Old Herborn University Seminar Monograph 5:
Effective and ineffective defence mechanisms in the gastrointestinal tract.
Editors: Hans Cottier, Peter J. Heidt, Volker Rusch, and Dirk van der Waaij.
Institute for Microbiology and Biochemistry, Herborn-Dill, Germany: 12-26 (1994).

PROPERTIES, FUNCTIONS AND BIOLOGICAL SIGNIFICANCE OF T LYMPHOCYTE SUBSETS

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SUMMARY

Since the discovery of the separation of killer T cells from helper T cells according to the cell-surface molecules CD8 and CD4, evidence has accumulated that further subdivision exist among the CD4+ T cell population. Mouse CD4+ T cells can be separated on the basis of different patterns of lymphokine secretion into Th1-type cells, which secrete IL-2 and IFN-γ, but not IL-4 and IL-5, and Th2-type cells which express the reverse lymphokine profile. Th1 and Th2 phenotypes are considered to represent mature stages of helper T cells. Their precursors are thought to express a mixed lymphokine profile not allowing to make the Th1/Th2 distinction. Human CD4+ T cells do not demonstrate a lymphokine profile analogous to the mouse Th1 or Th2 cells. Thus, a distinction of human CD4+ T subsets according to the lymphokine secretion pattern is not possible. Functionally, helpers and non-helpers for B cells, killers of MHC class-II antigen presenting cells and suppressors of antibody responses can be identified among human as well as mouse CD4+ T cells. However, the functions only partially correlate with the lymphokine expression in the mouse and not in the human system. Beside functional criteria, CD4+ T subsets can be defined according to surface markers, especially on the expression of CD45 isoforms. In man, CD45 isoforms do not define different lineages of CD4 T cells but rather represent maturational stages of a lineage. Thus, naive CD4+ T cells express the high molecular weight isoforms which are lost upon T cell activation.

Lamina propria lymphocytes and intraepithelial lymphocytes not only represent distinct subsets among gut mucosal T cells, they also seem to differ from T cells in other compartments of the immune system including peripheral T cells. Due to their location, both lymphocyte populations are of outstanding importance as barrier against invading agents.

INTRODUCTION

The importance of the immune system for the protection of the host against infectious agents is well recognised. The immune system is equipped in a very sophisticated way to recognise foreign antigens and to distinguish them from self molecules. The underlying mechanism, the specific immune response, is the result of a complex co-operation between T cells, B cells and antigen presenting cells (APC), as well as of various cytokines secreted by these cells. To initiate an immune response antigen is taken up by MHC class-II-positive (also called Ia+) APC and processed, e.g. proteins are proteolytically degraded to peptides. Such peptides are associated with MHC products, re-ex-

Table 1: CD4+ T subsets defined according to the LK-profile[1]

LK secreted[2]	LK not secreted	Mouse	Man
IL-2, IFN-γ	IL-4, IL-5, IL-6	Th1	not found
IL-4, IL-5, IL-6	IL-2, IFN-γ	Th2	Th2
IL-2, IL-4, IL-5, IFN-γ		Th0	Th0

[1] Only selected lymphokines are listed in the Table
[2] Cloned CD4+ T cells are stimulated with either mitogens or with antigens and APC. 24h later, SN are collected and tested for the presence of selected lymphokines.

pressed on the surface of the APC and presented to CD4+ T cells with the appropriate receptors. Thus, T cells recognise with their heterodimeric α/β receptors (TcR) combinations of peptide antigen (foreign) and MHC class-II molecules (self) (reviewed by *Grey* et al., 1990). Once activated, CD4+ T cells evoke various functions, e.g. they help B cells for antibody production or CD8+ T cells to become killer cells. CD8+ T cells - in order to perform their effector function - must recognise foreign antigen in context of MHC class-I determinants expressed on the surface of target cells. Recently, the existence of a second T cell lineage was revealed which expresses a γ/δ TcR instead of an α/β TcR (reviewed by *Raulet*, 1989; *Kaufmann* and *Kabelitz*, 1991). Both the α/β and the γ/δ TcR are noncovalently linked with the CD3 complex which transduces the activation signal upon contact with the antigen. The majority of the γ/δ T cells lack the CD4 and CD8 markers, although some have been shown to express the CD8 and to lesser extent the CD4 molecules. While the

Table 2: Representative CD4+ T cell subsets

Properties of T cell clones:	9A/B	9F/D	8/25-1	8/25-2	10H/A	9/6
LK-secretion:						
- IL-2 secretion	-	+	+	+	+	+
- IL-3 secretion	+	+	+	+	+	+
- IL-4 secretion	+	+	-	-	-	-
- IFN-γ secretion	-	+	+	-	+	+
Effect on B cells:						
- cognate help	+	+	+	-	-	-
- non-cognate help	+	n.t.	n.t.	+	-	-
- suppression of help	-	-	-	-	-	+
Effect on MHC class-II+ APC:						
- antigen-specific killing	-	-	-	-	+	+
Major characteristic:	helper	helper	helper	helper	killer	suppressor and killer
Th-phenotype:	Th2	Th0	Th1	Th1	Th1	Th1

n.t. : not tested
\+ : strong
\- : none

functions of the α/β T cells are well defined, the functional properties and the biological significance of the γ/δ T cells are not yet clearly revealed. Mycobacterial components and heat shock proteins have been found as frequent ligands for γ/δ T cells (*Kaufmann* and *Kabelitz*, 1991; *Janis* et al., 1989; *O'Brien* et al., 1989; *Haas* et al., 1990), implying that this population of T cells might be important non-MHC-restricted effectors in the antimicrobial immunity. The CD4 and CD8 determinants are so-called adhesion molecules, i.e. they bind to the non-polymorphic portions of either the MHC class-II (in the case of CD4) or class-I (CD8) products and stabilise cell interactions by this connection (*Parnes*, 1989; *Eichmann* et al., 1989). Thus, two classes of T cells can be defined according to the cell surface molecules CD4 and CD8, and both differ in their functional properties. The CD4+ T cells are commonly classified as helper/inducer and the CD8+ T cells as killer/ suppressor cells. However, already ten years ago provisional evidence emerged that the CD4+ T cells represent a rather heterogeneous population, a fact, which was confirmed when T cell cloning became available. In this review, we will discuss peripheral CD4+ T cell subsets in the two best investigated systems, mouse and man, with special emphasis on their characteristics, functional properties and biological significance. In addition, gut mucosal T cell subsets, which demonstrate some unique features will also be briefly reviewed.

PERIPHERAL CD4+ T CELL SUBSETS

T cell subsets can be defined according to either (A) their lymphokine secretion pattern, (B) their functional properties or (C) surface markers which they express. Preferentially, the concordance of all three criteria would be best for a unequivocal subset definition. However, this is only partially the case.

CD4+ T subsets defined according to the lymphokine profile:

Mosmann and colleagues (1986; 1989) were the first to describe two mutually exclusive subsets among mouse CD4+ T cell clones, termed Th1 and Th2, based on their ability to secrete different lymphokines (LK). Th1 essentially produce IL-2 and IFN-γ but not IL-4 and IL-5, while Th2 secrete IL-4, IL-5 and IL-6, but neither IL-2 nor IFN-γ (Table 1). However, the distinct LK-secretion pattern of Th1 and Th2-clones did not turn out to be exclusive. Recently, clones intermediate between Th1 and Th2 have been described (*Firestein* et al., 1989; *Gajewski* and *Fitch*, 1988; *Yokoyama* et al., 1989), termed Th0, which secrete IL-2, IL-4 and IFN-γ (Table 1).

In man, the clear-cut Th1/Th2 distinction cannot be made (*Paliard* et al., 1988; *Umetsu* et al., 1988; *Rotteveel* et al., 1988). The majority of human CD4+ T clones described demonstrate the characteristics of Th0, i.e. secret IL-2 and IFN-γ in addition to IL-4. Some human T cell clones have the phenotype of Th2, secreting IL-4, but not IL-2 and IFN-γ (Table 1). However, T cell clones similar to Th1 have not been identified so far. Thus, the Th1 and Th2 dichotomy may not hold true as far as human CD4+ T cells are concerned.

Characterising a number of CD4+ T clones generated by directly cloning splenic T cells from primed BALB/c mice we identified stable subsets which clearly fitted into the Th1/Th2/Th0 scheme in terms of the LK-secretion profile (Table 2) (*Erb* et al., 1991).

Table 3: Th2-type clones can switch into the Th0 phenotype.

Conditions of stimulation of clone 9A/B[1]	days between assay and last stimulation	mRNA expression[2]					
		IL-2	IL-3	IL-4	IL-5	IL-6	IFN-γ
A20.2J + KLH	9	-	+	+	+	+	-
	28	+	+	+	+	+	+
Con-A	9	-	+	+	+	+	-
	28	-	+	+	+	+	-

[1] 9A/B T cells (10^6/ml) were activated with either con-A (5 μg/ml) or with the B lymphoma A20.2J (10^6/ml) as APC and KLH (50 μg/ml). After 6h, the cells were harvested and mRNA was determined for selected lymphokines by Northern blot analysis.
[2] +: mRNA expression.
-: no mRNA expression.

However, clones with an unusual LK-secretion pattern were also found, such as clone 8/25-2, which expressed a LK-profile similar to Th1, but failed to secrete IFN-γ (Table 2). It is noteworthy that these clones kept their original phenotypes stable over years with an exception discussed below. Thus, it is likely that the CD4+ T cells are even more heterogeneous as originally thought.

In vivo, evidence for the existence of CD4+ subsets is also available, but the LK-secretion pattern is much less distinct than in cloned T cells (*Hayakawa* and *Hardy*, 1988; *Powers* et al., 1988; *Mohler* and *Butler*, 1990; *Schoenbeck* et al., 1989; *Heinzel* et al., 1989; *Bass* et al., 1989). Indeed, when CD4+ T cells from normal mice are stimulated with mitogens or antigen and APC, the LK-pattern that is produced does not match the Th1/Th2 pattern. In short-term cultured T cell lines LK-secretion phenotypes intermediate between Th1 and Th2 patterns are also frequently found (*Kelso* and *Gough*, 1988; *Carding* et al., 1989; *Street* et al., 1990; *Swain* et al., 1990; *Weinberg* et al., 1990). These observations lead to the suggestion that Th1 and Th2 subsets represent final stages in Th differentiation and thus, express mutually exclusive LK-secretion precursors, e.g. Th0, express a mixed LK-secretion pattern (*Firestein* et al., 1989; *Street* et al., 1990; *Mosmann* and *Moore*, 1991). Indeed, it was reported that Th0 obtained from unprimed mice converted into Th2 cells after prolonged culture *in vitro* (*Torbett* et al., 1990). A conversion of Th0 to Th1 or of Th1 to Th2 and the reverse was not found.

Recently, we found that a classical Th2 clone (9A/B, see Table 2) is able to transcribe and secrete IL-2 and IFN-γ in addition to IL-4 and IL-5 depending on the resting state of the Th2 cells as well as on the mode of activation (manuscript submitted). The resting state is defined as the time between the last stimulation of the T clone with antigen and irradiated feeder cells and the assay. Thus, short-term (<2 weeks) rested 9A/B cells demonstrated the classical Th2 LK-profile independent of the mode of activation, while long-term (>3 weeks) rested 9A/B cells showed the Th0 profile, provided they had been activated with antigen and APC, but not with mitogens (Table 3). Our results question the proposed unidirectional differentiation pathway of Th0 to Th2 and suggest that certain Th0 clones may represent an additional independent subset rather than a stage along the development from precursors to Th2 or Th1.

The differential LK-secretion pattern of CD4+ subsets could also stem from differences in their triggering require-

Table 4: CD4+ T cell subsets defined according to functions

Function	Mouse	Man
Help to B cells for antibody production	Th2, Th0, (Th1)	Th0, Th2
Killing of MHC class-II + APC	Th1	Th0, (Th2)
Suppression of antibody responses	Th1	Th0, Th2
Activation of macrophages	Th1	Th0
Delayed type hypersensitivity (DTH)	Th1	?

( ): Function has been demonstrated by some, but not all investigators

ments. *In vivo*, it is possible to induce either Th1-type or Th2-type responses depending on the immunogens used. Antigens that preferentially stimulate Th1-mediated responses include *Brucella abortus* and many viruses (*Finkelman* et al., 1988; *Coutelier* et al., 1987). Certain parasites and helminths induce a strong, predominant Th2 response, as manifest by a significant production of IgE and weak or absent DTH (*Heinzel* et al., 1989; *Liew* et al., 1990; *Pearce* et al., 1991). *In vitro*, Th2 cells, but not Th1 cells are reported to proliferate in response to IL-1 when costimulated with anti-TcR antibodies or mitogens (*Fernandez-Botran* et al., 1988; *Greenbaum* et al., 1988). In addition, the IL-2-induced proliferation of Th1, but not of Th2-clones is strongly inhibited by immobilised anti-CD3 antibodies (*Williams* et al., 1990). Finally, differences between Th1 and Th2-clones have also been found in their response to a tolerogenic signal (*Gilbert* et al., 1990).

CD4+ T cell subsets defined according to functions:

Functionally, both murine T cell subsets were originally described to help B cells for antibody production (Table 4). Indeed, Th2 cells, which produce IL-4, IL-5 and IL-6 efficiently provide noncognate or cognate help to B cells for antibody responses (*Erb* et al., 1991, see also Table 2). However, the capacity of Th1 cells to provide cognate MHC-restricted help for Ag-specific antibody responses is controversial. Some investigators found efficient B cell help provided by Th1-clones (*Mosmann* et al., 1986; *Dekruyff* et al., 1989; *Erb* et al., 1991), while others did not (*Killar* et al., 1987; *Boom* et al., 1988). We found very few real helper clones among many Th1-clones tested (e.g. clone 8/25-1, Table 2) which provided helper activity by cognate interaction. The majority of our Th1-clones did not help at all. Irrespective whether Th1 cells help B cells or not, it is clear that Th2 are much more efficient helper cells. In any case, it is of important biological significance that both Th2 and Th1 cells markedly influence isotype secretion of B cells (*Stevens* et al., 1988). Thus, Th2 preferentially help B cells for IgG1 and IgE production, due to the secretion of IL-4, while Th1 promote IgG2a and suppress IgE production due to IFN-γ secretion. Thus, IL-4 is the switch factor for IgE and IFN-γ for IgG2a. As already mentioned, infection of certain inbred strains of mice with protozoan or helminth parasites, e.g. *Leishmania*, evokes a strong IgE response mediated by Th2 cells which predominate in these mice (*Boom* et al., 1988; *Locksley* and *Scott*, 1991). Other functions have been more or less only found among the Th1 subset (Table 4). Thus, Th1-clones mediate strong antigen specific delayed type hypersensitivity (DTH) and they are, therefore, also called inflammatory Th cells (*Bottomly*,

1988). Some of the Th1 are cytotoxic, activate macrophages (due to IFN-γ secretion) or mediate suppression of antibody responses (*Killar* et al., 1987; *Erb* et al., 1990; *Erb* et al., 1991; *Yokoyama* et al., 1989).

In man, CD4+ T cells can be divided into helper and non-helper for B cells, but there is little correlation to the LK-secretion phenotype (Table 4). Thus, both Th0 as well as Th2 cells help or do not help, kill or suppress (*Umetsu* et al., 1988; *Rotteveel* et al., 1988).

It is of interest, that beside the well-known CD8+ CTL, cytotoxic T cells also exist among the CD4+ T cell population. CD4+ CTL lyse target cells in an antigen-specific and MHC class-II restricted way (*Fleischer*, 1984; *Tite* and *Janeway*, 1984; *Braakman* et al., 1987; *Ju* et al., 1990; *Erb* et al., 1990). In other words, CD4+ cytotoxic T cells eliminate their own MHC class-II+ APC. CD4+ CTL have originally been claimed to be an 'artefact' of *in vitro* cultured T cell clones (*Fleischer*, 1984). However, this possibility can now be ruled out as it has been recently shown that CD4+ CTL are present in the spleen of *in vivo* primed mice (*Erb* et al., 1990). Different types of APC express a differential sensitivity to killing. MHC class-II+ tumour cells or non-transformed, but activated APC (e.g. B cell blasts) are highly sensitive to killing, while non-activated APC (e.g. normal B cells) are resistant to killing (*Erb* et al., 1990). The differential susceptibility of MHC class-II+ APC to lysis suggests an important role of CD4+ CTL in immunoregulation, i.e. down-regulation of antigen presentation by eliminating stimulated APC. In addition, the preferential killing of MHC class-II+ tumour cells as well as the lysis of certain virus-infected cells (*Meurer* et al., 1991; *Jacobson* et al., 1984; *Schmid*, 1988; *Bourgault* et al., 1989; *Wing* et al., 1990) strongly supports the participation of CD4+ CTL in immune surveillance. Moreover, CD4+ CTL may also be involved in certain autoimmune diseases. Thus, they may be responsible for the elimination of cells which were accidentally stimulated and became Ia+, but whose primary function is not antigen presentation. Examples for such a role may be the CD4-mediated lysis of MHC class-II+ astrocytes of the brain (*Sun* and *Wekerle*, 1986) or of MHC class-II+ β-cells of the pancreas (*DeBerardinis* et al., 1988; *Wang* et al., 1991), a mechanism which could be responsible for the pathogenesis of the experimental autoimmune encephalomyelitis or of type I diabetes.

CD4+ T cell subsets defined according to surface markers:

Beside the lymphokine profile or functional properties, surface markers also represent a good tool for defining CD4+ T cell subsets. Functional dichotomy in normal CD4+ T cells was found in human, rat and recently in the mouse, using mAb that react with various isoforms of T200 leukocyte common antigen, also termed CD45 (*Morimoto* et al., 1985b; *Smith* et al., 1986; *Pulido* et al., 1988; *Spickett* et al., 1983; *Bottomly* et al., 1989; *Luqman* et al., 1991). CD45 is a major cell surface glycoprotein expressed on haematopoietic cells except mature erythrocytes. This cell surface antigen has been characterised in human, rat, mouse and has similar properties in all species (reviewed by *Thomas*, 1989). A unique feature of CD45 is its heterogeneity in molecular weight (Figure 1). The structural variation is cell type specific in that antibodies to CD45 distinguish between T cells and B cells, between CD4+ and CD8+ T cells and even between subsets of CD4+ T cells. Part of the heterogeneity is due to the presence of three exons which are differentially spliced in the mRNA. This gives theo-

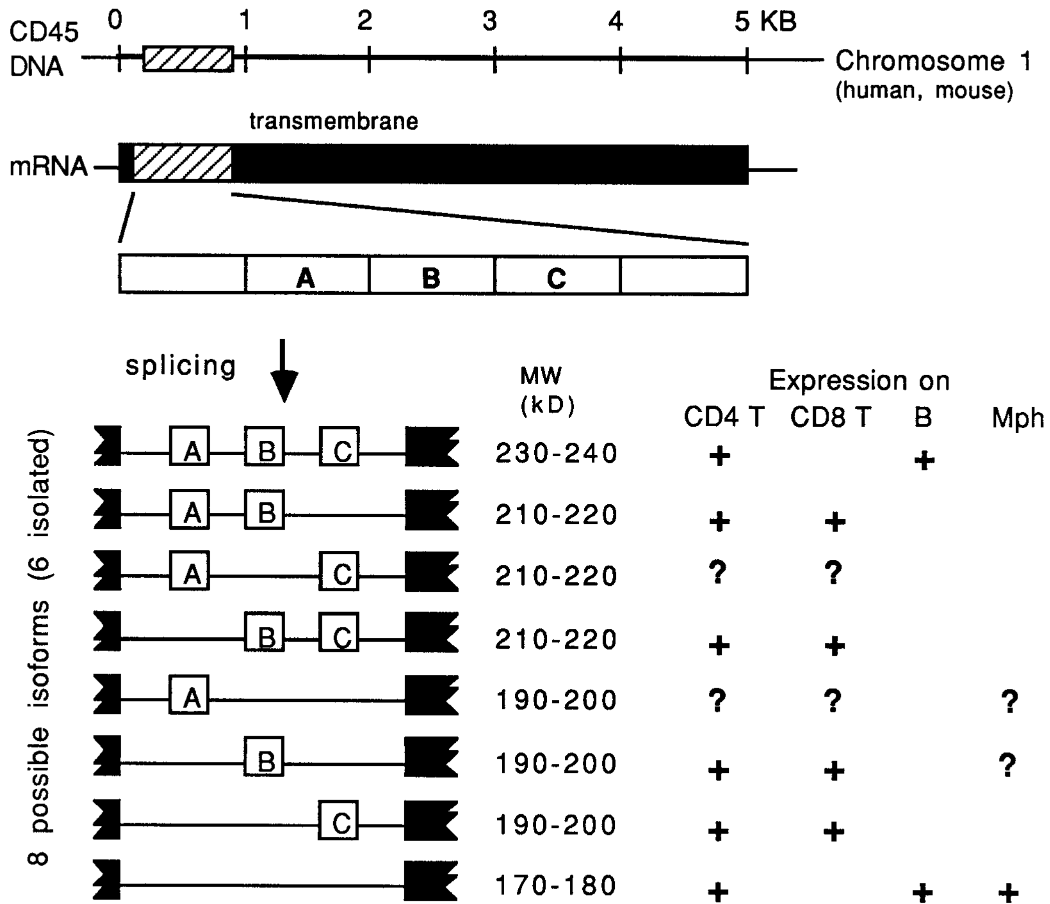

Figure 1: Schematic diagram of the CD45 complex.
The CD45 cDNA is 4991 base pairs (bp) long and contains 34 exons encoding 1291 amino acids. Exons 3-15 encode amino acids 1-537 of the external domain. The striped bar contains the three variably expressed exons A, B, and C. Splicing leads to 8 possible isoforms of which 6 have been identified. MW indicates the approximate molecular weights of the glycoproteins for each type of isoform. The expressed column indicates the possible expression patterns for different isoforms. Adapted according to *Thomas* (1989) and *Luqman* et al. (1991).

retically rise to eight different mRNA and hence eight isoforms (Figure 1) from which six have been identified. The differential splicing results in differences in the primary sequence of the extracellular domain. Monoclonal antibodies exist which have known specificity for particular CD45 isoforms referred to as CD45R (Table 5). Some mAb require the expression of exon A (anti-CD45RA) or exon B (anti-CD45RB) for binding, while others recognise a null isoform with all variable exons spliced out (anti-CD45R0). In human, the mAb 2H4 reacts with a high molecular weight form of CD45 (=CD45RA) (*Morimoto* et al., 1985b). This CD45 high molecular weight marker is lost upon T cell activation. The 2H4-positive subset which proliferates upon mitogen stimulation, but much less to antigen stimulation, provides poor help for specific immunoglobulin synthesis (*Morimoto* et

Table 5: List of mAb with known specificity for CD45 isoforms

Species	mAb	Reference	CD45RA	CD45RB	CD45RO
Man	2H4	Morimoto, 1985	+	-	-
	UCHL-1	Smith, 1986	-	-	+
	PD-7/26	Pulido, 1988	-	+	-
Mouse	C363.16A	Bottomly, 1989	-	+	-
	14.8	ATCC TIB 164	+	-	-
	M1/9.3.4HL2	ATCC TIB 122	+	+	-
Rat	MRC OX22	Spickett, 1983	_	+	-

al., 1985b). In contrast, the 2H4-low T subset poorly proliferates upon mitogen stimulation, but highly to soluble antigen and provides good help to B cells (*Morimoto* et al., 1985a). As mentioned, human T cells loose the 2H4 marker upon activation, whereas activated T cells are now reactive with an other mAb termed UCHL-1, which recognises a low molecular weight form of CD45R (=CD45R0) (*Smith* et al., 1986). These observations led to the assumption that 2H4+ T cells are naive, while UCHL-1+ T cells are of the memory type (*Sanders* et al., 1988). More recently, it has been reported, that memory T cells for IFN-γ secretion express the CD45RB isoform on the surface (*Mason* and *Powrie*, 1990). A summary of the human CD4+ T subsets characterised according to CD45 isoforms has been given in Table 6.

In the rat, mAb OX22 has also been found to bind to the high molecular weight form of CD45 (CD45RB) (*Spickett* et al., 1983). OX22+ T cells are mainly producing IL-2 and mediate DTH, while OX22- T cells provide help to B cells (*Powrie* and *Mason*, 1990).

In the mouse, anti-CD45 mAb (Table 5) raised against the high molecular weight isoform of CD45 preferentially bind to Th2-type cells (*Luqman* et al., 1991) Indeed, Th2-clones express the

Table 6: Expression of CD45 isoforms on CD4+ human T cells

Properties / Functions	CD45RA	CD45RO	CD45RB
Naive T	++	+/-	?
Inducer of suppression	++	+/-	?
Memory T for B help	+/-	++	?
Proliferation to recall antigen	+/-	++	?
Proliferation to mitogens	++	+	?
IL-2 secretion	++	++	?
IL-4 secretion	+	++	?
IFN-γ secretion	+/-	++	++
TNF secretion	++	++	?
CD29, CD2, LFA-1, LFA-3 expression	+	++	?
Phenotype change upon activation	yes	no	no

++ : high expression
+ : low expression
+/- : very low expression
? : not yet defined

Table 7: CD45 isoforms expressed on murine CD4+ T subsets

Isoform	Th1	Th2	Th0
CD45RA	-	++	?
CD45RB	-	++	?
CD45R0	++	-	?

++ : high expression
+ : low expression
+/- : very low expression
? : not yet defined

high molecular weight isoforms of CD45 containing two or three of the alternatively spliced exons, while the two-exon and three-exon forms are absent in Th1-clones, in which the CD45R0 dominates (Table 7) (*Luqman* et al., 1991). Nothing is known about the CD45 isoform expression on Th0 cells.

Taken together, CD45 isoforms do not define different lineages of cells but correspond to maturational stages of a lineage. Thus, the high molecular weight isoforms are lost from naive T cells upon activation. Murine Th2-clones seem to represent the exception of the rule in that the expression of the high molecular weight isoforms is still maintained, despite these cells are considered to be end stages of Th differentiation.

CD44, an extensively glycosylated one-chain molecule which is widely distributed on a diverse range of cell types, is also expressed on subsets of CD4+ and CD8+ T cells. In both cases, CD44-cells appear to correspond to

Table 8: Comparison of intraepithelial (IEL) and lamina propria lymphocytes (LPL)

Properties		IEL	LPL
Surface marker expression	CD3, CD2	>90%	>90%
	CD4	5-10%	65-80%
	CD8	75-90%	20-35%
	α/β TcR	90%	100%
	γ/δ TcR	10%	<1%
	CD45RA	high	low
	CD45R0 (UCHL-1)	high	high
	IL-2R (TAC)	none	high
	MHC class II	very low	high
LK secretion	IL-2	no	yes
	IL-3	yes	yes
	IFN-γ	yes	?
	GM-CSF	yes	?
Functions	Cytotoxicity	yes	yes(?)
	Help to B cells	uncertain	yes
	DTH	yes	?
	Proliferation to recall antigen	low	low

virgin, unstimulated T cells, while the memory cells that have been previously exposed to antigen are found in the CD44+ population (*Haynes* et al., 1989).

Another immunoglobulin-like surface glycoprotein, CD28 is found on about 95% of human peripheral CD4+ T cells and approximately 50% of CD8+ T cells (*June* et al., 1990). The density of CD28 expression divides human CD4+ T clones into two subsets (*Rotteveel* et al., 1988). The clones with low CD28 expression produce IL-2, IFN-γ and TNF-α and display anti-CD3-mediated cytotoxicity. The clones with high CD28 expression produce minimal amounts of LK and are not cytotoxic. Thus, both CD44 and CD28 seem to be activation markers rather than lineage markers.

Finally, *Takada* et al. (1989) discriminated human cytotoxic from non-cytotoxic CD4+ T cells by the cell surface marker Leu 8. Cytotoxic CD4+ T cells lack Leu 8 antigen, but express the CD2 marker in high density in contrast to non-cytotoxic CD4+ T cells.

In summary, murine CD4+ T cell subsets have been defined mainly on the basis of different lymphokine secretion patterns and functions, but both, LK-profiles and functions of the subsets correlate only partially. The classification of human CD4+ T cell subsets is primarily based on their functional properties and on certain surface markers, especially on the expression of CD45 isoforms. Lymphokine secretion profiles neither correlate with function nor surface marker expression.

INTESTINAL T CELL SUBSETS

T cells in the gut are either localised in organised lymphoid organs, such as the Peyer's patches and the lymphoid follicles in the colonic mucosa, or are disseminated in the intestinal lamina propria (lamina propria lymphocytes: LPL) and above the basement membrane between epithelial cells (intraepithelial lymphocytes: IEL). While the T cells in the gut organised lymphoid organs are more or less analogous to the peripheral T cells described above, gut mucosal lymphocytes, especially LPL and IEL seem to differ from T cells in other compartments of the immune system in various aspects (reviewed by *Jalkanen*, 1990; *MacDonald* and *Spencer*, 1990; *Mowat*, 1990; *Zeitz* et al., 1990). Indeed, evidence is accumulating that the gut mucosal T cells may form a discrete compartment of the immune system on its own. Despite their apparent importance, surprisingly little is known about their nature and their function is incompletely understood, especially in man.

A comparison - by no way comprehensive - of some major properties and functions of the IEL and LPL are given in Table 8. It is quite obvious that both, IEL and LPL, represent distinct subsets. While the majority of the intraepithelial T cells are CD8-positive, T cells from the lamina propria have almost similar CD4/CD8 expression to that of peripheral blood lymphocytes (2:1). Moreover, in contrast to LPL, IEL do not express conventional T cell activation markers, such as the IL-2 receptor (TAC) or MHC class-II antigens. However, the expression of UCHL-1 which is a marker for differentiated memory T cells is not consistent with IEL being entirely a resting population. It is, therefore, likely that IEL have already interacted with antigen before migrating into the epithelium (*Jalkanen*, 1990).

Functionally, IEL and presumably

Table 9: Mouse CD8+ IEL consist of two ontogenetically distinct populations

90% CD8+ IEL comprise 2 populations	
Thy-1 positive	Thy-1 negative
α/β TcR	γ/δ TcR or α/β TcR
heterodimeric α/β CD8+	homodemeric α/α CD8+
Thymus-dependent	Thymus-independent
Ag stimulation required	no Ag stimulation required
Peyer's patch ➔ blood ➔ TD ➔ mucosa of gut	directly bone marrow derived?

also LPL evoke cytotoxic activity. Whether the cytotoxicity of LPL is also due to CD4+ T cells is not known, but might be possible due to the fact that LPL lack the Leu-8 marker. Lamina propria T cells, but not IEL have been convincingly shown to provide high helper activity for Ig-synthesis. Finally, both IEL and LPL do not well proliferate to recall antigen, which in the case of LPL is again a difference to classical memory T cells. Lamina propria T cells can, therefore, be characterised as differentiated effector cells which respond to antigen challenge with the production of certain lymphokines and cells for antibody production (*Zeitz* et al., 1990).

CD8+ IEL have been recently characterised in more detail in the mouse model (*Guy-Grand* et al., 1991). Table 9 summarises the results. Two ontogenetically different subsets have been identified. One subset bears the α/β TcR, the α/β CD8 chains and expresses the Thy-1 marker. The other subset has either the γ/δ or α/β TcR, bears the homodimeric α/α CD8 chains and does not express the Thy-1 marker. The Thy-1+ subset, which is thymus-dependent, represents most likely the progeny of precursors cells arising in Peyer's patches under antigenic stimulation, which then by way of the blood and the thoracic duct colonise the mucosa of the gut due to their gut-homing property. The Thy-1 negative subset which does not require a thymus for differentiation, presumably derives directly from the bone marrow. Although the functional role of the Thy-1 negative subset is not known, it is highly likely that it recognises an antigenic repertoire different from the Thy-1+ subset.

Taken together, IEL are one of the least understood populations of lymphocytes with many unique features. According to their properties it has been suggested that IEL represent a population of committed end-stage effector cells similar to plasma cells, which have been fully differentiated before entering the epithelium. Both, IEL and LPL are of outstanding importance for the host' integrity due to the fact that they by virtue of their position have the closest direct connection to foreign antigen including many potential pathogenic organisms. Thus, they represent an important barrier against invading antigens.

ACKNOWLEDGEMENTS

This work was in part supported by the Swiss National Science Funds grant nr.31-29957.90

ABBREVIATIONS USED

APC	: antigen-presenting cells	LK	: lymphokine(s)
CTL	: cytotoxic T lymphocytes	LPL	: lamina propria lymphocytes
DTH	: delayed type hypersensitivity	MHC	: major histocompatibility complex
Ia	: I region associated	TcR	: T cell receptor
IEL	: intraepithelial lymphocytes	Th	: T helper cell(s)
IFN-γ	: interferon-gamma	TNF	: tumour necrosis factor

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