Section A-Research paper

CD45 in clinical medicine and Multiple Myeloma

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Abstract

CD45 is an evolutionary highly conserved receptor protein tyrosine phosphatase exclusively expressed on all nucleated cells of the hematopoietic system. It is characterized by the expression of several isoforms, specific to a certain cell type and the developmental or activation status of the cell. CD45 is one of the key players in the initiation of T cell receptor signaling by controlling the activation of the Src family protein-tyrosine kinases Lck and Fyn. CD45 deficiency results in T- and B-lymphocyte dysfunction in the form of severe combined immune deficiency. It also plays a significant role in autoimmune diseases and cancer as well as in infectious diseases including fungal infections. The knowledge collected on CD45 biology is rather vast, but it remains unclear whether all findings in rodent immune cells also apply to human CD45. Due to increasing mortality from multiple myeloma and CD45 expression was seldom used before as a prognostic biomarker in MM patients so, it is important to find new prognostic biomarkers and to find out prognostic effect of immunophenotyping in MM as little reports were performed on this subject before.

Keywords: CD45, Multiple Myeloma

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CD45 is a central player of immune cell activation. The huge amount of data contributing to our understanding of CD45 biology is based on experiments using either human blood samples, human cell lines (Jurkat cells) or non-human sources (mainly rodents). Whether all findings on murine CD45 also apply to human physiology remains unclear as differences in T cell physiology of humans and mice have been reported including differences between human and mouse CD45 molecules [1,2], which are distinguished by certain pathogens [3]. The dispersion of the various CD45 isoforms also differs between species: in mice, B220 is a pan-B cell-specific CD45 isoform while this particular isoform is developmentally regulated in humans and downregulated upon acquisition of CD27, a memory B cell-marker [4]{h}. There are a number of excellent reviews covering a variety of issues of CD45 biology. This review aims to focus on CD45's role in human physiology and clinical pathology. Literature based on experiments using human material is indicated by {h} directly after the quotation. 2. CD45 expression and CD45 isoforms CD45 is a receptor protein tyrosine phosphatase, also known as Ly-5 [5] or leukocyte common antigen [6]{h}. CD45 is expressed on the surface of all nucleated hematopoietic cells and their precursors, except mature erythrocytes and platelets. It is a large glycoprotein of 180–220 kDa and constitutes 5–10% of the total glycoprotein on the surface of T- and B-lymphocytes [7,8]. CD45 expression is not limited to mammals, as there are CD45 homoloques in chicken, shark and even mosquitos [9], an indication for a long-time existing and highly conserved genetic structure [10]. Although the sequence of the extracellular CD45 region strongly varies between different species, the cytoplasmic region of CD45 shows high conservation in all mammalians. In humans, CD45 expression is found on all leukocytes including peripheral blood fibrocytes [11]{h}, a leukocyte subpopulation that displays fibroblast-like properties [12]{h}. These cells play a role in children and young adults suffering from

pulmonary hypertension [13] {h} due to their involvement in vascular remodeling, one of the key elements of pulmonary hypertension pathophysiology. CD45 is also found on a relatively novel cell population in humans called peripheral blood insulin-producing cells, whose function is not fully understood [14]{h}. These cells express CD45 at high levels as well as CD117 (also known as tyrosine-protein kinase Kit) and CD9 (a member of the transmembrane 4 superfamily). They also express embryonic stem cellassociated transcription factors, including Oct-4 and Nanog and are negative for CD34, CD3 (T cell marker), CD20 (B cell markers.

There are several isoforms of CD45 expressed on hematopoietic cells, generated by differential splicing of exons 4, 5, and 6, thereby generating the CD45RA, RB and RC isoforms, respectively [15–18] (Fig. 1B). These exons encode a sequence of about 200 amino acids close to the extracellular N-terminus of CD45, which contains multiple sites for O-linked glycosylation. Thus, different CD45 isoforms vary in glycosylation patterns and size. The remaining extracellular domain contains a cysteine-rich region and three fibronectin type III repeats, which are heavily N-glycosylated. These complex N-glycans are necessary for CD45 stability and its transport to the cell surface [19,20]. The membrane-proximal region of CD45 is followed by a single transmembrane region and a long cytoplasmic tail, which harbors a tandem repeat of two tyrosine phosphatase domains, D1 and D2. Only D1 has tyrosine phosphatase activity (PTA) while the D2 domain binds to the cytoskeleton through the linker protein fodrin and acts as a regulator of D1 tyrosine PTA and specificity [21]. CD45 isoform expression varies depending on the stage of T-cell maturation, activation and differentiation. In humans, there are antibodies to CD45RA, CD45RB and CD45RO, the latter being the smallest isoform that contains neither exon A, nor B or C [22,23]{h}. Naive human T cells express the high molecular weight isoform containing exon 4, CD45RA. After cell activation, the extracellular domain of CD45RA undergoes alternative splicing and is replaced by CD45RO, which is also found on memory T cells [24]{h}[25]. The percentage of CD45RA+ T cells gradually decreases with age while the percentage of CD45RO+ T cells increases [16,26]. However, with regard to CD45RA+ cells as being naive and CD45RO+ T cells containing primed/memory T cells it has to be taken into account that human T cells can revert from CD45RO+ to CD45RA+ [27,28]{h}. Such highly differentiated CD45RA re-expressing CD4+ and CD8+ T cells seem to accumulate during aging and in patients with persistent viral infections or chronic inflammatory diseases like rheumatoid arthritis (RA). These cells can be reactivated to mediate potent effector function but rapidly die thereafter [29–31]{h}. The expression of alternatively spliced isoforms of CD45 is also modulated throughout T-cell development. The major populations of CD3−CD4−CD8− triple-negative human thymocytes are CD45RO− and can express CD45RA, CD45RB and CD45RC. Expression of these isoforms is downregulated on CD4+CD8+ double-positive thymocytes, which are predominantly CD45RO+RA−. Single positive CD3+CD4+ and CD3+CD8+ thymocytes initially express CD45RO but recover CD45RA, RB and RC before they exit the thymus. As a matter of fact, in human umbilical cord blood, the majority of T cells, representing virgin cells and recent thymic emigrants, are CD45RA+RB+RO− [22,32–34] {h}. Human natural killer (NK) cells have the ability to express both CD45RA and the short CD45RO form [35]{h}. Using CD45 isoforms to identify cells as being leukocytes is a long known technique and CD45bright lymphocytes can easily be distinguished from CD45dim monocyte/myeloid cells in flow cytometry. In more recent studies, new cell types were found with distinct CD45 co-expression patterns. The aforementioned fibrocytes for example, are identifiable by the combined surface expression of CD45RO, 25F9 and S100A8/A9 [11]{h}. The way CD45 interacts with ligands is determined by the level and type of CD45 glycosylation [21]. This is achieved by different enzymes being active at varying expression levels based on T-cell developmental or differentiation states. Such enzymes include core-2 O-N-acetylgalactosamine transferase (C2GnT), alpha (2,6)-sialyltransferase I (ST6Gal-I), alpha (2,3)-sialyltransferase IV (ST3Gal-IV), and alpha (1,3)-fucosyltransferase VII (FucT-VII) [36,37]{h}. When these enzymes are modulated, glycosylation of CD45 changes and, thereby, its function. For instance, C2GnT regulates galectin-3 binding to a subset of highly glycosylated CD45 glycoforms in patients with diffuse large B cell lymphoma (DLBCL) (see below). Also, the ability of Galectin-1 to bind CD45 (see below) depends on the type and the amount of glycosylation of the extracellular domain of CD45 [38,39]. 3. CD45 function and regulation When T cells encounter cognate antigen presented on MHC molecules of antigen presenting cells (APCs) they form long-lasting cell

conjugates and build an immunological synapse (IS) in the T cell-APC contact zone, which is essential for T-cell activation. In the IS, CD45 and Lck are initially recruited to the central supramolecular activation cluster (cSMAC) via the TCR. CD45 is then expelled from the cSMAC and clusters in the distal SMAC (dSMAC) [40–44]. One model, the 'kinetic-segregation' model, proposes that TCR signaling requires spatial segregation of MHC-bound TCRs from phosphatases [45–48]. Exclusion of CD45 from the narrow-spaced TCR-MHC interaction zone is thought to result from steric hindrance due to the large size and rigidity of the CD45 extracellular domain [45,49–52]. Indeed, truncation of the CD45 ectodomain enhances CD45 localization with ligated TCRs in the IS and inhibits TCR triggering [50,53,54]. Targeting CD45 activity to lipid microdomains on the T cell surface, which are associated with Srcfamily tyrosine kinase activity, also decreased TCR-mediated signaling [55]. The degree of CD45 segregation from TCR-MHC microclusters, and presumably other small-sized ligand pairs like PD-1-PD-L1 interactions, seems to be higher for CD45ABC than CD45RO isoforms [52]. Besides spatio-temporal organization, the cell surface density of CD45 molecules seems to be a decisive factor towards its functional effects. Low or medium local concentrations of CD45 lead to dephosphorylation of the Src family protein-tyrosine kinase Lck (lymphocytespecific kinase) at its C-terminal negative regulatory tyrosine Y505, thereby inducing an opening of the molecule and generating so-called 'primed' Lck [56,57]. Interaction of CD45 with Lck and Y505 dephosphorylation of Lck seems to depend on Y192 within the Src homology 2 (SH2)-domain of Lck [58]. A high local concentration of CD45 leads to additional dephosphorylation of Lck at the auto/transphosphorylation site Y394 within the kinase domain [59,60] (Fig. 1A). Both effects are antagonistic to each other, the former (Y505 dephosphorylation) being activating in nature, the latter (Y394 dephosphorylation) leading to decreased Lck kinase activity. Thus, CD45 can operate as a positive and negative regulator of Lck and other Src family kinases, which seems to depend on the cell type, CD45 isoform expression, and CD45's inclusion or exclusion from clustered signaling complexes [59,61,62]. A negative regulatory role of CD45 was also detected in integrin- [63] and CD44-mediated adhesion of T cells, where CD45 is recruited to downregulate Lck activity [64], in neutrophil migration [65], and MyD88-dependent Toll-like receptor (TLR) signaling [66]. In addition, CD45 dephosphorylates and inhibits tyrosine kinases of the Janus kinase (JAK) family [67–69]{h}, which activate transcription factors of the STAT (signal transducers and activators of transcription) family, crucial regulators of cytokine and chemokine gene expression, thus linking CD45 to cytokine/chemokine responses. The interaction between CD45 and Src kinases is vital for successful antigen receptor signaling in T and B cells [70–72] and is required for the development and activation of lymphocytes as shown by genetic experiments using CD45 mutant cell lines and CD45 knock-out mice [73–77]. Other CD45 substrates have been identified and include the CD3ζ and CD3ε chains [78–80] and tyrosine kinase Zap 70 [81]. DAP12 in NK cells [82] and the transmembrane adaptor molecule PAG (phosphoprotein associated with GEMs) [83]{h} in thymocytes are hyperphosphorylated in the absence of CD45 [84], suggesting that they are direct or indirect substrates of CD45. CD45 can directly dephosphorylate the receptor-like protein tyrosine phosphatase PTPα in vitro [85], which dephosphorylates Fyn but not Lck in T cells [86]. How various CD45 ligands (see Section 4) could regulate CD45 PTA is unresolved [71,87–89]. All CD45 isoforms show basal PTA, but different CD45 isoforms differ in their capacity to modulate TCR signaling [90–97]{h}. Different CD45 monoclonal antibodies display differing abilities to activate or inactivate CD45 PTA independent of their CD45 cross-linking capacity [98]. CD45 ligands may exert direct effects on CD45 PTA by ligand-induced conformational changes or ligand-induced compartimentalization or segregation of CD45 (see above) resulting in altered accessibility of CD45 to substrates. Other data proposes that spontaneous or ligand-induced dimerization of CD45 inhibits CD45 PTA [99–103]{h}. Dimerization of EGFR-CD45 chimera proteins in CD45- deficient cells resulted in the loss of TCR signaling [104]. Different CD45 isoforms exhibit differing capabilities for homodimerization, with CD45RO isoforms dimerizing more efficiently than CD45ABC isoforms [105]. Recently, it was reported that hypoxic conditions in monocytic myeloid-derived suppressor cells (MDSC) at tumor sites facilitate the transport of sialic acid to the cell surface and its binding to CD45. This seems to result in disruption of CD45 dimerization, enhanced CD45 PTA and dephosphorylation of STAT3, thereby promoting MDSC differentiation into tumor-associated macrophages [106]. Further, posttranslational

modification of CD45 might become accessible after ligand binding. Phytohemagglutinin (PHA) [107]{h}, CD3 antibodies [108]{h} and activated tyrosine kinase C-terminal Src kinase (Csk) [109], which phosphorylates the inhibitory tyrosine in Src kinases, lead to a transient phosphorylation of CD45 tyrosines and an increase of CD45 PTA. In contrast, the calcium ionophore ionomycin decreases phosphorylation of serine residues in CD45 reducing CD45 activity [110]. Another mode to regulate control of substrate access or CD45 PTA could result from association of CD45 with other molecules at the cell surface or within the cell [87]. CD45 was found to associate with CD2, CD7, CD28, CD26, CD100 [111–115]{h}, CD4/CD8 [116]{h}, [117], and Thy-1 [118]. Intracellularly, CD45 interacts with the cytoskeleton proteins fodrin and spectrin, presumably stimulating CD45 PTA [119,120]. Other molecules interacting with CD45 include proteins of 29–34 kDa [121–123], one of them being lymphocyte phosphatase associated phosphoprotein (LPAP) [124,125]{h} as well as CD45-associated protein (CD45-AP) in murine cells [126]. However, deletion of LPAP in Jurkat cells had no major effect on CD45 enzymatic activity [127]{h} and LPAP- or CD45-AP-deficient mice showed modest and controversial phenotypes [128–130]. The currently available data makes it clear that CD45 acts as a rheostat for signal transduction. It is conceivable that CD45 ligands may employ different modes (utilizing a variety of mechanisms) of CD45 regulation, an issue which remains controversial and requires further experimentation. Although the function of CD45 was investigated for many years in T cells and to a lesser extend in B cells, it seems that the entire sequence of CD45-dependent signaling events has never been delineated in experiments where only human blood samples were used. As a result, it is possible that there are CD45 functions exclusive to human cells that are still undiscovered. There are only a few publications on humans with CD45 deficiency or minimal CD45 surface expression, a condition leading to severe combined immunodeficiency (SCID) [131–133]{h}. The first case of an immune cell tyrosine phosphatase deficiency in humans reports on a 2-year old patient showing a large deletion at one CD45 allele and a point mutation at the other allele. The peripheral blood T lymphocyte population was greatly diminished and unresponsive to mitogen stimulation. Moreover, serum immunoglobulin levels decreased with age, however, the long-term clinical parameters in this child were not further described [131]{h}. At least in mice, CD45-deficiency might not fully unmask the role of CD45 in B cells due to the expression of the receptor protein tyrosine phosphatase CD148 [134]{h}. CD45 and CD148 share a certain level of functional redundancy in B cells and the myeloid lineage [135]. Indeed, mice doubly deficient in CD45 and CD148 show a very early block in Bcell development [136]. To date, there is no publication of any clinical case of CD45-CD148-double-deficiency or CD148-single-deficiency in humans. Yet, there seems to be an involvement of CD148 in Cogan's Syndrome, a rare inflammatory disease characterized by ocular and audiovestibular symptoms [137]. Its pathogenesis is unclear, but the current hypothesis favors autoimmune mechanisms with CD148 as an autoantigen. IgG antibodies purified from patients‘ sera, among others, recognize CD148, which is also expressed on the sensory epithelia of the inner ear and on endothelial cells [138]. 4. CD45 and its natural ligands For a long time, it has been unclear whether there is any natural CD45 ligand at all. There is a variety of artificially created extracellular ligands, but this review will only focus on natural extracellular CD45 ligands. A number of CD45 ligands has been identified, but most of them are not binding exclusively to CD45. Some of the ligands are only present under certain clinical conditions like an ongoing infection or in pregnancy and there seems to be no natural extracellular ligand that can be found in all healthy adults (Fig. 2).

One CD45 ligand is pUL11, a transmembrane protein of the cytomegalovirus RL11 (CMV RL11) family [139]{h}. It is generated from the UL11 open reading frame in CMV-infected human cells. The extracellular domain of pUL11 interacts with CD45RA and CD45R0, leading to disrupted TCR signaling and inhibition of T cell proliferation [3]{h}, suggesting that pUL11 reduces CD45 PTA. Indeed, the same group reported later that high concentrations of pUL11 (in vitro) lead to phosphorylation of the inhibitory Y505 residue of Lck. This increase in Y505 phosphorylation was mostly lost at intermediate and low concentrations of pUL11. The activatory Y394 residue of Lck showed comparatively increased phosphorylation at all concentrations of pUL11. Therefore, the effect on CD45 PTA seems to depend on pUL11's concentration [140]{h}. pUL11 can currently be seen as an exclusive, natural ligand of CD45, although it is a ‘situational‘ ligand as it requires a CMV-infection. A CD45 ligand that does not require any pathological condition is placental protein 14

(PP14), also known as Glycodelin-A or PAEP (progesterone-associated endometrial protein) [141]. It is a glycoprotein expressed by endometrial decidua during the first and second trimesters of pregnancy [142]{h}. Due to its lectin-like properties, it binds to CD45 (but also other targets on T cells), allegedly leading to dimerization and disruption of CD45 PTA [143]{h}. It seems that CD45RA+ T cells are significantly more sensitive to PP14-mediated inhibition than CD45RO+ T cells, but the underlying mechanisms are not fully understood. CD45 inhibition by PP14 leads to decreased T cell activity, which can be considered a 'healthy' response in a pregnant woman as in formal terms of biological systems, pregnancy is a hostparasite situation with the fetus being the parasite. Therefore, PP14 can be seen to provide a form of immune suppression during pregnancy. 5. CD45 and lectins Another group of ligands binding CD45 are lectins. They are hardly exclusive CD45 binding partners as they are ubiquitously expressed and are known to interact with a large variety of molecules. One of the lectins binding CD45 is CD22, a B cell surface molecule belonging to the SIGLEC family of lectins [144]. CD22 exerts an inhibitory effect on basal B cell receptor (BCR) signaling. CD45 restricts the inhibitory function of CD22 in a phosphatase independent manner, presumably by sequestering CD22 from the BCR via its ectodomain [145]. Among others, CD22 binds to alpha-2-6-linked sialic acid. Van der Merwe and colleagues [146] compared the affinity of CD22 binding to CD45, CD22 binding to CD4 carrying alpha-2-6-linked sialic acid and CD22 binding to a synthetic alpha-2-6-sialoglycoconjugate. The authors found that the affinity of CD22 to either ligand did not differ significantly. Thus, CD22 may bind to CD45 not because CD45 presents a higher affinity ligand but because it carries multiple copies of alpha-2-6-linked sialic acid. Galectin-1 is another phylogenetically conserved lectin and binds beta-galactoside-rich glycoconjugates [147]. Galectin-1 is involved in fetomaternal tolerance [148], at least in mice, and a variety of other processes in reproduction and reproductive organs [149]. In addition, it plays a role as a possible predictive marker to evaluate a patient's prognosis in perineurally spread cutaneous head and neck cancer [150] {h} or after liver transplantation [151]{h}. CD45 PTA is inhibited by galectin-1. This appears to be essential for galectin-1-induced death of CD45-expressing T cells [2,152,153]{h}. CD45 also enhances phagocytic clearance of T cells killed by galectin-1 [154]{h}. During galectin1-induced T cell death, CD45-associated fodrin, a spectrin family member which attaches CD45 to the cytoskeleton, undergoes proteolytic degradation. CD45 is essential for fodrin degradation, which accompanies apoptosis triggered by many death signals in many cell types. Macrophages phagocytose dying T cells with cleaved fodrin more efficiently than dying cells in which fodrin proteolysis is prevented. Another lectin interacting with CD45 is galectin-3, which is involved in the pathophysiology of different diseases like cancer [155], heart failure [156]{h}, and renal fibrosis [157]. Galectin-3 also plays a role in DLBCL where it regulates the susceptibility to cell death by binding to glycans on CD45, thereby reducing CD45 PTA [158]. CD45 function depends on its glycosylation pattern and can be modified via its N-acetylgalactosamine (GalNAc) moieties. Macrophage galactose-type lectin (MGL) binds to CD45 carrying terminal GalNAc, thereby regulating macrophage and T-cell interactions. MGL recognizes all CD45 isoforms, except CD45RO [159]. It reduces the proliferation of human effector T cells and the production of proinflammatory cytokines and is able to induce T-cell death [160]{h}. Furthermore, an interaction between the macrophage mannose receptor (MR) and CD45 has been shown, particularly with low molecular weight isoforms of CD45 [161]. In a recent study, the presence of the MR on dendritic cells inhibited CD45 PTA of CD8+ T cells and led to cytotoxic T-lymphocyteassociated protein 4 (CTLA-4) upregulation and induction of CD8+ Tcell tolerance [162]. Thus, endocytic MRs expressed on DCs contribute to the regulation of T-cell functionality

CD45 possible expression in MM patients

Several studies have confirmed the presence of significant intra-clonal heterogeneity within the clonal PC population of patients with MM [20], [21], [22], [23]. Similarly, with respect to CD45 expression on clonal PCs, prior studies have demonstrated the presence of two subsets of clonal PCs within patients with MM [24]; i.e. those that highly express CD45 and those that have dim or do not express CD45. Furthermore, CD45 is expressed mostly in early stages of clonal PCs and subsequent more mature clonal PCs in patients with MM lose their CD45 expression [5]. Prior functional studies have evaluated the role of CD45 and its relationship to the IL-6 cytokine axis and have demonstrated that CD45 expression on clonal PCs can be induced by IL-6 [25], [26]. However, only the CD45 (+) PC population, but not the CD45 (−) clonal PCs proliferate after

IL-6 stimulation. Furthermore, CD45 (+) clonal PCs have been found to be the predominantly proliferative fraction when compared to the CD45 (−) clonal PC population and the proliferation decreases parallel to that of CD45 expression [27].

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