T cell subsets

A synopsis of the lecture by Dr. Steve Cobbold for the FHS Physiology Immunology Option

1/ Definitions and relationships of different T cell subsets

There are many different, and sometimes confusingly named, T cell and related cell subsets, although much of the confusions arises where subsets have been separately defined on the basis of molecular markers (eg. CD4+ T cell) and functional properties (eg. cytotoxic T cell) and the two definitions "overlap" (eg. most cytotoxic T cells are CD8+, but CD4+ T cells can be cytotoxic in appropriate assays too). The only absolute definition is that a T cell must express either the γδ or γδ T cell receptor (as this is a genetically irreversible decision) - all other subset definitions are somewhat dependent on the assay used to measure them!

2/ Subsets of T helper cells (Th1 and Th2) defined by cytokines

The original observation that mouse CD4+ T cell clones could be divided into two different sets based on their pattern of cytokine expression has become the paradigm for heterogeneity within the T cell response in vitro and in vivo. Th1 and Th2 cells are thought to derive from a non-polarised, naive Th0 precursor that makes a wide range of cytokines, that can differentiate after activation in the presence of IL-12 and IL-18 (from DCs) into Th1 cells that secrete IL-2, IFN-γ and lymphotoxin (LT) or in the presence of IL-4 (from B cells or lymphoid DCs?) into Th2 cells that secrete IL-4, IL-5 and IL-10. This initial polarisation of the response towards Th1 or Th2 is then self perpetuating as Th1 cytokines enhance further Th1 responses and down regulate Th2 cytokines, and vise versa.

3/ Antigen presentation for Th1 versus Th2 responses

It is still not clear how the initial polarisation towards either Th1 or Th2 is controlled, but it is thought to involve a number of factors including the route of immunisation and the type of APC (eg. skin -> LC -> Th1 or i.v. -> B cell -> Th2), the antigen density/affinity (v. high or v. low antigen dose -> Th2), and the innate immune response (NK cells -> IFN-γ -> Th1 or NKT cells -> IL-4 -> Th2). With respect to T cells interacting with the APC it seems that CD40 -> CD40L promotes Th1 responses, while B7 (CD80, CD86) -> CD28 is more important as costimulation for Th2 cells. Once a Th1 or Th2 response has been polarised and established the antigen may be presented directly or indirectly for activation of different effector cells - macrophages, neutrophils and cytotoxic T cells for Th1 responses and eosinophils, mast cells and B cells for the Th2 response. B cells are also dependent on cytokines to promote maturation and isotype switching, with IL-2 and IFN-γ promoting IgG2, IL-4 promoting IgG1 and IgE, and IL-5 promoting IgA.

4/ Phenotypic and functional markers for Th1 and Th2 cell subsets

Th1 and Th2 clones were defined by their cytokine production pattern in vitro, and there has been much effort to find good markers to identify Th1 or Th2 cells in vivo, but with overall little success. The CD4-like molecule LAG-3 was thought to be a surface marker for Th1 cells, while CD30 (TNF-R family) and ST2L (IL-1R family) were thought to be specific for Th2, but all these markers probably more accurately reflect IFN-γ or IL-4 responsive cells respectively, as does the expression of the cytokine receptor signalling molecules Stat-4 and Stat-6. The loss of the IL-12Rβ4 chain is thought to be a marker for Th2 commitment, while the transcription factor GATA-3 is lost on Th1 cells. It was originally thought that chemokine receptor expression would reliably distinguish the different subsets, and although there is some functional division (CCR1, CCR5 and CXCR3 on Th1 while Th1 express CCR3 and CCR4), it is becoming clear that this association is less well defined in vivo. The best way to identify Th1 and Th2 cells is therefore immunofluorescent staining for the appropriate cytokines on fixed and permeabilised cells, after a brief activation step in vitro in the presence of Brefeldin or Monensin that amplify staining by holding the cytokines in the golgi.

5/ Th1 and Th2 responses in disease

The Th1/Th2 paradigm has been used to explain a wide variety of disease and pathological conditions, both in experimential rodent models and in man. The classical example is that of Leishmania infection of C57Bl/6 mice that induces a protective Th1 response, compared to BALB/c mice that insetad make an ineffective Th2 response and die from a progressive infection (the genetic basis is still not clear). A similarly classical example in man is that of Tuberculoid Th1 lesions compared to lepromatous Th2 disease. Generally speaking, Th1 responses protect from invasive bacterial, protozoal and viral infections, and cause autoimmune diseases, while Th2 responses protect from extracelluar parasites, helminths, and cause allergic responses in atopic individuals.

6/ Th1 and Th2 in transplantation and pregnancy

The Th1/Th2 paradigm has also been applied to transplantation, with Th1 responses being implicated in most forms of acute rejection and graft versus host disease, while Th2 responses have been variably associated with either protection or chronic rejection. However, cloned Th1 or Th2 cells have a similar capacity to reject skin grafts in experimental models, and Tr1/Treg cells are now being implicated in protection and tolerance induction. The foetus is also analogous to an allograft, and Th2 or Treg responses are thought to be protective, while Th1 may lead to resorption or spontaneous abortion.
T cell subsets - selected references

The primary literature on Th1, Th2 and other T cell subsets is massive, and I have therefore provided mainly review articles for this lecture, and these will obviously contain original references to those particular aspects of the field that may interest you further.

Mosmann, T.R., and Sad, S.
The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunology Today* 17: 138-146 (1996)

Fallon, P.

Murphy, K.M.

Louis, J., Himmelreich, H., et al.

Abbas, A.K., Murphy, K.M., Sher, A.

Sallusto, F., Lanzavecchia, A., and Mackay, C.R.

Rejection of H-Y disparate skin grafts by monospecific CD4+ T helper 1 (Th1) and T helper 2 (Th2) cells: no requirement for CD8+ T cells or B cells. *J. Immunol.* 161: 1868-1874 (1998)

Hammond, KJ., Pelikan, SB., et al.

Carter, LL., Swain, SL.

Groux-H; O'Garra-A; Bigler-M; Rouleau-M; Antonenko-S; de-Vries-JE; Roncarolo-MG
Lymphocyte Subset: CD4 T-cell
Defined by: CD4 (L3/T4)
Also expresses: CD3, CD2, TCR (usually a, b)
Function: MHC-class II restricted T-cell responses

Lymphocyte Subset: Helper T-cell
Defined by: Functions
Also expresses: CD3, CD2, TCR, CD4 (usually)
Function: Help for antibody (B-cell) Help for T-cells (lymphokines)

Lymphocyte Subset: Activated T-cell
Defined by: Activation markers eg. CD25 (IL-2 receptor) but note may also be expressed on Treg
Also expresses: CD2R, CD26, CD71 (Tf-rec), CD3, CD4 or CD8, TCR
Function: Proliferation in response to antigen

Lymphocyte Subset: Memory T-cells
(Th1, Th2 and cytotoxic T-cells)
Defined by: "Secondary responses in vitro"
Also expresses: CD3, CD2, CD4 or CD8, TCR
Function: Immunity to previous Ag encounter

Lymphocyte Subset: T-regulatory cell
Poorly defined as yet!
Defined by: Th3 = TGFβ, Tr1 = IL-10, Treg = CD25/anergy
Also expresses: CD3, CD2, CD4 or CD8 (usually)
Function: Down regulation of Th1 (and Th2?) Ag presentation?
  Control of autoactivity
  Oral tolerance to food and gut flora
  Transplantation tolerance

Lymphocyte Subset: Suppressor T-cell
Defined by: "Suppression" of responses in vitro or transfer in vivo
Also expresses: CD8 (or CD4), CD3, CD45RA?
Function: Immuno-regulation?
Existence controversial

Lymphocyte Subset: Cytotoxic T-cell
Defined by: MHC restricted killing
Also expresses: CD3, CD2, TCR, CD4 or CD8
Function: Killing of virus infected cells, and rejection of foreign tissue.

Lymphocyte Subset: CD4 T-cell
Defined by: CD4 (L3/T4)
Also expresses: CD3, CD2, TCR, CD4 (usually)
Function: MHC-class II restricted T-cell responses

Lymphocyte Subset: Helper T-cell
Defined by: Functions
Also expresses: CD3, CD2, TCR, CD4 (usually)
Function: Help for antibody (B-cell) Help for T-cells (lymphokines)

Lymphocyte Subset: Activated T-cell
Defined by: Activation markers eg. CD25 (IL-2 receptor) but note may also be expressed on Treg
Also expresses: CD2R, CD26, CD71 (Tf-rec), CD3, CD4 or CD8, TCR
Function: Proliferation in response to antigen

Lymphocyte Subset: Memory T-cells
(Th1, Th2 and cytotoxic T-cells)
Defined by: "Secondary responses in vitro"
Also expresses: CD3, CD2, CD4 or CD8, TCR
Function: Immunity to previous Ag encounter

Lymphocyte Subset: T-regulatory cell
Poorly defined as yet!
Defined by: Th3 = TGFβ, Tr1 = IL-10, Treg = CD25/anergy
Also expresses: CD3, CD2, CD4 or CD8 (usually)
Function: Down regulation of Th1 (and Th2?) Ag presentation?
  Control of autoactivity
  Oral tolerance to food and gut flora
  Transplantation tolerance

Lymphocyte Subset: Suppressor T-cell
Defined by: "Suppression" of responses in vitro or transfer in vivo
Also expresses: CD8 (or CD4), CD3, CD45RA?
Function: Immuno-regulation?
Existence controversial

Lymphocyte Subset: Cytotoxic T-cell
Defined by: MHC restricted killing
Also expresses: CD3, CD2, TCR, CD4 or CD8
Function: Killing of virus infected cells, and rejection of foreign tissue.
Lymphocyte Subset: NK-cell

Defined by: Killing of K562 (human) YAC-1 (mouse)

Also expresses: Killer inhibitory receptors (KIRs)

Function: Innate response/Th1 amplification of cytotoxicity

Killing of syngeneic tumours?

Cross-linking activates

NK-cell

K-Cell

Defined by: CD16 (FcR-III)

Also expresses: CD2, CD3, CD8

Function: Antibody dependent cell mediated cytotoxicity (ADCC)

CD16

NK-Cell

Defined by: NK1.1, CD4 low (mouse)

Also expresses: CD3, CD2, limited TCR

Function: Amplification of Th2 T-cell responses?

NK cell

CD16

K-cell

Defined by: CD3, CD2, TCR, CD4 (usually)

Also expresses: CD4, CD30, ST2L

Function: Activation of Type 2 effectors

IL-4, IL-5, IL-10

B cells [esp. IgG1, IgE, IgA] eosinophils, mast cells

Down regulation of Th1 response

Type 2 Cytotoxic T-cell (Tc2)

Defined by: CD8 plus Type 2 cytokines

Also expresses: CD3, CD2, TCR

Function: Killing of infected cells in ongoing Th2 response?

CD8
Regulation of Th1 versus Th2 responses

Microbial factors eg. LPS

NK cells
Activated macrophages and dendritic cells

Activated Th0

GATA-3

Th0

Activated Th0

GATA-3

IL-2

IL-12

IL-12Rβ

Th1

IFN-γ

LAG-3

RANTES

IL-12Rβ

Macrophage

Inflammatory Protein-1 (MIP-1α, MIP-1β)

IP-10

To Node

Secondary Lymphoid Chemokine (SLC)

Stromal cell Derived Factor (SDF-3)

DC-CK1R

Dendritic cell chemokine 1

Other sources eg. NKT cells

Eotaxin

Macrophage derived Chemokine (MDC)

CD62L

CXCR7

CCR4

Th0

CXCR4

Activated macrophages and dendritic cells

Loss of GATA-3 (irreversible?)

Loss of IL-12Rβ (irreversible?)

IL-4

IL-12Rβ

Th2

GATA-3

CD30

ENG

IL-4R

IP-10

ST2L

CD30

Th1 versus Th2 responses in Disease

Bacterial infection eg. Leishmania

Viral infection eg. Influenza

Allergens eg. Derp-1 (dust mite)

AspF1 (aspergilus)

Helminths eg. Schistosomes, Nippostrongylus

Mucosal epithelium

Protection from:
Leishmaniasis (BALB/c mice)
HIV (late)
Tuberculoias, Candida

Delayed Hypersensitivity

Protection from:
Leishmaniasis (C57Bl/6 mice)
Bacterial Leprosy Lesions
Hepatosplenic Schistosomiasis
Graft rejection, fetal resorption?

Pathology generated:
Psoriasis, IDDM, RA
Tuberculoias, Candida
Graft rejection, fetal resorption?

Immediate Hypersensitivity

Protection from:
Schistosomiasis, Brugia etc
Malaria (late)
Autoimmunity: EAE, EAU

Pathology generated:
Psoriasis, IDDM, RA
Tuberculoias, Candida
Graft rejection, fetal resorption?
Monospecific female (A1xRAG-/-) anti-HY+H-2Ek TCR Tg mice generate both Th1 and Th2 responses as a consequence of rejecting male skin grafts.

Rejection of male (but not female) skin by A1(M)xRAG-/-
Th1 and Th2 lines
(by transfer into "empty" ATX-depleted CBA/Ca female mice)

1. R2.2 Th1 clone  
   MST = 11 days
2. R2.4 Th2 clone  
   MST = 13 days
3. D1 Treg clone  
   MST > 25 days

All female grafts

Treg

% male skin graft survival

Th1

Th2

P value (1 vs 2) <= 0.035378

Time (days)