8. Sensing and Signaling Danger

Pathogens

Toll like Receptors (TLRs) are molecular pattern sensing receptors. They recognize pathogen associated molecular patterns (PAMPs) such as dsRNA, CpG DNA, lipopolysaccharide (LPS), or proteolglycan (PGN).

Each TLR signals through a specific combination of adapters, which result in different combinations of transcription factors and specific activation dynamics.
Several Signaling networks and transcription are activated by these signaling adapter proteins. The main axes to remember are: IKK-NF-κB, MAPK/p38, ERK-ATF, JNK-AP-1, IKKe/i/TBK1-IRF3/7. These factors function combinatorially to regulate gene expression programs that are stimulus-specific.

Biological functions
- inflammation
- innate immunity
- initiate / signal to adaptive immunity
- death vs. survival

Pathogens interfere with signaling to:
- inhibit inflammation/immunity (parasites Toxo, yersinia, viruses)
- to kill cells (anthrax)
- to keep cells alive (intra-cellular parasites, viruses)

Genotoxic stress

DNA damage (in particular double stranded breaks, DSBs) is sensed by ATM/ATR via associated repair proteins, the toroidal Rad9-Rad1-Hus1 checkpoint complex (9-1-1). ATM/ATR phosphorylate many substrates; among them is p53 causing stabilization of this transcription factor and induction of cell cycle inhibitor proteins (e.g. p21). In addition NF-κB and JNK are activated.

Biological consequences:
- cell cycle arrest
- DNA repair
- apoptosis

We will discuss the current understanding of the regulatory circuitry that determines these:
- JNK as a pro-apoptotic pathway via regulation of cFLIP
- Activation of the anti-apoptotic transcription factor NF-κB in response to DSBs
- how NF-κB may in fact have pro-apoptotic effects in response to UV irradiation
- the skewed circuitry of tumor cells