Allergy and Immunology Review Corner: Chapter 10 of *Middleton's Allergy Principles and Practice*, 7th Edition, edited by N. Franklin Adkinson, et al.

Chapter 10: Cytokines in Allergic Inflammation – Pages 165-179

Prepared by John Seyerle, MD, Ohio State University, and Christopher Martin, MD, Walter Reed Army Medical Center

1. TNF assists egress of granulocytes into sites of inflammation by what mechanism?
A. Inducing an IL-4 chemokine gradient that mononuclear cells traffic to.
B. Inducing endothelial cells to present ICAM-1, VCAM-1, and E-selectin.
C. Accelerating lipid breakdown locally which attracts macrophages.
D. Up-regulating GM-CSF production increasing leukocyte counts.

2. The most potent inducer of hepatic acute-phase reactants, this cytokine is also the major determinant of differentiation for Th17 lymphocytes?
A. IL-1
B. IL-6
C. IL-10
D. IL-12

3. Production of what cytokine by Th2 lymphocytes renders them refractory to the anti-inflammatory effects of corticosteroids?
A. IL-1
B. IL-2
C. IL-4
D. IL-5

4. The primary T cell source for IL-10 is?
A. Activated Th1 cells
B. Naïve Th0 cells
C. Effector T memory cells
D. T regs

5. Cytokines common to both Th1 and Th2 cells include?
A. GM-CSF, IL-2, and TNF-α
B. IL-2, IL-3, and IL-5
C. GM-CSF, IL-2, and TNF-β
D. GM-CSF, IL-9, and TNF-β

6. What is the most important source of IFN-α?
A. Plasmacytoid DC
B. Epithelial cells
C. Treg cells
D. eosinophils

7. What cytokine triggers B-cell isotype switching to promote the production of IgA?
A. IL-4
B. TGF-β
C. IL-10
D. IL-17

8. IL-12 interacts with naïve T helper lymphocytes to activate what protein to express Tbet for Th1 differentiation?
A. IL-2
B. STAT-1
C. STAT-4
D. GATA-3

9. Which of the following cytokines promotes a Th1 response?
A. IL-19
B. IL-25
C. IL-27
D. IL-33

10. IL-19 is primarily produced by what cells?
A. Mononuclear phagocytic cells
B. Eosinophils
C. Th2 cells
D. Activated mast cells

Answers

1. B, pages 166-167
Additionally, TNF induces vascular leakage, activates neutrophils, has negative inotropic effects and is a mediator of shock.

2. B, page 167
The most important source of IL-6 is mononuclear phagocytes, but production also occurs in T and B cells, fibroblasts, endothelial cells, keratinocytes, hepatocytes, and bone marrow cells.

3. C, page 170
IL-4 is also important in maintaining the allergic response by preventing apoptosis of T lymphocytes. Additionally, it leads to increased expression of MHC molecules and CD23 on macrophages, as well as down-regulating antibody-dependent cellular cytotoxicity, inhibiting expression of Fcγ receptors, and inhibiting monocyte differentiation into macrophages.

4. D, page 172
IL-10 inhibits various cytokines and expression in Th1, Th2, mononuclear phagocytes, and NK cells.

5. A, page 173
In humans, Th1 helpers make IFN-γ and TNF-β, Th2 cells make IL-4, IL-5, IL-9, IL-13, and IL-25. Both can make GM-CSF, TNF-α, IL-2, IL-3, and IL-10.

6. A, page 168
The most important source of IFN-α is plasmacytoid DC (pDC), reflecting their activation by viral RNA acting through TLR7 or immunostimulatory bacterial DNA acting through TLR9

7. B, page 168
Cytokines that trigger isotype switching include IL-4 and IL-13, which induces the IgE isotype, TGF-β, which triggers IgA, and IL-10, which contributes to the generation of IgG4

8. C, page 173
IL-12 interacts with naive T helper lymphocytes to activate STAT4, leading to expression of T-bet. T-bet is a nuclear transcription factor that is the master regulator responsible for the differentiation of Th1 cells.

9. C, page 173
IL-27 activates stat4 leading to increased expression of T-bet and IFN-γ. IFN-γ then increases expression of T-bet by increasing expression of stat1; negative regulator of Th17 and Th2 differentiation. IL-19, IL-25, and IL-33 promote differentiation and survival of Th2-like cells

10. A, page 176
IL-19, a member of the IL-10 family, is primarily produced by mononuclear phagocytic cells and its expression is upregulated by IL-4 and downregulated by IFN-γ. Reflecting these contrasting influences of IL-4 and IFN-γ, IL-19 promotes Th2 immune deviation and in the presence of IL-19, increased IL-4 and fewer IFN-γ producing cells are observed

Allergy and Immunology Review Corner: Chapter 11 of *Middleton's Allergy Principles and Practice*, 7th Edition, edited by N. Franklin Adkinson, et al.

Chapter 11: Chemokines in Cell Movement and Allergic Inflammation (Pages 181-201)
Prepared by Martha Elias, MD, Mayo Clinic, & Christopher Martin, MD, Walter Reed Army Medical Center

1. While all chemokines are soluble chemoattractants, these two are initially membrane bound and also function as cell adhesion receptors.
A. IL-8 (CXCL8) & IP-10 (CXCL10)
B. MCP-1 (CCL2) & TARC (CCL17)
C. XCL1 & SCM-1β
D. CXCL16 & CX3CL1

2. Up-regulated in patients with atopic dermatitis and psoriasis, this chemokine is involved with lymphocyte homing to the skin.
A. CCL19
B. CCL21
C. CCL25
D. CCL27

3. Heterodimerization of CCR2 and CCR5 leads to?
A. Decreased sensitivity to ligands
B. Blocked cell adhesion
C. Resistance to Pertussis toxin
D. Increased chemotaxis

4. A decoy receptor which also acts as an entry receptor for certain malarial strains is?
A. D6
B. DARC
C. CCX-CKR
D. CXCR6

5. Clustering of LFA1 on lymphocytes and the resulting interaction with ICAM and arrest in the lymph nodes is primarily due to the presence of?
A. CCL21, CXCL12, & CXCL13
B. CCL2, CCL17, & CXCL16
C. CXCL12, CXCL13, & CXCL21
D. CCL5, CCL24, CXCL21

6. Which cytokine augments eosinophil degranulation in response to CCR3 ligands?
A. IL-4
B. IL-1
C. IL-5
D. IL-13

7. In atopic dermatitis, which cytokine produced by epithelial cells and keratinocytes activates $CD11c^{+}$ dendritic cells?
A. IL-5
B. IL-6
C. CXCL14
D. TSLP

8. CCR7 interacts with which chemokine to home naïve T cells to Peyer's patches?
A. CCL21
B. CCL25
C. CCL26
D. CCL5

9. A mutation in the coding region of which chemokine receptor results in protection

form HIV infection despite having a functional CXCR4?
A. CCR4
B. CCR5
C. CCR3
D. CCR7

10. Which chemokine receptor is mutated in WHIM syndrome?
A. CXCR3
B. CXCR4
C. CXCR5
D. CXCR6

Answers
1. D, page 181
CXCL16 & CX3CL1 when cleaved from the cell surface become soluble chemoattractants. CXCL16's receptor is CXCR6 while CX3CL1's receptor is CX3CR1 (p.184)

2. D, page 182
CCL25 brings lymphocytes to the GALT, while CCL19 & CCL21 draw lymphocytes to lymph nodes.

3. C, page 184
Heterodimerization leads to increased sensitivity of the receptor to ligand, recruits new signaling pathways, renders the receptor resistant to Pertussis toxin, and induces cell adhesion but not chemotaxis.

4. B, page 188
Duffy antigen receptor for chemokines was first recognized as a blood group antigen and binds many CC and CXC chemokines without signaling. D6 and CCX-CKR are also decoy receptors.

5. A, page 191
Arrest of lymphocytes on the endothelial surfaces of lymph nodes is mediated by LFA1-ICAM interactions, and is the result of chemokine (CCL21, CXCL12, CXCL13) interactions with receptors on the lymphocytes, resulting in clustering of LFA1.

6. C, page 194
IL-5 augments the degranulation seen in response to CCR3 ligands.

7. D, page 195
Epithelial cells and keratinocytes in the lesions of atopic dermatitis produce high levels of thymic stromal lymphoprotein (TSLP). TSLP activates $CD11c^{+}$ dendritic cells.

8. A, page 197
The homing of naïve T cells to Peyer's patches is mediated by the interaction between

CCR7 with CCL21 expressed on Peyer's patch high endothelial venules.

9. B, page 198
Individuals who lack a functional CCR5 due to a mutation in the coding region, the null CCR5δ32 allele, are protected from HIV infection despite having functional CXCR4.

10. B, page 199
The disease causing mutations in WHIM syndrome are in the carboxy terminus cytoplasmic tail of CXCR4 and result in prolonged responsiveness to CXCL12.