Histol Histopathol (2000) 15: 587-591
DOI: 10.14670/HH-15.587
http://www.hh.um.es

Histology and Histopathology
Cellular and Molecular Biology

Invited Review

Abnormal distribution of CD45 isoforms expressed by CD4+ and CD8+ T cells in rheumatoid arthritis

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Summary. CD45RO+ T cells are referred to as memory or helper-inducer while CD45RA+ T cells are regarded as naive or suppressor-inducer T cells. The former population predominates in the peripheral blood and even more in the synovial fluid of patients with rheumatoid arthritis, to the expense of the latter population. Within the CD45RB+ compartment, there appears to be more of the fully-differentiated than of the early-differentiated CD4+ T cells. In spite of the fact that these lymphocytes are close to undergoing apoptosis, this programmed cell death is inhibited in the rheumatoid synovium.

Key words: CD45 isoform, T cell, Rheumatoid arthritis, Apoptosis

Introduction

The leukocyte-common antigen CD45 comprises of a family of transmembrane glycoproteins, of which the members are abundantly expressed on all nucleated hematopoietic cells (Thomas, 1989). They differ not only by protein sequence but also by carbohydrate composition. Importantly, both the quantity and the quality of individual isoforms within lymphoid populations are controlled in a cell type-specific fashion (Thomas and Lefrançois, 1988). These isoforms are, in fact, all encoded by a single gene consisting of 34 exons (Ralph et al., 1987). Exons 3 and 7 to 15 account for the extracellular domain common to all isoforms, whereas exons 4 (A), 5 (B) and 6 (C) can be combined to generate eight possible messenger RNA (Trowbridge and Thomas, 1994). Their alternative splicing results in synthesis of high (220-240 kDa) to low (180 kDa) molecular weight isoforms. Though they have all been demonstrated by polymerase chain reaction, some of them have not yet been detected as proteins. To distinguish the different isoforms, Trowbridge and Thomas have proposed that each isoform be designated a greek letter (1994).

Monoclonal or polyclonal antibodies (Ab) that target epitopes depending upon exons 4, 5 and 6 have been developed, but hardly any discriminates among several isoforms: anti-CD45RA Ab (for example 2H4) recognizes CD45α, CD45ß, CD45γ and CD45η; anti-CD45RB Ab (for example PD-7) recognizes CD45α, CD45ß, CD456 and CD45ζ; and anti-CD45RC Ab (for example YTH 80.103) recognizes CD45α, CD45γ, CD456 and CD45η. However, anti-CD45RO Ab (UCHL-1) identifies exclusively the θ isoform which is derived from the removal of exons 4 to 6 (Terry et al., 1998).

A major advance took place when functional distinction between CD45RA+ and CD45RO+ T lymphocytes was determined, in that they represent unprimed or "naive" cells, and primed or "memory" cells, respectively (Tedder et al., 1985). In this respect, it is of substantial interest that memory T cells are gradually acquired in children with aging, presumably owing to sequential encoutering of natural pathogens (Pirrucello et al., 1989). It was then established that CD4+CD45RA+ T lymphocytes act as inducers for suppressor CD8+ T cells (Morimoto et al., 1985b), while CD4+CD45RO+ T lymphocytes provide help for B cells in pokeweed mitogen-stimulated cultures (Morimoto et al., 1985a). The former population is referred to as suppressor-inducer T cells, and the latter as helper-inducer T cells. An adjunct classification system has since been proposed. The CD4+CD45RA+ or RO+ T cell compartment may be subdivided into three subsets according to intensity of the co-expression of CD45 RB: CD45RA+ $CD45RB^{bright}$ cells, CD45RO+ $CD45RB^{bright}$ cells that secrete interleukin (IL)-2 and interferon-γ, and $CD45RO+CD45RB^{dim}$ that supply B cells with help (Mason and Powrie, 1990). In parallel, CD8+ T lymphocytes were classified as CD45RA+ or CD45RO+ cells with different requirements for activation and differentiation (de Jong et al., 1991).

The transition from naive to memory cells remains a matter for debate. This has been merely associated with

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a switch in surface expression from CD45RA+ to CD45RO+ (Akbar et al., 1988), but several studies indicate that the expression of low molecular weight isoforms (CD45RO) may, in some circumstances, be reversible, thus reflecting activation status, rather than a permanent differentiation (Bell and Sparshott, 1990). No matter what that means, the cytoplasmic domain of CD45 is associated with protein tyrosine phosphatase activity, implying that this molecule plays a pivotal role in lymphocyte activation (Charbonneau et al., 1988). It has also been shown that CD45 ligation induces programmed cell death in T and B lymphocytes through the surface protein Fas, i.e. CD95 (Klaus et al., 1996). In a way, the expression of this receptor is related to the CD45 isoforms and, to some extent, increases with aging (Shinohara et al., 1995).

Though the significance of such an abnormality has not hitherto been settled, aberrant distribution of CD45 isoforms in CD4+ and CD8+ T lymphocytes has been described in a variety of chronic inflammatory conditions, most notably rheumatoid arthritis (RA). This lends weight to the concept that CD45 isoforms are important (Emery et al., 1987), and raises the question as to whether they play a significant part in the pathophysiology of autoimmune disorders. In the present paper, we would like to limit ourselves to the analysis of the current literature dedicated to CD45 isoforms in RA, to discuss these data in the light of our own results and to study the relationships between the selection of a given CD45 isoform and the expression of the Fas receptor in RA patients.

CD45 isoforms in rheumatoid arthritis

Using two-color immunofluorescence analysis (fluorescein isothio-cyanate-conjugated anti-CD4 or anti-CD8, and phycoerythrin-conjugated anti-CD45 Ab), there appeared to be a tendency for elevated numbers of CD45RO+ CD4+/CD45RO+CD8+T cells, and reduced CD45RA+CD4+/CD45RA+ CD8+ as well as CD45RB+CD4+/CD45RB+CD8+ T cells in the peripheral blood of patients with RA (Table 1). We found also a marked increase in the percentages of the CD45RC+CD4+/CD45RC+CD8+ subpopulations. These values were found not to correlate with either disease activity or medication. Of note are the variations of CD45RB+ T cells, which is in accord with the evidence that this population is heterogeneous. Our observations are perfectly in line with previous findings related to CD4+ (Emery et al., 1987; Kingsley et al., 1987; Pitzalis et al., 1987; Cush et al., 1992; Braun et al., 1994) and CD8+ T cells (Pitzalis et al., 1987; Sohen et al., 1991) and support the view that memory T lymphocytes are significantly more adherent to resting or activated endothelial cells than naive T lymphocytes. Furthermore, enhanced transendothelial migration by CD45RO+ T cells has been established in several *in vitro* (Masuyama et al., 1992) and *in vivo* systems (Pitzalis et al., 1991). This abnormality is far from being specific for RA. The results showed a majority of memory rather than naive resting CD4+T lymphocytes in a number of inflammatory diseases, such as multiple sclerosis (Rose et al., 1985), systemic lupus erythematosus (Morimoto et al., 1987b), primary biliary cirrhosis (Leon et al., 1995), myasthenia gravis (Mokhtarian et al., 1990) and systemic sclerosis (Morimoto et al., 1987a), but not in Graves' hyperthyroidism (Ishikawa et al., 1987), Crohn's disease (James et al., 1986), reactive arthritis (Braun et al., 1994) and primary Sjögren's syndrome (Skopouli et al., 1991). Surprisingly, the percentage of circulating memory CD4+ T cells was found to be elevated in mixed connective tissue disease (Becker et al., 1992), and, curiously enough, reduced in the women but not in the men with idiopathic thrombocytopenic purpura (Mylvaganam et al., 1989).

Next, we undertook a phenotypic analysis of the T cells present in the synovial fluid of patients with RA. As can be seen in table 2, there was a virtual absence of CD45RA- expressing CD4+ and CD8+ in the synovial fluid, whereas CD45RO was over-expressed in CD4+ and CD8+ T lymphocytes. It is worth stressing that the mean fluorescence intensity of the CD45RO marker was strikingly augmented. These findings are in accordance with recent reports (Emery et al., 1987; Pitzalis et al., 1987; Cush et al., 1992; Braun et al., 1994) and agree with the demonstration by immunohistology that, in the synovial membrane, most of the T cells, whether CD4+ or CD8+, are CD45RA-negative. In fact, this phenotypic distribution in the joint is not specific for RA, inasmuch as the predominance of helper-inducer lymphocytes is a general feature of chronic inflammatory lesions. The infiltration of mononuclear cells into sites of tissue infiltration characterizes such disorders. Thus, CD45RO+ T cells have been shown to predominate in the thyroid tissue of patients with Graves' hyperthyroidism (Ishikawa et al., 1987), the lamina propria of Crohn's disease (James et al., 1986), the joint of reactive arthritis (Braun et al., 1994), the cellular infiltrate associated with allergen-induced late-phase skin reactions in atopic subjects (Frew and Kay, 1991),

Table 1. Distribution of CD45RA, CD45RB and CD45RO on CD4+ and CD8+ T cell subsets in the peripheral blood of eight patients with rheumatoid arthritis and 12 normal controls.

CD45 ISFORMS	CD4+ T CELLS		CD8+T CELLS	
	Controls	Patients	Controls	Patients
CD45RA				
%	18.0±7.7*	16.2±8.0	12.9±4.7	10.8±4.6
MFI**	4.3±0.7	4.4±2.2	7.6±3.4	5.7±1.8
CD45RB				
%	42.3±7.7	31.6±14.2	42.3±6.7	15.0±7.6
MFI	67.1±29.1	57.2±26.9	96.6±47.5	70.6±49.0
CD45RO				
%	17.0±6.7	23.0±9.2	3.7±1.3	5.5±3.2
MFI	5.5±0.1	4.9±1.9	3.7±3.4	3.1±4.4

*: mean ±SD; **: MFI: mean fluorescence intensity

Table 2. Distribution of CD45 isoforms on CD4+/ and CD8+ T cells in the peripheral blood and synovial fluid of patients with rheumatoid arthritis.

SAMPLES	CD4+ T CELLS				CD8+ T CELLS			
	RA*	RB	RC	RO	RA	RB	RC	RO
Peripheral blood								
%	16.2±8.0**	31.6±14.2	40.0±7.8	23.0±9.2	10.8±4.6	15.0±7.6	37.7±10.6	5.5±3.2
MFI	4.4±2.2	57.2±26.9	22.3±12.3	4.9±1.9	5.7±1.8	70.7±4.9	24.6±6.7	3.1±4.4
Number	12	12	6	12	12	12	6	12
Synovial fluid								
%	0.7±0.6	38.9±4.9	12.7±8.7	4.1±1.0	1.0±1.2	23.2±3.1	10.7±5.6	22.3±2.4
MFI	3.6±1.3	17.0±3.2	3.0±0.8	9.3±4.0	3.2±1.6	41.9±3.9	3.7±0.9	6.1±2.3
Number	6	6	5	6	6	6	5	6

*: CD45 isoforms; **: mean ± SD; MFI: mean fluorescence intensity

Table 3. Distribution of $CD45RB^{bright}$ and $CD45RB^{dim}$ on CD4+ and CD8+ T cells in patients with rheumatoid arthritis and controls.

CONTROLS				PATIENTS							
Peripheral blood				Peripheral blood				Synovial fluid			
CD4		CD8		CD4		CD8		CD4		CD8	
Bright	Dim	Bright	Dim	Bright	Dim	Bright	Dim	Bright	Dim	Bright	Dim
84.9±6.9	14.8±7.2	96.5±1.3	4.5±3.5	71.8±12.8	28.1±12.6	86.6±10.0	13.4±10.1	42.3±23.9	57.7±23.9	78.6±12.7	21.4±12.7
n=6	n=6	n=6	n=6	n=7	n=7	n=7	n=7	n=7	n=7	n=5	n=5

*: mean ± SD (% of positive cells)

the exocrine glands of patients with primary Sjögren's syndrome (Skopouli et al., 1991), the liver-infiltrating lymphocytes of primary biliary cirrhosis (Leon et al., 1995) and the cerebrospinal fluid of multiple sclerosis (Chofflon et al., 1989). Owing to the enhanced expression on the helper-inducer cell membrane of adhesion molecules, such as lymphocyte function associated (LFA)-1, CD2 and LFA-3 (Sanders et al., 1988), CD45RO+ are thus selectively recruited to the site of inflammation.

CD45RB phenotype of T cells in rheumatoid arhtirits

The CD45RO+ T lymphocyte population can express the B exon product at high ($CD45RB^{bright}$) or low levels ($CD45RB^{dim}$), and functionally different subsets of CD4+ T cells are defined on the basis of this dichotomy (Mason and Powrie, 1990). As shown in Table 3, there appears to be more circulating $CD45RB^{dim}$ CD4+ and CD8+ T cells in the RA patients (28.1±12.6 and 13.4±10.1%, respectively) than in the controls (14.8±7.2 and 4.5±3.5%, respectively). Furthermore the synovial fluid was strikingly enriched in this fraction of CD4+ and CD8+ T cells (57.7±23.9 and 21.4±12.7%, respectively). Thomas et al. (1992) and Braun et al. (1994) have previously reported the same observation. The fact that cells progress from $CD45RB^{bright}$ to $CD45RB^{dim}$, following several cycles (Salmon et al., 1994), suggests that the latter cells are more differentiated that the former (Horgan et al., 1994). Fully-activated memory CD4+ T lymphocytes are potent helpers for B cell differentiation (Thomas et al., 1992). Not only do the $CD45RB^{dim}$ T cells favor the production of immunoglobulins, but it has also been shown that, among them, the terminally-differentiated memory T cells do not express CD27 and represent those migrating through endothelial cells (Kohem et al., 1996). This enrichment in synovial membrane and synovial fluid may reflect chronic antigenic stimulation.

Relationships between CD45 isoforms and CD95

Another interesting point is that the progressive differentiation of primed T cells is associated with an increasing susceptibility to apopotosis (Salmon et al., 1994). An important question relates, therefore, to the relationships between CD45 isoforms and CD95 in RA. Conceivably T cell apoptosis may be inhibited in the rheumatoid synovium (Salmon et al., 1997), despite the fact that these cells are extremely close to their programmed death.

In our study, significantly more T cells, CD4+ and CD8+ T cells were CD95+ in the synovial fluid than in the peripheral blood of patients with RA (46.0±21.3 vs 22.5±14.1%, $p<0.01$; 40.0±10.2 vs 11.3±8.5%, $p<0.02$; and 16.0±1.4 vs 5.4±4.0%, $p<0.02$; n=12, Wilcoxon's test for paired data). There were 6, 17, 26 and 13% of the circulating CD4+CD45RA+, CD45RB+, CD45RC+ and CD45RO+, and 2, 35, 20 and 37% of the circulating CD8+CD45RA+, CD45RB+, CD45RC+ and CD45RO+ to express CD95. Interestingly the CD4+CD95+ and CD8+CD95+ cells were more often $CD45RB^{dim}$ (52 and

Table 4. Apoptosis* of T cells, following a 7-day activation with interleukin-2 and phytohemagglutinin A.

	PERIPHERAL BLOOD		SYNOVIAL FLUID
	Control	Patient	Patient
Medium**	10.1	22.3	12.7
C2-ceramide***	57.2	38.8	25.0
Anti-CD95 antibody	18.3	24.9	15.9

*: apoptosis was evaluated using the propidium iodine technique; **: negative control; ***: positive control

22%, respectively) than CD45RB^{bright} (18 and 16%, respectively), as established by a three-color flow cytometric examination. CD95, CD45 and CD11a/CD18 participate in the apoptotic process (Wu et al., 1996). CD45-induced cell death is rapid in normal T cells (Klaus et al., 1996), but the Ab specific for CD45RA isoform is less effective than that specific for CD45RO isoform. This data is consistent with our results.

However, following a 7-day stimulation with IL-2 and phyto-hemagglutinin A (PHA), T lymphocytes from RA peripheral blood and synovial fluid appeared to be insensitive to CD95-triggered apoptosis. The results of a representative experiment are provided in table 4. These may be accounted for by a shedding of Fas receptor in the rheumatoid blood and synovial fluid (Asumuna et al., 1997), or a defect in CD45 ligand (Cantwell et al., 1997). Relevant to this phenomenon is our observation that a 72-hour activation with IL-2 and PHA resulted in 1.5, 58.6 and 40% of Ao, Go/G1 and S/G2M normal T cells, compared with 4.1, 57.8 and 20.0% of patients' CD45RB^{bright} and 3.1, 75.0 and 18.2% of patients CD45RB^{dim} T cells (Mamoune et al., unpublished observations). That is, we observed a 50% reduction in the proliferative capacity of both CD45RB^{bright} and CD45RB^{dim} T cells in patients with RA. A blocking factor, such as IL-15 or integrins should thus be operating in this disease.

Conclusions

To conclude, the CD45 antigen, sometimes referred to as leukocyte common antigen, plays a central role in regulating the immune response. Although many uncertainties remain, there is some agreement that chronic autoimmune stimulation reflects the augmentation of mature memory T cells, i.e. CD45RB^{dim} CD45RO+, in the circulation and synovial fluid of patients with RA.

Acknowledgements. We gratefully acknowledge Simone Forest and Sylvie Hamon for their expert secretarial help.

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Accepted October 26, 1999