice develop autoimmune diabetes (Wang *et al*, 2005). PD-1 also has a critical role in murine experimental encephalomyelitis (Salama *et al*, 2003).

PD-1 has two ligands, which belong to the B7 superfamily: PD-L1 (B7-H) and PD-L2 (B7-DC). The mRNA expression patterns of PD-L1 and PD-L2 are different. PD-L1 is broadly expressed in different human and mouse cells, such as leukocytes, non-haematopoietic cells and non-lymphoid tissue (Freeman *et al*, 2000), while PD-L2 is present exclusively on dendritic cells and monocytes (Latchman *et al*, 2001; Liang *et al*, 2006). The differential expression patterns of PD-L1/PD-L2 and CD80/CD86 are crucial differences between CTLA-4 and PD-1, and this fact raises the hypothesis that CTLA-4 has a key role in the early stages of tolerance induction, while PD-1 functions late for the maintenance of long–term tolerance. The expression of PD-1 ligands limits T-cell function within tissue-specific sites, while CTLA-4 limits T cells in lymphoid structures because CD80 and CD86 are expressed on antigen-presenting cells.

The *PD-1* gene is also located on the long arm of chromosome 2, but in the 37.3 region. Similar to the *ICOS* gene, it consists of 5 exons: exon 1 encodes leader peptide, exon 2 extracellular IgV-like domain, exon 3 the transmembrane domain, exon 4 and 5 the intracellular domain. So far, more than 30 SNPs have been identified in the *PD-1* gene. These

polymorphisms have been investigated mainly in context of susceptibility to autoimmune disease, such as rheumatoid arthritis (RA) (Kong *et al*, 2005), type I diabetes (Flores *et al*, 2010), ankylosis spondylitis (AS) (Lee *et al*, 2006), and systemic lupus erytrhomatosus (SLE) (Velazquez-Cruz *et al*, 2007), but only a few studies have been devoted to determining the functional significance of these genetic variations. Among the *PD-1* gene polymorphisms, seven namely PD-1.1, PD-1.2, PD-1.3, PD-1.4, PD-1.5, PD-1.6 and PD-1.9, have been studied the most frequently. Two SNPs (PD-1.5 (*57785C>T* - rs2227981) and PD-1.9 *(7625C>T* - rs2227982)) occur in exon 5. The C>T transition in the PD-1.9 SNP causes a change in amino acid from valine to alanine, while PD1.5 is a synonymous coding variant.

PD-1.1 (*−538G>A* - rs58398280) is located in promoter region, PD-1.2 (*6438G>A* - rs34819229), PD1.3 (*7146G>A - rs11568821*), and PD1.4 (*7499G>A* - rs6705653)) are situated in introns 2, 4, and 4, respectively, while the PD1.6 (*8737G>A*) SNP is in the 3′ UTR (Ferreiros-Vidal *et al*, 2004).

The data describing the functional roles of the *PD-1* gene polymorphisms are limited. It has been shown that the PD-1.3 (7146G>A) polymorphism has functional significance, and the presence of PD-1.3. The [A] allele has been associated with a significantly lower expression of the PD-1 receptor in SLE patients, their relatives and healthy individuals (Kristjansdottir *et al*, 2010).

Patients homozygous for PD-1.3[AA], but not heterozygous for PD-1.3[AG], had reduced basal and induced PD-1 expression on activated $CD4^+$ T cells. In an autologous mixed lymphocyte reactions (AMLRs), activated $CD4^+$ cells from SLE patients had defective PD-1 induction, and this abnormality was more pronounced in homozygotes than heterozygotes. Moreover, the A allele conferred decreased transcriptional activity in transfected Jurkat cells (Bertsias *et al*, 2009).

The *7209C>T* SNP located in intron 4 of the *PD-1* gene was also found to be associated with protein expression. Using a luciferase reporter assay, it was shown that the *PD-1 7209C>T*[T] allele creates a negative *cis*-element for gene transcription (Zheng *et al*, 2010).

The promoter polymorphism *PD-1-606G>A* (rs360488323) alters the promoter activity. The significantly higher promoter activity was observed with the construct with the *PD-1-606G>A* [G] allele than with the *PD-1-606G>A* [A] allele *(*Ishizaki *et al, 2010).*

2.5 B and T lymphocyte attenuator (BTLA)

Although BTLA shares only 9-13% amino acid identity with CTLA-4 and PD-1, it is structurally similar to them. The presence of two ITIM motifs in its cytoplasmic region suggests, that it has an inhibitory function. In mice, it is expressed at a very low level on resting T cells, and it is induced during activation. Interestingly, after T-cell differentiation, only T helper type Th1, but not Th2, cells express BTLA, and its expression is independent of interleukin 12 (IL-12) or IFN-γ, suggesting a specific role for BTLA in Th-1 cells (Watanabe *et al*, 2003). However, BTLA transcripts have been detected in primary B cells and B-cell lines, which indicates its role in the regulation of the B-cell response. In comparison with other co-inhibitory molecules, BTLA is more widely expressed than CTLA-4, which is expressed only on T-cells, but has more limited expression than PD-1, which is expressed on T, B and myeloid cells.

Blocking BTLA prevents proliferation and cytokine production by T cells. BTLA-deficient mice exhibit a moderate increase in specific antibody responses and increased susceptibility to experimentally induced autoimmune encephalomyelitis (EAC) (Watanabe *et al*, 2003).

In humans, BTLA is highly expressed on $CD14^+$ monocytes and $CD19^+$ B cells, constituently on $CD4^+$ and $CD8^+$ lymphocytes and weakly on $CD56^+$ NK-cells. Among normal B cells, the highest level of BTLA-expression is found in naïve B cells. Of normal T cells, high levels of BTLA expression are found in T follicular helper (T_{FH}) cells (M'Hidi *et al*, 2009). When PBMCs were stimulated 2 days with LPS, the expression of BTLA on $CD14^+$ monocytes and $CD19^+$ B cells decreased to some extent, while the expression on the other cell types, $CD4^+$ and $CD8^+$ lymphocytes and $CD56^+$ NK cells, is upregulated.

BTLA binds the herpes virus entry mediator (HVEM). Interestingly HVEM is a member of the TNFR family, and its interaction with BTLA is the first demonstration of crosstalk between CD28 and the TNFR family. HVEM is expressed on resting T cells, B cells, macrophages and immature dendritic cells, and its expression is downregulated on activated T cells (Sedy *et al*, 2005; Gonzalez *et al*, 2005)

Unlike the other co-signalling molecules described, the *BTLA* gene is located on chromosome 3 in q13.2 region. However, like *ICOS* it has 5 exons (Garapati VP & Lefranc MP, 2007). Because *BTLA* was relatively recently described in the literature, there are only a few studies that address *BTLA* gene polymorphisms, and most have investigated its role in susceptibility to autoimmune diseases, such as RA (Lin *et al*, 2006; Oki *et al*, 2011), SLE and type 1 diabetes mellitus (Inuo *et al*, 2009). The non-synonymous *BTLAc.800G>A* SNP (rs9288952) which leads to a Pro 219 to Leu exchange, has been associated with susceptibility to RA (Lin *et al*, 2006).

Another study has described a functional polymorphism, *BTLAc.590A>C* (rs76844316) (Oki *et al*, 2011). This polymorphism is located in forth exon of the *BTLA* gene gene and leads to the exchange of asparagine to threonine in the intracellular domain. It was found that the C allele is associated with decreased inhibitory activity of BTLA in ConA- and anti-CD3-induced IL-2 production, although the surface expression level is similar in transfectants of both the A and C alleles. It was postulated that the change in amino acids interferes with BTLA signalling and downregulates the association of an unidentified kinase that phosphorylates BTLA or SHP1/SHP2 (Oki *et al*, 2011).

3. Polymorphisms in co-signalling genes and susceptibility to cancer

Because the significance of co-signalling molecules in the regulation of immune response has been clearly documented, polymorphisms in the genes encoding those molecules have been widely investigated, previously as susceptibility determinants for autoimmune disease and recently for cancer. Among others, *CTLA-4* gene polymorphisms have been investigated the most intensively. It was found that the *CTLA-4c.49A>G*[A] allele was associated with an increased risk of many types of cancers, including oesophageal cancer, gastric cardia cancer (Sun *et al*, 2008), non-Hodgkin's lymphoma (Piras *et al*, 2005), breast cancer (Ghaderi *et al*, 2004; Sun *et al*, 2008), renal cancer (Cozar *et al*, 2007) and lung cancer, esophagus and gastric cardia cancer (Sun *et al*, 2008). Wong *et al* (2006) reported that although the *CTLA-4c.49A>G*[AA] genotype did not increase the risk of oral squamous cell cancer, it correlated

significantly with a younger age at onset and poorer survival. Notably, the *CTLA-4c.49A>G*[GG] genotype was found to be prevalent in mucosa-associated lymphoid tissue lymphoma (Cheng *et al*, 2006) and in multiple myeloma (Karabon *et al*, 2011c). There was no association between the *CTLA-4c.49A>G* SNP and colorectal cancer (Solerio *et al*, 2005; Hadinia *et al*, 2007), B-cell chronic lymphocytic leukaemia (Suwalska *et al*, 2008), cervical squamous cell carcinoma (Su *et al*, 2007), malignant melanoma (Bouwhuis *et al*, 2009), or non-malignant melanoma (Welsh *et al*, 2009).

The *CTLA-4*g.319C>T polymorphism was shown to be associated with female-related cancers such as sporadic breast cancer (Wong *et al*, 2006) cervical cancer (Su *et al*, 2007; Pawlak *et al*, 2010) and lung cancer in women (Karabon *et al*. 2011). However, this polymorphism was not associated with lung cancer (without stratification by gender) (Sun *et al*, 2008) or other cancers, such as colon cancer (Cozar *et al*, 2007), colorectal cancer (Dilmec *et al*, 2008) or multiple myeloma (Karabon *et al*, 2011c).

A limited number of studies have been devoted to the association between the CT60 and Jo31 SNPs and cancers. No association was found between CT60 and Jo31 and lung cancers (Karabon *et al*, 2011b; Sun *et al*, 2008), cervical squamous cell carcinoma (Su *et al*, 2007;Pawlak *et al*, 2010) or malignant melanoma (Bouwhuis *et al*, 2009). However, the CT60 [AA] homozygosity correlated with an increased risk of renal cell cancer and with tumour grade (Cozar *et al*, 2007), while the presence of the A allele is associated with increased susceptibility to non-melanoma skin cancer (Welsh *et al*, 2009). In contrast, the CT60[G] alleles were found to be prevalent in patients with sporadic breast cancer (Wong *et al*, 2006) and in multiple myeloma patients (Karabon *et al*, 2011c).

Only one study indicates a possible predisposing role for the *CTLA-4g.1661A>G* [G] allele in susceptibility to oral squamous cell carcinoma (OSCC) (Kammerer *et al*, 2010).

In summary, the latest meta-analysis, which summarised data from 48 studies, confirmed that the presence of the G allele in *CTLA-4c.49A>G* polymorphisms decreased the risk of cancer compared with that with the homozygous *CTLA-4c.49A>G*[AA] genotype. Interestingly, the *CTLA-4c.49A>G*[AG+GG] genotype was associated with a decreased risk of cancer in Asians, but not among Europeans, while the *CTLA-4*g.319C>T[T] allele was associated with an increased risk among Europeans but not Asians. The meta-analysis did not confirm the role of the CT60 SNP as a cancer risk factor (Zhang *et al*, 2011).

Polymorphisms in the *CD28* gene have not been as widely investigated. The *CD28*c.17+3T>C SNP was not associated in an indirect way with non-solid tumour cancer, while several conditioner associations were established. Our study revealed a lack of association between the *CD28*c.17+3T>C polymorphism and CSCC, while we found an association with well-differentiated tumours (Pawlak *et al*, 2010). No association with the *CD28*c.17+3T>C polymorphism was found in a previous study with cervical cancer, but Guzman showed an epistatic effect between *CD28* and *IFNG* genes in susceptibility to cervical cancer (Guzman *et al*, 2008). Recently a Chinese study and a Swedish study confirmed the *CD28*c.17+3T>C polymorphism as an independent risk factor for the development of that cancer (Ivansson *et al*, 2010;Chen *et al*, 2011).

The *CD28c.17+3T>C* SNP is not susceptibility locus for gastric mucosa-associated lymphoid tissue (MALT) lymphoma (Cheng *et al*, 2006), colorectal cancer (Dilmec *et al*, 2008) or,

together with other tag polymorphisms in the *CD28* gene, malignant melanoma (Bouwhuis *et al*, 2009). Two polymorphic sites, rs3181100 and rs3181113, were shown to not be associated with OSCC (Kammerer *et al*, 2010).

ICOS gene polymorphisms have been widely examined for their potential role as susceptibility locus for melanoma (Bouwhuis *et al*, 2009), but none of the tested tag polymorphisms was associated with this disease. The *ICOSc.602A>C* and *ICOSc.1624C>T* polymorphisms are not related to the risk for MALT (Cheng *et al*, 2006). Similarly, the distribution of alleles and genotypes of *ICOSc.602A>C* and *ICOSc.1599C>T* polymorphisms were no different between OSCC patients and controls (Kammerer *et al*, 2010).

The *PD-1* gene polymorphism mentioned in the previous subsection (2.4) has been widely explored as a susceptibility locus for autoimmune diseases (Kong *et al*, 2005; Flores *et al*, 2010; Lee *et al*, 2006; Velazquez-Cruz *et al*, 2007). Only a few studies have been devoted to the relationship between *PD-1* polymorphisms and cancer. Recently, it has been shown that polymorphisms (PD-1.1, and PD-1.5) alone and as a part of haplotype confers susceptibility to breast cancer in Chinese population (Hua *et al*, 2011). In contrast, in an Iranian population, neither PD1.3 nor PD-1.5 was associated with the risk of breast cancer (Haghshenas *et al*, 2011).

Polymorphisms in the gene of another co-signalling molecule *BTLA* have been investigated mostly in context of autoimmunity. Only one Chinese study was performed to investigate the relationship between *BTLA* polymorphisms and breast cancer (Fu *et al*, 2010). A strong association was found between three polymorphisms, rs9288952, rs2705535 and rs1844089, and the risk of breast cancer. Moreover, associations were also found with tumour size, the oestrogen receptor, the progesterone receptor, C-erbB-2 and the P53 status.

The more important polymorphisms in *CD28, CTLA-4, ICOS, PD-1 and BTLA* genes and their associations with susceptibility to cancer are displaying on Figure 1.

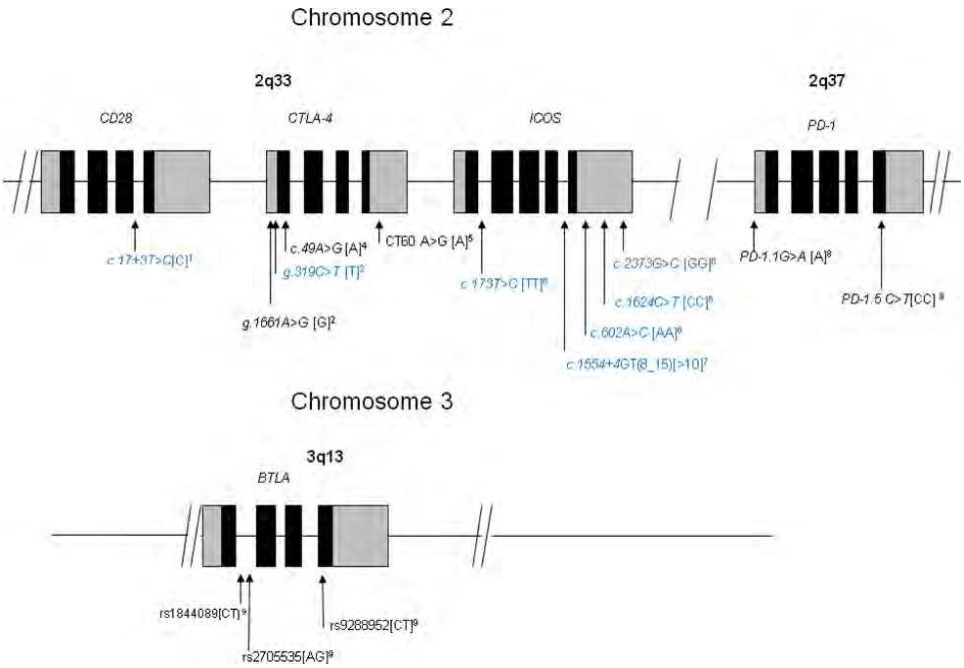
4. Expression of co-signalling molecules in B-cell chronic lymphocytic leukaemia

One of the mechanisms by which neoplastic cells escape elimination by host cells is the downregulation of the co-stimulatory pathway. Actually, a decreased expression of co-stimulatory molecules and the overexpression of co-inhibitory molecules in peripheral blood (PB) T cells have been reported in patients with several neoplastic diseases.

The downregulated expression of the CD28 antigen on peripheral blood T lymphocytes was reported in patients with solid tumours such as: gastric carcinoma, cervical cancer and malignant melanoma (reviewed by (Bocko *et al*, 2002)), and in patients with multiple myeloma (Brown *et al*, 1998; Robillard *et al*, 1998) and hairy-cell leukaemia (van de Corp *et al*, 1999)

Considering the pivotal role of the co-signalling pathway in the antitumour response, several studies have been devoted to examining the expression level of co-signaling molecules in patients with CLL. The investigation by Rossi et al. (Rossi *et al*, 1996), which

was confirmed by Van den Hove et al. (1997) showed significantly lower expression of CD28 on T-cell subsets of chronic lymphocytic leukaemia, and this lower expression was more pronounced in the $CD8^+$ subset than in the $CD4^+$ subset. Scrivener et al. (2003) reported a decreased proportion of $CD2^+/CD28^+$ cells in unstimulated and stimulated PB from CLL patients.



1. predisposing to cervical cancer (Ivansson *et al*. 2010, Chen *et al*. 2011) and CLL (Suwalska *et al*. 2008)
2. predisposing to oral squamous cell carcinoma (Kammerer *et al*, 2010)
3. predisposing to breast cancer (Wong *et al*, 2006), cervical cancer (Su *et al*, 2007;Pawlak *et al*, 2010), lung cancer in women (Karabon *et al*. 2011) and CLL (Suwalska *et al*. 2008); in general for cancer especially in European (Zhang *et al*, 2011)
4. predisposing to oesophageal cancer, gastric cardia cancer (Sun *et al*, 2008), non-Hodgkin's lymphoma (Piras *et al*, 2005), breast cancer (Ghaderi *et al*, 2004; Sun *et al*, 2008), renal cancer (Cozar *et al*, 2007), lung cancer, esophagus and gastric cardia cancer (Sun *et al*, 2008); in general for cancer especially in Asian (Zhang *et al*, 2011)
5. predisposing to renal cell cancer (Cozar *et al*, 2007), non-melanoma skin cancer (Welsh *et al*, 2009).
6. associated with lower rate of CLL progression (Karabon et al. 2011a)
7. predisposing to CLL (Suwalska *et al*. 2008)
8. predisposing to breast cancer (Hua *et al*, 2011)
9. predisposing to breast cancer (Fu *et al*, 2010)

Fig. 1. Structure of genes *CD28*, *CTLA-4*, *ICOS, PD-1* and *BTLA* and location of polymorphisms associated with susceptibility to cancer and in particular to CLL – (distances are not to scale). Genetic variants associated with cancer are marked in black, those associated with cancer and CLL in blue.

In contrast, increased CTLA-4 expression has been observed on peripheral blood T-cells in multiple myeloma (Brown *et al*, 1998; Mozaffari *et al*, 2004), Hodgkin's disease (Vandenborre *et al*, 1998; Kosmaczewska *et al*, 2002), non-Hodgkin's lymphoma (Vyth-Dreese *et al*, 1998), and neoplastic skin diseases (Alaibac *et al*, 2000).

Results from our lab indicated abnormal kinetics and levels of CD28 expression on T cells in CLL patients. The mean percentages of $CD4^+$ and $CD8^+$ cells expressing CD28 were significantly lower in CLL patients than in controls. Moreover, after anti-CD3 and rIL-2 stimulation, the mean percentages of those cells decreased rapidly, and the return to the basal level took longer than it did in healthy individuals (Frydecka *et al*, 2004)

In contrast to the results above, we observed a markedly increased expression of CTLA-4 on unstimulated $CD4^+$ and $CD8^+$ T cells in CLL patients than in controls. The pattern and kinetics of CTLA-4 expression on $CD4^+$ and $CD8^+$ cells in CLL patients after stimulation also differed from that observed in normal subjects. In CLL patient samples, the highest proportion of T cells co-expressing CTLA-4 was found after 24 h of culture as compared to 72 h in samples from normal individuals, and the basal levels were achieved after 5 days compared to 4 days in normal individual samples (Frydecka *et al*, 2004). The dysregulated expression of both the co-stimulatory CD28 and the inhibitory CTLA-4 molecules in peripheral blood T cells might contribute to the T cell-mediated anti-tumour responses in CLL.

Our group also observed a higher expression of both intracellular and surface CTLA-4 in malignant B cells from CLL patients compared with the normal population of $CD19^+/CD5^+$ cells, and the level of its expression in leukaemic cells positively correlated with the progression of the disease. The upregulated CTLA-4 expression in CLL cells was also previously described by (Pistillo *et al*, 2003) in 3 of 4 studied patients. Furthermore, we observed positive correlations between the frequency of $CD19^+/CD5^+/CTLA\text{-}4^+$ cells with the frequency of leukaemic B cells co-expressing the inhibitory protein p27KIP1 and the early G1 phase regulator cyclin D2. We also found a negative association between $CD19^+/CD5^+/CTLA\text{-}4^+$ lymphocytes and $CD19^+/CD5^+$ positive for cyclin D3, which is expressed in the late G1 phase of cell cycle progression. These findings led us to hypothesise that CTLA-4 might contribute to the arrest of leukaemic cells in the G0/G1 phase of the cell cycle (Kosmaczewska *et al*, 2005).

Similar to our results, it has been shown that both BTLA and PD-1 are strongly expressed on malignant B cells from chronic lymphocytic leukaemia/small lymphocytic leukaemia (CLL/SLL) compared with other small-cell lymphomas, such as follicular lymphoma, mantle cell lymphoma and marginal zone lymphoma (M'Hidi *et al*, 2009; Xerri *et al*, 2008). An explanation for why the expression of both BTLA and PD1 is increased in CLL/SLL was proposed by M'Hidi *et al*., (2009). According to this hypothesis, CLL is considered a monoclonal expansion of antigen selected B lymphocytes with varying degrees of autospecificity. The upregulation of inhibitory receptors on CLL precursor cells may result from an attempt by the immune system to prevent autoimmune disorders. To this extent, the simultaneous expression of BTLA and HVEM in CLL cells suggests the triggering of an inefficient autocrine inhibitory loop. This hypothesis is strongly supported by the study of Costello *et al* (2003) who described the upregulated expression of HVEM in human B-cell malignancies.

5. Polymorphisms in co-signalling molecules' genes and susceptibility to B-cell chronic leukaemia

Despite the strong familial basis to CLL, with the risk in first-degree relatives being increased approximately sevenfold, the inherited genetic basis of the disease is yet largely unknown, and the major disease-causing locus has not been established. Therefore, a model of genetic predisposition based on the inheritance of multiple risk variants has been proposed (Houlston & Catovsky, 2008).

Our group focused on the co-signalling pathway, because the development of CLL could be regarded as a failure of immunological surveillance. Therefore genes involved in the regulation of the immunological response might be predisposing loci for disease development. We found that among the three polymorphisms studied in the *CTLA-4* gene (*CTLA-4c.49A>G*, *CTLA-4*g.319C>T and CT60) only one, *CTLA-4*g.319C>T, which is located in the promoter region, confers susceptibility to CLL. We have shown that the presence of the [T] allele or a [T]-positive phenotype increases the risk of the disease about twofold. Moreover, the [T]-positive phenotype correlates with the progression of disease (about 30% of patients with this phenotype increased their Rai stage during the 24 months follow–up compared with 12% of the [CC] patients) (Suwalska *et al*, 2008).

Interestingly, we observed that the intracellular distribution of CTLA-4 was markedly higher in CLL patients possessing *CTLA-4*g.*642AT(8_33) [AT_8] repeat allele compared to patients possessing longer alleles. That allele was shown by Wang et al., (2002) to be associated with higher mRNA transcription than longer alleles (Kosmaczewska *et al.* 2005).

Moreover, we found an association between the *CD28* gene polymorphism with the incidence of CLL. The presence of the *CD28c.17+3T>C* [C] allele and the [C] phenotype confers an approximately twofold increased risk of CLL in the Polish population. Additionally, the *CD28c.17+3T>C* polymorphism tended to associate with a higher frequency of Rai stage progression (Suwalska *et al*, 2008).

We also studied a polymorphism of the *ICOS* gene. We found a relationship between micro satellite gene *c.1544+4GT(8_15)* polymorphism and susceptibility to disease. The long alleles (>11 repeats) were associated with protection from disease, while short alleles (< 10) predispose to CLL (Suwalska *et al*, 2008). Further studies on functional the *ICOS SNP: ICOSISV1+173C>T[TT]*, *ICOSc.602A>C*, *ICOSc.1624C>T*, and *ICOSc.2373G>C* showed that these SNPs do not modulate the risk of CLL in the Polish population. However, we noted that *ICOSISV1+173T>C*[TT] alone, *ICOSc.602A>C*[AA] alone, and together as part of the genotype AA defined by Casteli et al (2007), (*ISV1+173T>C*[TT], *ICOSc.602A>C*[AA], *ICOSc.1624C>T*[CC], and *ICOSc.2373G>C*[GG]) were associated with a lower rate of disease progression. Only about 20% of patients carrying the genotype *ICOSISV1+173T>C* [TT], *ICOSc.602A>C*[AA], *ICOSc.1624C>T*[CC], and *ICOSc.2373G>C*[GG] increased in the Rai stage during the 60 months of follow-up, compared to more than 40% of the patients possessing other genotypes (Karabon *et al*, 2011a).

Polymorphisms in the 2q33 region were also investigated by (Monne *et al*, 2004; Piras *et al*, 2005) in non- Hodgkin's lymphoma. In both studies the group of patients was very heterogenous and patients with small lymphocytic leukaemia/chronic lymphocytic leukaemia, marginal zone lymphoma, follicular lymphoma, mantle-cell lymphoma, large B-

cell lymphoma and T-cell lymphoma were included in these studies. The results obtained by the Sardinian group differed from ours, wherein the *CTLA-4c.49A>G* and the microsatellite *CTLA-4g*.*642AT(8_33) polymorphism alone and as a part of the *CTLA-4c.49A>G/CTLA-4g*.319C>T/*CTLA-4g*.*642AT(8_33) haplotype were related to the risk of NHL. No independent association was found between *CD28* or *ICOS* gene polymorphisms and NHL in that study.

The explanation for the different results might be the fact that the patients and controls originated from a Sardinian population, which is genetically distinct from other European populations. Moreover, the Sardinian study was performed on a patient group comprising different subtypes of non-Hodgkin`s lymphoma, with only 29 (of a total of 100) patients with CLL/small lymphocytic lymphoma.

Recently, we have focused on *BTLA* gene polymorphisms. Our preliminary (not published) results indicate that the *BTLA+800A>G* (rs9288952) non-synonymous polymorphism is not associated with susceptibility to CLL in a Polish population.

To the best of our knowledge, there have been no studies on *PD-1* gene polymorphisms and CLL risk.

The described association between polymorphisms in *CD28, CTLA-4* and *ICOS* gene and their associations with susceptibility or course of CLL are displaying on Figure 1.

6. Conclusions

Considering the pivotal role of co-inhibitory molecules in tumourgenesis and, genetic predisposition to various rates of gene transcription, translation and amino acid sequence caused by polymorphisms, investigation for genetic markers predisposing to the development and influencing prognosis of cancer, in particular CLL is eligible and important.

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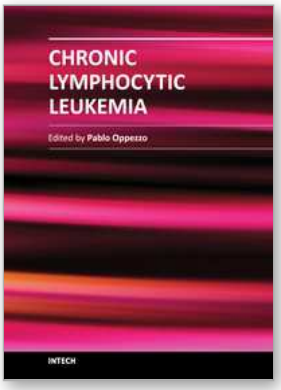

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B-cell chronic lymphocytic leukemia (CLL) is considered a single disease with extremely variable course, and survival rates ranging from months to decades. It is clear that clinical heterogeneity reflects biologic diversity with at least two major subtypes in terms of cellular proliferation, clinical aggressiveness and prognosis. As CLL progresses, abnormal hematopoiesis results in pancitopenia and decreased immunoglobulin production, followed by nonspecific symptoms such as fatigue or malaise. A cure is usually not possible, and delayed treatment (until symptoms develop) is aimed at lengthening life and decreasing symptoms. Researchers are playing a lead role in investigating CLL's cause and the role of genetics in the pathogenesis of this disorder. Research programs are dedicated towards understanding the basic mechanisms underlying CLL with the hope of improving treatment options.

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