REVIEW OF LITERATURE
MHC proteins and their tissue distribution: 7
MHC-peptide interaction: 9
T cell receptor (TCR) interaction with MHC-peptide complex: 11
Ligand generation for MHC class I: 12
Ligand generation for MHC class II: 14
Ligand generation for nonclassical MHC: 16
Immunogenicity for T cells: 18
T cell effector pathways: 19
Scavenger receptor and macrophages: 23
MHC proteins and their tissue distribution:

MHC molecules are heterodimeric integral membrane proteins, expressed on the surface of many cell types. Based on their structure and function, MHC proteins are broadly classified into three categories: the highly polymorphic MHC class I, MHC class II, and oligomorphic to monomorphic nonclassical MHC molecules. In mouse, MHC molecules are coded by a region of chromosome 17 called major histocompatibility complex (MHC) region [Schwartz et al., 1986]. Some of the nonclassical MHC molecules are coded by the genes located outside the MHC region, such as CD1 [Martin et al., 1986], FcRn [Simister et al., 1989].

MHC class I molecules are ubiquitous proteins, and expressed on all nucleated cells at varying levels. Normally, MHC class II molecules are expressed on B lymphocytes, cells of monocyte/macrophage and dendritic lineage [Unanue et al., 1987] and on activated T cells in humans [Evans et al., 1978]. Under some conditions, as in inflammation and treatment with some cytokines a variety of endothelial and epithelial cells can express MHC class II molecules [Geppert et al., 1985]. Nonclassical MHC molecules are expressed in a tissue specific fashion, [Stroynowski et al., 1990] and their expression can be induced on many cells by treatment with cytokines, e.g. TL on peripheral T cells by IFN-γ treatment [Wang, 1993] and CD1 on monocytes with a combination of GM-CSF and IL-4 [Porcelli, 1992].

The MHC class I molecule is an integral membrane glycoprotein, consisting of a membrane bound heavy chain, noncovalently associated with β2-microglobulin (β2-M) [Bjrokman et al., 1990]. The heavy chain consists of two distinct extracellular units: the membrane distal peptide-binding region, formed by association of α-1 and α-2 domain, and the membrane proximal α-3 domain. The α-3 domain associates with β2-M. T cell receptor
recognises the peptide bound to \( \alpha-1 \) and \( \alpha-2 \) domain [Ajitkumar et al., 1988], while CD8 coreceptor recognises the \( \alpha-3 \) domain [Salter et al., 1990].

Like MHC class I molecules, nonclassical MHC molecules have similar domains in the mature protein, i.e. \( \alpha-1 \ \alpha-2 \) and \( \alpha-3 \) domains, in which the latter associates with \( \beta 2-M \), and are coded by genes having a similar exon-intron organization [Stroynowski et al., 1990]. In the human intestinal epithelial cells, CD1d can be expressed on the cell surface, independent of \( \beta 2-M \) [Balk et al., 1994]. The interactions between H-2M3 and \( \beta 2-M \), are stronger than the interactions between H-2K\( ^b \) and \( \beta 2-M \). This may explain why, empty H-2M3, and also TL and CD1 are more thermostable than MHC class I molecules [Holocombe et al., 1995]. The nonclassical MHC molecules coded by MHC region are more similar to MHC class I, than those which are coded by the genes located outside the MHC region. Many of the nonclassical MHC molecules are membrane bound (H-2M, Qa-1, CD1 and TL) [Lindahl et al., 1980; Bradbury et al., 1988], but some are soluble proteins as H-2Q10 [Kvist et al., 1979], while others are either membrane bound or secretory depending upon the cell stage or cell type; e.g., Q4 is secretory in T cells [Robinson et al., 1988] and membrane bound in transfected B10.P fibroblasts [Day et al., 1987]. Qa-2 is attached to the membrane via a glycosphatidilinositol anchor [Stroynowski et al., 1987] on the resting T cells, while in the activated T cells it is both membrane bound and secreted [Soloski et al., 1986]. Qa-1 is also expressed as a heterodimer with H-2L\( ^d \) or with a 50-kD glycoprotein encoded by a gene centromeric to I-E\( ^b \) [Wolf et al., 1995].

MHC class II proteins are made of two integral membrane protein, a heavy \( \alpha \) chain and a light \( \beta \) chain, noncovalently associated with each other [Kaufman et al., 1984]. The extracellular portion of each chain is divided into two domains: \( \alpha-1, \alpha-2, \beta-1 \) and \( \beta-2 \). The \( \alpha-1 \) and \( \beta-1 \) domain of these chains form the peptide binding groove, and contribute to the allelic polymorphism. Site directed mutagenesis studies show that CD4 binding
site on MHC class II molecule is located into the β-2 domain [Koning et al., 1992].

**MHC-peptide interaction:**

Peptides bind to the peptide binding groove, located in the α-1 and α-2 domain of MHC class I. Peptide binding grooves are responsible for MHC restricted recognition of peptides, by TCRs. The side walls of the peptide binding groove are formed by the α-helices (of α-1 and α-2 domain), flanking the eight antiparallel β-pleated sheets (four each from α-1 and α-2 domain), which form the platform of the groove. Eluted peptides from purified MHC class I are of mostly 8-9 amino acids long [Jardetzky et al., 1991]. Crystal structure of MHC class I bound to peptide, from both human and mouse [Bjrokman et al., 1987; Madden et al., 1992; Fremont et al., 1992,] show a general mechanism of peptide binding. A series of depressions extend from the peptide binding groove, and these depressions are called peptide-binding pockets [Saper et al., 1991]. Some of the polymorphic residues constitute the peptide-binding pockets, and some point into the peptide binding groove. Thus, the peptide binding groove controls the ability of the different MHC alleles to bind different set of peptides. Out of the six pockets identified, four are located at the junction of α-helix and β-pleated sheets (pockets B, C, D, and E), two between the two α-helices (pockets A and F).

The N and C terminus of the peptides are anchored in the peptide binding groove, with a network of hydrogen bonds with conserved residues in MHC class I molecule. This restricts the length of the peptide bound to MHC class I molecule to 8-9 residues [Fremont et al., 1992]. The peptide binds into the peptide-binding groove in an extended conformation [Madden et al., 1991] along the groove with further contacts between main chain atoms of peptide and conserved amino acid side chains that line the groove. As the N
and C terminus of the peptides are fixed in the groove, longer peptides are
accommodated with a kink in the middle [Guo et al., 1992]. Peptides bound
to a given MHC class I allele have same or very similar amino acids at two or
three positions along the peptide length and these residues are called anchor
residues [Falk et al., 1991]. The side chains of anchor residues insert into the
pocket and interact with polymorphic residues lining the pocket. The
binding of the anchor residues to pockets anchor the peptide to MHC
molecule and hence anchor residues are very important for binding of the
peptide to MHC molecules. Most of the peptides, which bind to MHC class I
molecule have an anchor residue at the carboxy terminal, which is a small
hydrophobic residue in the most cases. The discovery of peptides that do not
bind to MHC class I molecule, despite having appropriate anchor residues
[Rupert et al., 1993; Hill et al., 1992], or of peptides binding to MHC class I
molecules without anchor residues makes the point [Huczko et al., 1993] that
peptide binding to MHC class I molecule is also governed by some other
rules.

The peptide binding groove of the MHC class II molecule is formed by
α-1 and β-1 domains and is similar to that of MHC class I molecule in some
ways. The subtle differences lies in the MHC class II α-helical region, both
towards its NH₂ and COOH-terminus, which makes the peptide binding
groove open at it both ends [Brown et al., 1993]. Peptides bind in an extended
conformation with their both ends projecting out of the groove, and thus,
longer peptides can be accommodated in the groove. This is consistent with
the length heterogeneity (12-24 amino acids) and the "ragged" end nature of
the naturally processed peptides, isolated from MHC class II molecules
[Rudensky et al., 1991, Chicz et al., 1992]. Clustering of the polymorphic
residues within the peptide binding groove, suggest the basis on which
different MHC class II alleles bind to different set of peptides.
T cell receptor (TCR) interaction with MHC-peptide complex:

The TCR contains a Ti α/β or γ/δ heterodimer, which recognises the MHC-peptide complex. The Ti subunits are transported to the surface, in association with five invariant chains, although the precise stoichiometry of these chains in the whole TCR complex is uncertain [Blumberg et al., 1990]. These are the CD3 complex and a dimer of ζ-ζ or ζ-η [Baniyash et al., 1988]. The CD3 complex is made of a heterodimer of ε-γ and ε-δ noncovalently linked transmembrane proteins [Alarcon et al., 1991 and Manolios et al., 1991].

T cell antigenic receptor (TCR) has a dual-combined specificity for the antigenic peptides bound to major histocomptability molecules (MHC-peptide) [Yague et al., 1985; Dembic et al., 1986; Saito et al., 1987] on the surface of antigen presenting cells (APCs). Diversity in TCRs is generated through a similar mechanism as that responsible generation of diversity in immunoglobulins. There are three variable loops, CDR1, CDR2 and CDR3. There is less variation in CDR1 and CDR2 while CDR3 is a hypervariable loop. The analysis of the crystal structure of the TCR complex with MHC class I-peptide complex reveals a general mechanism of interactions between TCR and MHC [Garboczi et al., 1996; Garcia et al., 1996]. The TCR interacts with MHC-peptide complex by its variable loops, which lie on almost all the exposed peptide and a much larger area of MHC. The TCR interacting site is relatively flat except for a central pocket formed by convergence of CDR3 loops. The TCR fits diagonally across the MHC-peptide-binding site, thus making contact with peptide buried in the peptide binding groove. The diverse CDR3 region loops over the peptide residues (diverse) and the less variable CDR1 and CDR2 loop over the correspondingly less diverse MHC molecule. This is consistent with the inherent bias of TCRs for self MHC.
and, it helps us to explain how one MHC-peptide complex positively selects a vast repertoire of TCRs.

**Ligand generation for MHC class I:**

The newly synthesized MHC class I heavy chain is inserted to endoplasmic reticulum (ER) cotranslationally, and it hardly gets any chance to assemble and bind to peptides and β2-M in the cytosol. Thus MHC class I molecule assembles and binds to the β2-M and peptides present in the ER lumen [Townsend et al., 1989]. The chaperones IP90 [Hochstenbach et al., 1992] or p88/calenexin [Degan et al., 1991; Ahluwalia et al., 1992], associate with MHC class I heavy chain after its translocation into the ER lumen and retain the immaturesly folded heavy chain in ER lumen. It has been suggested that, the binding of the peptide and β2-M facilitates the release of class I heavy chain from these chaperones [Degan et al., 1992], and its further transport [Williams et al., 1989]. But in the absence of the β2-M, class I molecule can be expressed on the cell surface [Bix and Raulet 1992] and peptide specific CTL responses can be generated from β2-M deficient mice [Cook et al., 1995]

The ER lumen contains peptides from the cytosol and the signal sequences generated in the lumen itself [Huczko et al., 1993 and Henderson et al., 1992]. In the cytosol, proteins are degraded into smaller fragments and peptides by proteasome complexes: the 20S and 26S proteasomes. Peptide aldehyde inhibitors, which block the activity of both 20S and 26S proteasomes, inhibit presentation of peptide from cytosolic proteins in context of MHC class I molecule [Rock et al., 1994]. Two of the subunits of proteasome, LMP-2 and LMP-7, are coded by MHC region [Brown et al., 1991 and Ortiz-Navarrete et al., 1991] and their expression is IFN-γ inducible [Yang et al., 1992]. These subunits get incorporated into proteasomes by replacing
Review of Literature

their homologous subunits [Yang et al., 1992] and they alter the peptidase activity of proteasomes so that it favors the generation of peptides having an anchor residue for MHC class I molecules [Driscoll et al., 1993; Gaczynska et al., 1993]. Mice deficient in LMP7 show a reduced level of MHC class I expression on the surface, and inefficient presentation of many intracellular antigens [Fehling et al., 1994]. However, mutant cell lines lacking LMP2 and LMP7 can present peptides from some intracellular proteins [Momburg et al., 1992; Arnold et al., 1992; Yewdell et al., 1994].

Peptides generated in the cytosol after peptidase activity of proteasome are transported to ER lumen by ER membrane inserted transporters associated with antigen processing (TAP). TAP is a heterodimer and made of two subunits TAP-1 and TAP-2. TAP-1 and TAP-2 deficient cell lines express very low amounts of empty MHC class I on the surface [Rock et al., 1991]. These cell lines are also defective in presentation of peptides from intracellular antigens in context of MHC class I molecule [Attaya et al., 1992; Powis et al., 1991; Spies et al., 1992; Kelley et al., 1992]. At 37°C, peptide transport to microsomes are both TAP and ATP independent [Levy et al., 1991], while at 23°C, it is both TAP and ATP dependent [Shepherd et al., 1993]. TAP-1 and TAP-2 are coded by genes located in MHC locus [Cerundolo et al., 1990]. TAP proteins are polymorphic [Momburg et al., 1994; Neefjes et al., 1993; Heemels et al., 1993]. This affects the quality of peptides transported through them into ER lumen. It has been shown that, before binding to the peptide, MHC class I-β2-M complexes interact with TAP in the ER lumen [Ortman et al., 1994]. However, the infection of TAP deficient cell lines with Sendai virus or Vesicular Somatitis viruses, leads to their presentation on MHC class I molecule [Zhou et al., 1993a and 1993b]. However, exogenous antigens can also be processed in endocytic compartments for presentation in context of MHC class I [Rock et al., 1996; Harding et al., 1994]. Only a few
antigen presenting cells have this capability to present exogenous antigens in the context of MHC class I [Rock et al., 1996; Reise et al., 1995].

**Ligand generation for MHC class II:**

In the ER lumen, MHC class II molecule associates with a type II transmembrane glycoprotein; the invariant chain (Ii), which inhibits peptide binding to MHC class II [Roche et al., 1990]. Shortly after synthesis, MHC class II molecule assembles into Ii-containing oligomers in association with calnexin [Anderson et al., 1994]. The release of the calnexin coincides with the formation of (αβ)3Ii3 complexes that are unable to bind to the peptides [Anderson et al., 1994; Cresswell et al., 1994]. The (αβ)3Ii3 complexes are directed to trans-golgi network en route to the cell surface, and subsequently localize to the endocytic compartments. The cytoplasmic tail of Ii chain contains a signal that targets (αβ)3Ii3 to the endocytic compartments [Lotteau et al., 1990; Bakke et al., 1990]. In the endocytic compartments, a pH dependent sequential proteolysis of Ii chain occurs. Pulse chase studies show that a nested set of MHC class II-associated Ii chain peptides (CLIP), spanning the residue 81-140 of Ii, is the final product of Ii degradation. Like intact Ii, CLIP also inhibits peptide binding to MHC class II molecules. HLA-DM mediates rapid dissociation of CLIP from MHC class II molecules at endosomal pH, in a dose dependent manner [Denzin et al., 1995]. HLA-DM or H-2M are relatively non-polymorphic, MHC encoded heterodimeric glycoproteins, with a weak similarity to MHC class II molecule [Denzin et al., 1995]. Removal of CLIP from MHC class II molecules facilitate the peptide binding to MHC class II molecules. HLA-DM also catalyzes the removal of some peptides from MHC class II molecules [Sloan et al., 1995]. Mutant cell lines lacking the HLA-DM express majority of MHC class II bound with CLIP on their surface, resulting in a defective presentation of exogenous antigens.
and certain alloantigens to T cells [Sette et al., 1992; Riberdy et al., 1992]. Data suggests the final Ii cleavage, CLIP release and peptide loading occur in the same compartment [Amigorena et al., 1995; Xu et al., 1995]. The endosomal/prelysosomal compartments, where peptide loading occurs, are called as MIIC or CIIV or CPL [Tulp et al., 1994; West et al., 1994]. However, HLA-DM molecules and MHC class II-peptide complexes are broadly distributed throughout the endocytic compartment. This compartment differs in composition and characteristics in various cell types [Castellino et al., 1995; Mellman et al., 1995; Wolf et al., 1995]. Proteins present in the endocytic compartment (exogenously internalized antigen and cell surface proteins) are degraded into shorter fragments, peptides which binds to MHC class II molecules. This degradation is blocked by treatment of APCs with lysosomotropic agents as ammonium chloride, chloroquine, which raise pH of endocytic vesicles [Ziegler et al., 1981; Unanue et al., 1983]. Ii chain-negative cells also express MHC class II molecules at lower level on their surface and many of those are SDS unstable at room temperature [Viville et al., 1993].

The availability of different putative peptides to bind MHC class II molecules depends upon many factors such as, 1) mode of antigen entry into endocytic compartments (fluid-phase versus receptor-mediated uptake), 2) the ability of different receptors to deliver the antigen to MHC class II containing compartments and to modulate fragmentation of bound antigen in receptor mediated delivery, 3) the location of proteolytic sites in relation to T cell epitopes within the antigen [Lanzavecchia 1995]. Peptide loaded MHC class II molecules are transported to the cell surface. The cell surface MHC class II molecules recycle back into endocytic compartments and can acquire new peptides [Pinet et al., 1995] a process not involving Ii or HLA-DM/H-2M.
Ligand generation for nonclassical MHC:

Detailed knowledge about the biology of nonclassical MHC molecules is limited. Antigen presentation by some of them is known. Data support that they have unique functions. H-2M3 is specialized in presenting N-terminal methionine formylated peptides, a characteristic of prokaryotic and mitochondrial protein synthesis [Loveland et al., 1990]. It has been shown that, H-2M3 presents such peptides from facultative intracellular bacteria such as *Listeria monocytogenes* to T cells [Pamer et al., 1992; Kurlander et al., 1992]. Indication that Qa-1 binds peptides, and presents them to T cells, had been suggested from the data that Qa-1b recognition by alloreactive T cells is affected by nonfunctional TAP [Attya et al., 1992] and that Qa-1b cell surface expression is reduced in TAP-mutant cells compared to the wild type cells. The addition of tryptic digest of *Mycobacterium bovis* 65 kDa heat shock protein [Hsp 65], increases the cell surface expression of Qa-1 [Imani et al., 1991]. The leader sequence from H-2D region, AMAPRTLL (amino acids represented by single letter code) is presented by Qa-1b, to the many of alloreactive T cell clones [Aldrich et al., 1994].

Qa-2 restricted allogenic T cell responses have been detected [Forman et al., 1979]. The ability of Qa-2 proteins to present antigen is strictly dependent on TAP [Stroynowski, 1996]. The naturally processed peptides, extracted from membrane bound Qa-2 from spleen or thymus, or from secreted Qa-2 made by melanoma cells are almost identical and very much similar to MHC class I molecule [Rotzschke et al., 1993]. These naturally processed peptides are nonamers, peptides with two dominant anchors; histidine at position at 7, and a hydrophobic amino acid at position 9. Studies [Joyce et al., 1994] suggest that the minimum size of peptide repertoire for Qa-2 is over 200, which is comparable to the MHC class I peptide repertoire, determined by the same technique. Antigen presentation by CD1 is quite interesting. It
Review of Literature

presents mycobacterial mycophenolic acid [Beckman et al., 1994],
lipoarabinomannan (LAM) and phosphatidylinositolmannan (PIM) [Seiling
P et al., 1995] to T cells. Three MHC-encoded class I like molecules: HLA-E,
HLA-F and HLA-G have been reported in humans. HLA-G is expressed
highly in the fetal cytotrophoblast and chorionic membranes. It has been
postulated that it plays an important role in maternal-fetal immune
interactions [Schmidt et al., 1993].

Some non classical MHC molecules have the same peptide loading
pathway, as MHC class I molecules, others have more similarity with MHC
class II than class I, while some others still display features of both class I and
class II molecules. The binding of Qa-1 to Qdm epitope, which is leader
sequence for ER targeting is TAP dependent. The binding of some epitopes
of Qa-1 is TAP dependent, while for others, it is TAP independent [Aldrich et
el 1994]. Qa-1 has been shown to present antigens to γδ T cells [Vidovic et al.,
1989]. The deletion of CD4+Vβ8+ T cells in response to Staphylococcus
enterotoxin B (SEB), is dependent upon CD8+ T cells, and this deletion can
be blocked by anti-Qa-1 antiserum [Jiang et al., 1995].

The epitope loading pathway for CD1 involves the endocytic
compartments and this is true even for lipid epitopes [Sieling et al., 1995].
The trafficking of CD1b shows that it appears in MHC class II containing
compartments. However, the epitope loading to CD1 is both TAP and HLA-
DM independent [Cardell et al., 1995; Porcelli 1995]. CD1 has been shown to
present antigens to a wide variety of T cells, such as NK 1.1+ T cells, γδ T
cells, CD4-8- αβ T cells, CD8+ T cells in human intestinal mucosa, as well as a
variety of CD4+ T cells in MHC class II knock-out mice [Blumberg et al.,
1996].
**Immunogenicity for T cells:**

Most sustained adoptive immune responses involve the activation of antigen specific T lymphocytes. A successful initiation of T cell response requires two signals from APC: the first is antigen specific and mediated by the MHC-peptide complex, and is recognized by the T cell receptor (TCR), and the second non-specific signal is delivered from APCs (costimulatory signal). Immunogenicity requires that both of these signals should be delivered appropriately. The delivery of the costimulatory signal/s, determines the consequence of TCR engagement [Lafferty et al., 1983; Mueller et al., 1989]. Immunization with many antigens in saline/PBS leads to functional inactivation of antigen specific T cells [Bursein et al., 1993; Hoyne et al., 1993] or elicits a very poor response. Therefore, adjuvants are used to enhance the immunogenicity of the antigens [Claassen et al., 1992]. An alternative approach is to replace the adjuvants, by use of molecules (such as IL-1) which can directly or indirectly increase the costimulatory signals delivered to the T cells [Collins et al., 1991; Rao et al., 1990]. Surface molecules involved in delivering costimulatory signals are expressed differentially on different APC populations [Liu et al., 1992 and Steinman 1991]. The main costimulatory molecules expressed on the APCs are CD40, CD80, CD86, CD54, CD102, CD106 and CD58 [Banchereau et al., 1994, Liu et al., 1992, Steinman et al., 1991]. The most important of these are CD40, CD80 and CD86. The blocking of the interaction between CD80 and CD86 with their ligand CD28 and CTLA-4 on T cells leads to inhibition of T cell responses both *in vivo* [Harding et al., 1992:] and *in vitro* [Liu et al., 1992]. CD40 or CD40 ligand deficient mice have abolished T cell-dependent humoral responses, and are more susceptible to *Leishmania* [Grewal et al., 1995; Campbell et al., 1996; Kamanka et al., 1996; Soomg et al., 1996].
Antigen presentation by naive B cells can turn T cells off [Eynon et al., 1992, Ephraim et al., 1992]. Denis et al., (1993) have shown that targeting of antigen to B cells leads to the generation of antigen-specific antibody response. In contrast, dendritic cells have been shown to be necessary for priming of T cells in vivo [Inaba et al., 1990; Levin et al., 1993]. Targeting of the antigen to APCs through a bispecific antibody, which recognises the antigen with one arm, and MHC class II on the APCs with other arm, has yielded a specific antibody response in vivo [Snider, 1992]. The role of macrophages in priming of T cells is controversial. Miyazaki et al., (1993) have shown that macrophages tolerize the T cells, while the studies done by Unanue et al., (1987) suggests a role of macrophages in priming of the T cells. Data from other groups suggest that an antibody response to a T cell dependent antigen can be generated in mice lacking the expression of relevant MHC class II on the B cells [Van-Ewijk et al., 1987]. The targeting of the antigen to macrophages has been extended to in vivo situations, but the readout is the production of antigen specific antibodies [Chu et al., 1994], which is an indirect assay to measure T cell priming.

T cell effector pathways:

After activation T cells manifest their effects in two ways; either by killing the APCs or helping them. Cytotoxic 'killer' T cells kill those target cells which display the relevant MHC-peptide complex on the cell surface. Helper T cells either help B cells produce antibody, or activate other APCs such as macrophages to kill intracellular pathogens more efficiently. Based on the cytokines they secrete, helper T cells fall in two categories; the 'type-1' and 'type-2' T cells [Kim et al., 1985; Cherwinski et al., 1987]. The type-1 T cells secrete IFN-γ and TNF-β and contribute to the generation of inflammation [Cher et al., 1987]. Type-2 T cells make IL-4, IL-5 and IL-10 and
help B cells in generating the IgE and IgG1 isotype of antibodies [Cherwinski et al., 1987; Stevens et al., 1988]. IL-4 preferentially induces the switching to IgG1 and IgE [Gauchat et al., 1990; Esser 1989]. IFN-γ has been shown to increase the frequencies of precursors secreting IgG2a isotypes in bacterial lipopolysaccharide stimulated B cells [Snapper et al., 1988]. Type-2 T cells also help in activation of eosinophils and mast cells. Type-1 and type-2 cytokine secretion patterns are applicable not only to MHC class II-restricted 'helper' CD4 T cells, where they are more commonly called as Th1 and Th2, but also to MHC class I restricted 'cytotoxic' CD8 T cells (where they are called Tc1 and Tc2) and even to γδ T cells [Carter et al., 1996].

Type-1 and type-2 T cell responses have been differentially implicated to play important roles in many autoimmune diseases and infections [Carter et al., 1996]. Type-1 T cell responses would have a beneficial role in clearing intracellular pathogens (such as Leishmania, Mycobacteria and viruses) and in allergic conditions, while type-2 T cell responses have detrimental effect in these conditions. However, the reverse is likely to be true in arthritis, autoimmunity and helminthic infections [Carter et al., 1996].

The factors governing T cell differentiation into the type-1 or type-2 phenotype are therefore of much interest. Kamogawa et al., (1993) have shown that effector T cells producing either IL-4 or IFN-γ have a common precursor, which expresses IL-4. The question, is how does the same precursor differentiate into two different mutually exclusive phenotypes? Experimental data support the view that these two types of T cell responses inhibit each other [Seder et al., 1994]. Thus, IL-4 inhibits priming for IFN-γ production and vice versa. The initial production of IL-12 or IL-4 during an immune response leads to priming for type-1 or type-2 phenotypes respectively [Afonoso et al., 1994; Hsieh et al., 1993; Swain et al., 1990]. So what are the sources of these cytokines? It has been suggested that initially macrophages, dendritic cells and natural killer cells produce IL-12 in

Review of Literature
response to bacterial stimulation [Hsieh et al., 1993; Macatonia et al., 1995; Wherry et al., 1991]. IL-12 gene disrupted mice are defective in generating type-1 T cell responses [Magram et al., 1996]. IL-4 may be produced from either non CD4 T cells [Sabin et al., 1995] or NK1.1 T cells [Yoshimoto et al., 1995]. Mice lacking CD1.1 (a ligand for NK1.1 T cells) have diminished NK1.1 T cells and spleen cells from these mice are defective in producing IL-4 in response to CD3ε stimulation [Mendiratta et al., 1997]. Apart from the differential production of cytokines which favor either type-1 or type-2 T cell responses, it has been shown that different APCs can stimulate type-1 T cell clones better, while others stimulate type-2 T cell clones better. Macrophages have been shown to stimulate Th-1 T cell clones better than B cells, while the reverse is true for Th-2 T cell clones [Gajewski et al., 1991]. Antigen presentation through dendritic cells favors synthesis of IgG2a and IgG1 (type-1 response) isotype of antibody as compared to antigen presentation by macrophages leads to generation of IgG1 and IgE isotype of antibody [Becker et al., 1994]. Experiments done with TCRαβ transgenic T cells in vitro suggest that both macrophages and dendritic cells are capable of directing T cells towards type-1 phenotype [Hsieh et al., 1993; Macatonia et al., 1995]. However, in the later study the capability of macrophages or dendritic cells to help in development of type-1 phenotype for T cells is dependent on addition of heat killed Listeria monocytogens or anti-IL4 respectively. Antigen presentation by naive B cells has been shown to tolerize T cells [Eynon et al., 1992; Ephraim et al., 1992]. Recently Stockinger et al., 1996, have shown that the involvement of B cells in antigen presentation during T cell priming, lead to a type-2 phenotype as compared to involvement of dendritic cell and macrophages. IL-10 is a strong suppressor of priming of type-1 T cells [Seder et al., 1994]. B cells from Schistosoma mansoni infected mice produce IL-10 in response to oligosaccharide from the parasite egg, and this may explain the shift from type-1 to type-2 responses with egg deposition in
Review of Literature

Schistosomasis [Velupillai et al., 1994]. The role of IFN-\(\gamma\) and IFN-\(\alpha\) in triggering the type-1 or type-2 responses is controversial [Seder et al., 1994]. Using antigen specific T cells from TCR transgenic mice, Wenner et al., (1996) have shown that IFN-\(\gamma\) and/or IFN-\(\alpha\) alone cannot induce differentiation to type-1 T cell phenotype, but that IFN-\(\gamma\) augments the IL-12 induced type-1 phenotype development of naive T cells in vitro.

Apart from such secretory cytokine-mediated regulation, certain APC surface molecules have also been argued to affect the qualitative outcome of T cell priming. These are primarily; the first signal, namely the MHC-peptide complexes, and the costimulatory signals. It has been shown that costimulation through CD80 and CD86 stimulates equal production of IL-2 and IFN-\(\gamma\), but CD86 induces relatively higher production of IL-4, and this is more pronounced when naive T cells are used for the study [Freeman et al., 1995]. Treatment with anti-CD80 antibody decreases the incidence of experimental encephalomyelitis (EAE) in vivo with predominant generation of type-2 T cells, while treatment with anti-CD86 antibody increases the severity of disease, and the generation of type-1 T cells [Kuchroo et al., 1995].

A number of studies suggest that the number of relevant MHC-peptide complexes on the surface of APCs can modify the phenotype of effector T cells. Using a chemically modified Salmonella flagellin antigen, Parish and Liew (1972) showed that low and very high doses of antigen elicit a better delayed type hypersensitivity response, while an intermediate dose favored antibody production. Bretscher et al., (1992) were able to reverse the normal susceptibility of BALB/c mice to infection (associated with type-2 dominated T cell response) with L. major by initially injecting a small number of parasites, with development of type-1 T cell response. A peptide with a high affinity for MHC class II molecule generates a type-1 T cell response, whereas a mutant variant which binds weakly to MHC class II, generates a type-2
dominated response [Pfeiffer et al., 1995]. In the same study, higher dosages of low affinity mutant peptide evoked a type-1 response, clearly implicating a role for MHC-peptide density in qualitative priming of the T cells. The most importantly the type-1 and type-2 T cell responses are defined always in comparison with each other and so the similar pattern of cytokine can be defined as a type-1 or type-2 T cell response depending upon its comparison with a comparatively stronger type-2 or type-1 T cell response.

Scavenger Receptors and Macrophages:

Mature macrophages express acetyl low density lipoprotein (LDL) receptors that have a broad ligand-binding specificity, which are not present on precursor monocytes, and are called the macrophage scavenger receptors (SRs) [Brown and Goldstein 1983]. The scavenger receptor is a homotrimer of an N-glycosylated type II transmembrane polypeptide, with an approximate molecular weight of 220 kDa [Kodama et al., 1988]. Until recently, only two type of scavenger receptors were known, but now several new receptors have been reported, by their binding to acetylated LDL, or oxidized LDL [Pearson 1996]. Scavenger receptors have been classified into three classes; classes A, B and C.

Class A SRs are homotrimers, and are of three kinds, SR-AI, SR-AII and macrophage receptor with a collagenous structure (MARCO) [Kodama et al., 1990; Rohrer et al., 1990; Elomaa et al., 1995]. SR-AI and SR-AII are product of the same gene [Kodama et al., 1990; Rohrer et al., 1990]. They consist of six domains, including an extracellular α-helical coiled coil and a positively charged collagenous region. The SR-A1 has an additional C-terminal extracellular SR-cysteine rich domain. However, SR-A1 and SR-AII have identical ligand binding properties. It has been shown that the positively charged collagenous domain of SR and that of the complement component
C1q mediate similar binding specificities for polyanionic ligands [Acton et al., 1993] such as maleyl-BSA. SR-AI and/or SR-AII are primarily expressed on monocytes, peritoneal macrophages, and on most tissue macrophages. However, certain dendritic cells [Geng et al., 1995], some endothelial cells and smooth muscle cells in atherosclerosis lesions have been found to express SR-AI/SR-AII [Pearson 1996]. MARCO binds to acetylated LDL and bacteria. It is expressed on peritoneal macrophages and on a limited subset of tissue macrophages in the spleen and lymph nodes [Elomma et al., 1995]. Structurally, it is homologous to SR-AI, but its collagenous domain is much longer. SR-A has a broad ligand binding specificity, which includes acetylated and oxidized LDL, maleylated bovine serum albumin, certain polyribonucleotides as poly G and poly I [Brown and Goldstein, 1983], bacterial polysaccharides [Krieger 1992; Hampton et al., 1991], lipoteichoic acid of gram positive bacteria [Dunne et al., 1994] and some carbohydrates such as fucoidin, carrageenan or dextran sulfate [Krieger 1992].

Class B SRs include SR-B1 and CD36 (thrombospondin receptor) family of proteins. SR-B1 is expressed primarily on non-placental steroidogenic tissues and liver and it binds to high density lipoprotein (HDL) [Acton et al., 1996]. Class B SRs are expressed on monocytes, macrophages, B lymphocytes, capillary endothelial cells, platelets and adipocytes [Pearson 1996]. They bind to a wide variety of ligands, such as maleylated bovine serum albumin, acetylated and oxidized LDL, Plasmodium falciparum infected red blood cells, and negatively charged phospholipids [Pearson 1996]. Structurally, class-B SRs are not homologous to Class-A SRs, but they have similar binding properties. A third type of scavenger receptor, class-C (Drosophila scavenger receptor, dSR-CI) has been reported, which is expressed by Drosophila embryonic hemocytes [Abrams et al., 1992]. It exhibits high affinity binding to a broad array of polyanionic ligands, [Pearson 1996] but also binds to β-glucans unlike the SR-AI and SR-AII. CD32 (IgG Fc receptor; FcγRII) and
Review of Literature

CD68 have also been shown to bind oxidized LDL [Stanton et al., 1992; Ramprasad et al., 1995].

Many roles for the scavenger receptors have been implicated in the physiological conditions. They bind to bacterial components like lipid A, lipoteichoic acid, and to intact bacteria, thus helping in uptake and clearance of bacteria or toxic components (such as lipid A) from the system [Hampton et al., 1991; Elomma 1995]. SRs also mediate the adhesion of macrophages to lymphoid tissue sections [Hughes et al., 1995], which may be responsible for homing of macrophages to these organs. Activated platelets secrete thrombospondin, and express phosphatidylserine on surface, both of which are ligands for SRs [Pearson 1996]. This will mediate adhesion/or recognition, and subsequent clearance of debris at wounded sites, by macrophages. Scavenger receptors have also been implicated in clearance of apoptotic cells. It has been shown that binding and/or uptake of oxidized red blood cells, or apoptotic cells by peritoneal macrophages are mediated by SR [Sambrano et al., 1995]. Anti SR-AI/II monoclonal antibody inhibits 50% of apoptotic thymocyte uptake, by thymic macrophages and elicited macrophages [Pearson 1995]. Thymic macrophages from SR-AI/II deficient mice also exhibit 50% reduction in uptake of apoptotic cells [Pearson 1996]. CD36 is involved in binding of P. falciparum infected red blood cells to the macrophages. Maleylated bovine serum albumin coupled with cytotoxic drugs have been used for specific drug delivery to macrophages in various neoplasms and pathogenic infections [Mukhopadhyay et al., 1989 and 1992].