Check Points During Inflammation

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Inflammation

- Complex set of interactions among soluble factors & cells that can arise in any tissue in response to traumatic, infectious, post-ischaemic, toxic or autoimmune injury.
- This process normally leads to recovery from infection and to healing.
- Persistent inflammation can oxidize DNA badly enough to promote neoplastic transformation.

Such a complex system can be characterized by its checkpoints.

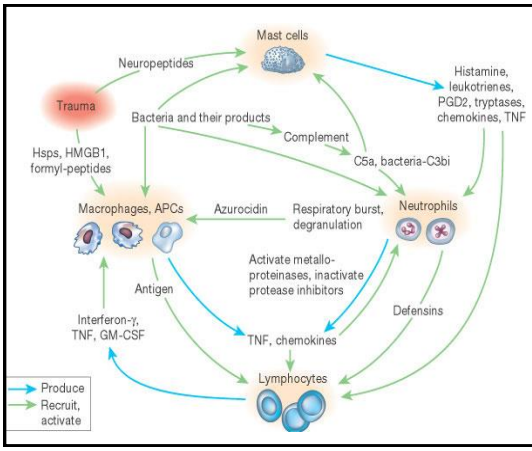
- Go signals in early checkpoints
- Stop signals in early checkpoints
- Signals for switching from killing to healing

- Inflammation may be considered in terms of its check-points,
- where binary or higher-order signals drive each commitment to escalate (be increased in extent)
- go signals trigger stop signals & molecules responsible for mediating the inflammatory response also suppress it, depending upon timing & context

Go signals in early checkpoints:

- Tissue damage (mild trauma with infection) release three types of go signals.
- **First**, in response to pain, neurons release bioactive peptides.
- **Second** , broken cells release intracellular proteins that trigger cytokines production when found in extracellular space.

- **Third**, microbes & their shed or secreted products are sensed through soluble receptors/molecules such as,
  - Complement
  - mannose-binding protein
  - lipopolysaccharide –binding protein
  - Cell surface receptors (Toll family members)
  - Peptidoglycan recognition proteins
  - Scavenger receptors



- The importance of **mast cells** (perivascular) as first responders release,
  - Histamine
  - Eicosanoids
  - Pre-formed TNF (tumor necrosis factors)
  - Newly synthesized cytokines
  - Tryptases
  - Proteases
  - Chemokines

- Histamine, Eicosanoid & Tryptases cause vasodilatation and extravasation.

Neutrophils are partially activated by the TNF & leukotrienes produced by mast cell leading to release of small amounts of elastase.
Binary signal of **integrin** (transmembrane receptors that are the bridges for cell-cell and cell-extracellular matrix (ECM) interactions) plus stimulation by TNF, chemokines or C5a triggers degranulation & a massive respiratory burst releases,

- Proteinases(cathepsin G & protease 3)
- Hydrolases
- Antibiotic proteins (BPIF, ɑ-defensins, serprocidins, their proteolytically inactive homologue & azurocidin)
- Oxidants (hydrogen peroxide, hypohalites & chloramines)

Stop signals in early checkpoints

- Neutrophil derived arachidonate serves as substrate for neutrophil 5-lipoxygenase to generate the inflammatory LB4.
- Neutrophils infiltrate tissue pass arachidonate to tissue cells expressing 15-lipoxygenase which produces lipoxins.
  - **Lipoxins** are a class of oxidized eicosanoids that bind cellular receptors & block neutrophil influx.
- In this manner, cell-cell interactions favors a transition in the profile of arachidonate products from pro-inflammatory leukotrienes to anti-inflammatory lipoxins.

- At the same time, COX2 (an enzyme responsible for inflammation and pain) is induced in macrophages by microbial products & cytokines.
  - COX2 converts arachidonate → PGE2
  - Fluid leaks from blood vessels.
  - PGE2 ↑ feedback to inhibit COX2 & lipoxygenase.
- **Delayed effects** shift arachidonate metabolism towards lipoxin formation in neutrophil, in this way over several hours, PGE2 at first a go signal becomes a stop signal.

- **CD39** (**C**luster of **D**ifferentiation **39**) is a human membrane-bound protein.
  - Break down extracellular ATP & ADP secreted by activated cells or leaking from broken cells generating adenosine.
  - **Adenosine** acts to suppress inflammatory responses by neighboring cells.

Signals for switching from killing to healing

- A crucial commitment made late in inflammation is to convert the response from the antibacterial, tissue damaging mode to a mode that promotes tissue repair & epithelial closure.
- The transformation from tissue damage to tissue repair begins as complement, neutrophils & macrophages kill microbes & secrete more **SLPI** (serine protease inhibitor).
- **SLPI** has anti-inflammatory & wound healing effects, binds & synergizes with pro-epithelin.

- **Pro-epithelin** is a cytokine that promote epithelial growth & suppress neutrophil activation,

  ROIs and **RNIs** (reactive nitrogen intermediadtes) are two additional sets of molecules that can either promote or suppress inflammation.