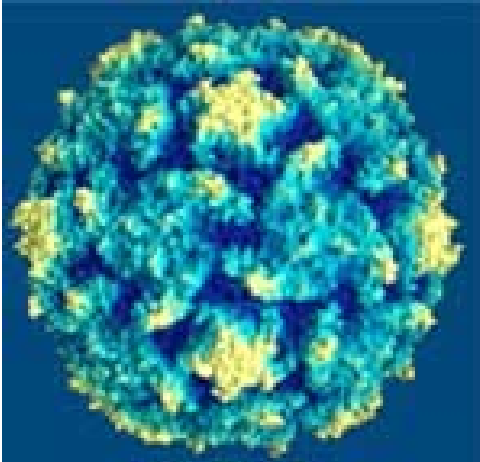


Introductory slides for Session 8

EPSTEIN-BARR VIRUS



Courtesy of NASA.

Source: "Space Flight-Induced Reactivation of Latent Epstein-Barr Virus (Epstein-Barr),"

http://spaceresearch.nasa.gov/research_projects/ros/eb.html

Epstein-Barr virus (EBV), is the herpesvirus that causes **infectious mononucleosis** and is associated with a number of cancers, particularly **lymphomas** in immunosuppressed persons, including persons with AIDS.

EBV is a ubiquitous virus, so common that it has been difficult to determine whether it is the cause of certain diseases or whether it is simply there as an artifact. In Third World nations, most children are infected with EBV; in most industrialized nations, about 50% of the people are infected. Research has found that all of the lymphomas associated with AIDS and most lymphomas in other immunocompromised persons are connected with latent EBV infection.

EBV has been found in biopsy tissue of patients with **Hodgkin's disease**, breast cancer, and some smooth muscle tumors. EBV also was formerly suspected as the cause of **chronic fatigue syndrome** (originally named chronic EBV syndrome).

EBNA1 is the only viral protein regularly detected in all EBV-associated malignancies as well as in healthy virus carriers.

It escapes the efficient major Histocompatibility complex (MHC) class I-restricted cytotoxic T lymphocyte (CTL)-mediated surveillance.

EBNA1 binds to four recognition sites in the origin of latent DNA replication of Epstein-Barr virus and activates latent-phase replication of the viral genomes.

Diagram removed due to copyright considerations.

See "Ebna1 nuclear protein" at

http://www.biochem.ucl.ac.uk/bsm/prot_dna/family_descriptions/1b3t_single/1b3t_single.html

Epithelium in contact with microbial flora

Systemic Immune Competence

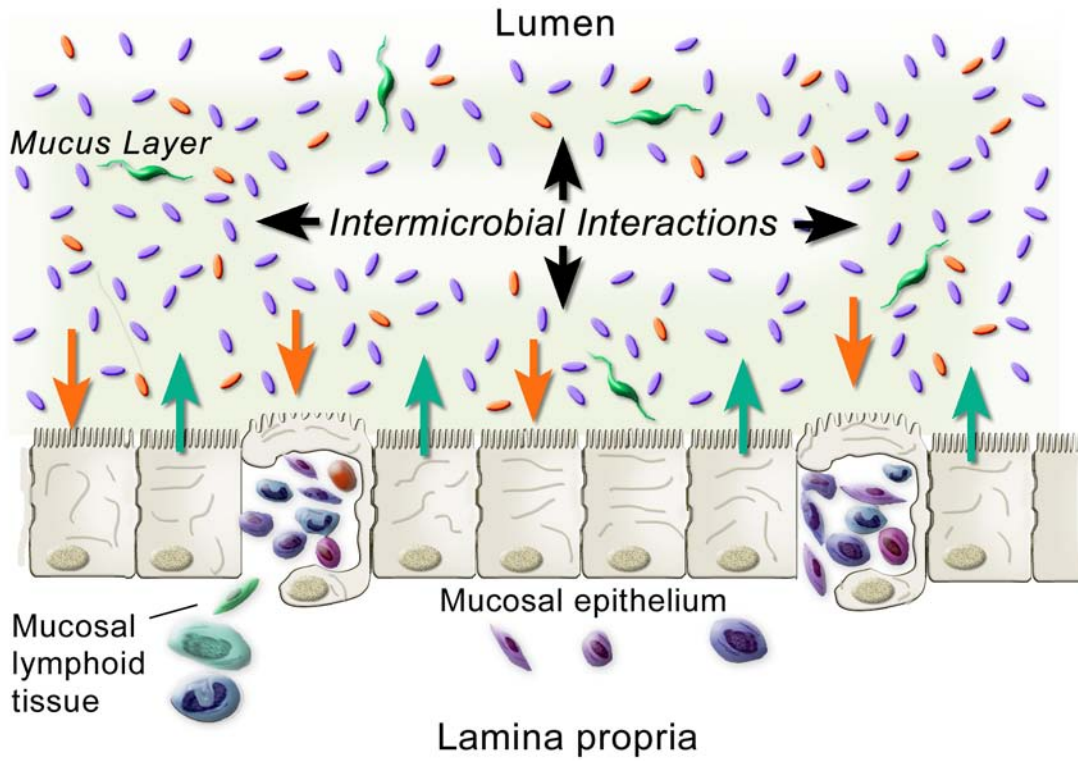
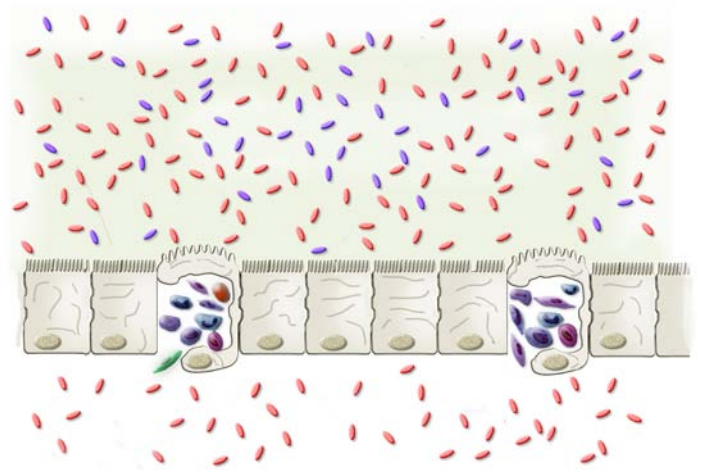


Figure by MIT OCW.

Opportunistic Infection

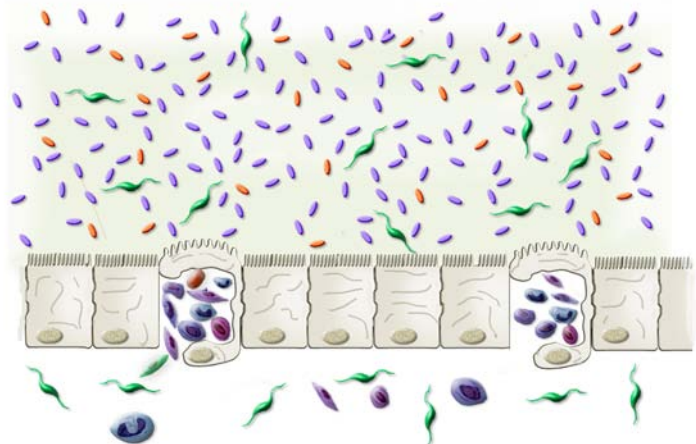


Normal Intestinal Ecosystem

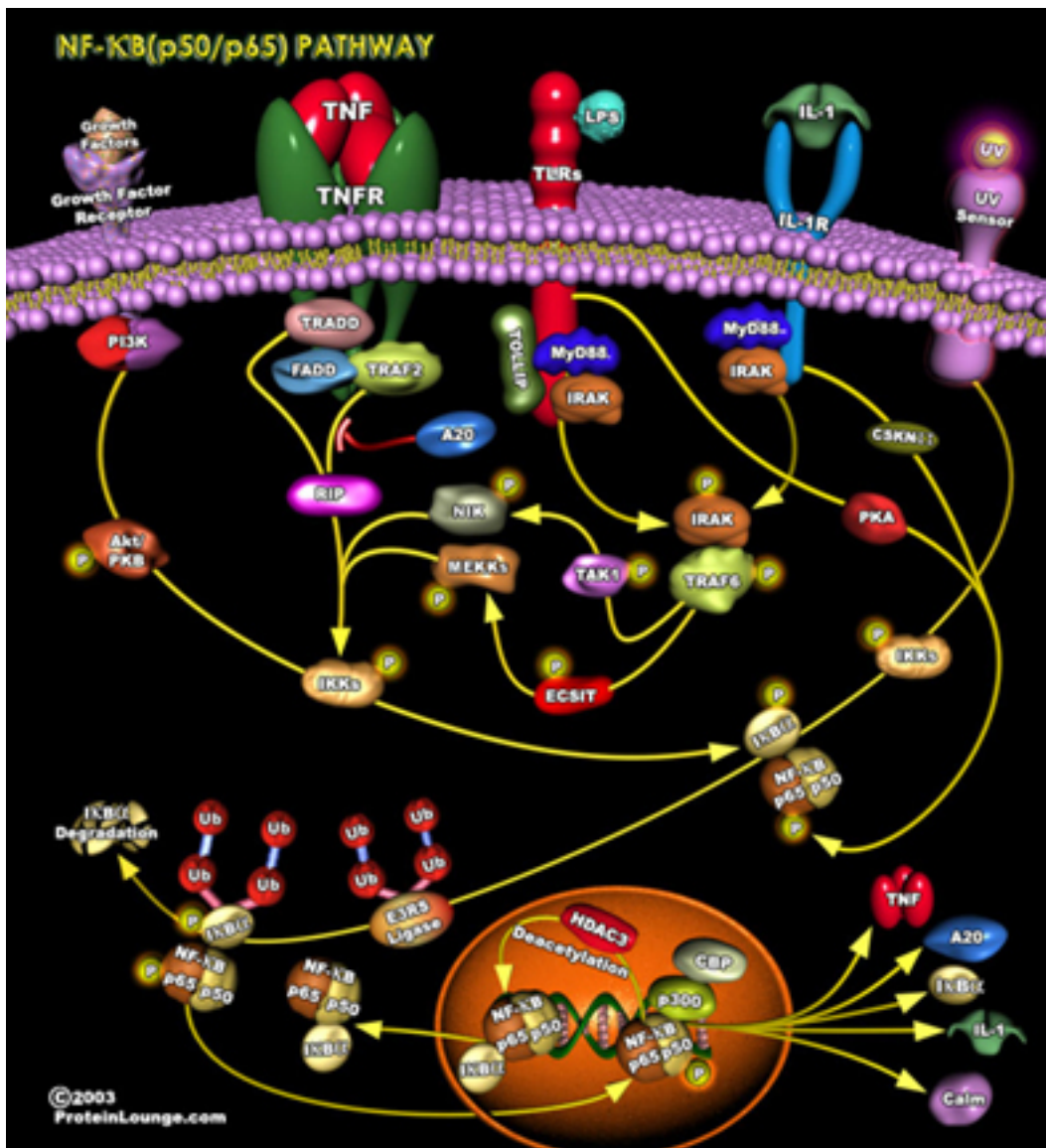


Figure by MIT OCW.

Infection with Overt Pathogen



Figures by MIT OCW.



Courtesy of The Protein Lounge (<http://www.proteinlounge.com>). Used with permission.

NF-kappaB transcription factors play an important role in the regulation of immune response, embryo and cell lineage development, cell apoptosis, inflammation, cell-cycle progression, oncogenesis, viral replication, and various autoimmune diseases.

The activation of NF-kappaB is thought to be part of a stress response as it is activated by a variety of stimuli that include growth factors, cytokines, lymphokines, UV, pharmacological agents, and other stresses. In its inactive form NF-kappaB is sequestered in the cytoplasm, bound by members of the IkappaB family of inhibitor proteins. The various stimuli that activate NF-kappaB cause phosphorylation of IkappaB, which is followed by its ubiquitination and subsequent degradation. IκB proteins are phosphorylated by a IkappaB kinase complex consisting of IKKalpha, IKKbeta, and IKKgamma. This phosphorylation results in the exposure of the nuclear localization signals (NLS) on the NF-kappaB subunits and the subsequent translocation of the molecule to the nucleus. In the nucleus, NF-kappaB binds with a consensus sequence (5' GGGACTTCC-3') of various genes, activating their transcription. A total of five NF-kappaB subunits that form dimers have been identified in mammalian cell; RelA (p65), p50, RelB, c-Rel, and p52. The most common and best characterized form of NF-kappaB is the p65-p50 heterodimer. Each dimer combination exhibits differences in DNA binding affinity and transactivation potential. TNF is one of the most potent physiological inducers of NF-kappaB, mediating inflammation, cellular immune response, and affects the functions of virtually every cell type. TNF has also been shown to protect several cell types against apoptosis, suggesting that NF-kappaB could participate in resistance to cancer treatment. IL-1 has similar downstream effects through NF-kappaB, including immunoregulation, proinflammatory, and hematopoietic activities. LPS (bacterial lipopolysaccharide) activates NF-kappaB through the Toll-Like receptors, and induces the transcription of various interleukins (e.g. IL-1) and cytokines (e.g. TNF) as a immune response against the bacteria.

Tumor Necrosis Factor-alpha (TNF- α) Receptors and the NF- κ B Pathway

Diagram removed due to copyright considerations.

See TNF- α /NF- κ B pathway diagram at <http://www.panomics.com/sr1000nfkb.html>.

TNF- α is made by macrophages and other cells of the immune system.

Receptors

Trimers of 3 identical cell-surface transmembrane proteins.

Ligands

- TNF- α (hence the name)
- Lymphotoxin (LT; also known as TNF- β)

Mechanisms

- NF- κ B resides in the cytosol bound to an **inhibitor** called I κ B.
- Binding of ligand to the receptor triggers phosphorylation of I κ B
- I κ B then becomes ubiquitinated and destroyed by proteasomes.
- This liberates NF- κ B so that it is now free to move into the nucleus where
- it acts as a transcription factor binding to the promoters and/or enhancers of more than 60 genes:
 - NF- κ B got its name from its discovery as a transcription factor bound to the enhancer of the kappa light chain antibody gene.
 - However, it also turns on the genes encoding IL-1 and other cytokines that promote inflammation. The monoclonal antibody **Infliximab** binds to TNF- α , and shows promise against some inflammatory diseases such as rheumatoid arthritis.
 - NF- κ B also turns on genes needed for cell proliferation, cell adhesion, and angiogenesis. In May 2003, the US FDA approved a proteasome inhibitor, called bortezomib (Velcade®) for treatment of multiple myeloma, a cancer of plasma cells (we will learn more about it in the Session 13.