

Innate Immunity and the Paradoxes of Viral Pathogens and Tissue Injury in Gene Therapy

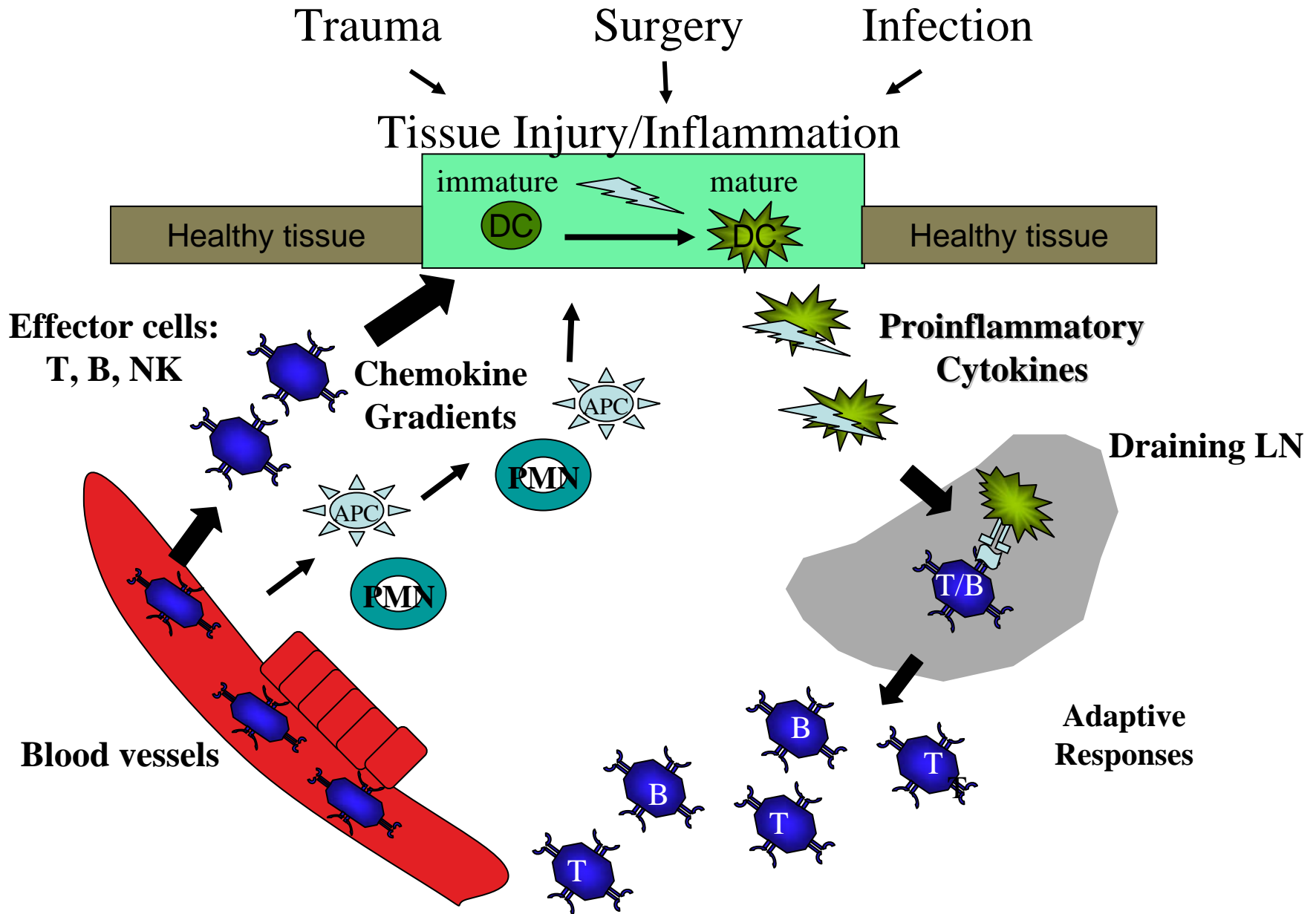
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Tissue and Cell Injury as a Paradigm for Gene Therapy

- Many gene delivery vectors are built on pathogen skeletons, some still with pathogen genes
- Many strategies for delivery of therapeutic gene cause direct tissue injury
 - Injection/Inhalations
 - Ex vivo cell separations and manipulations
- By nature, therapeutic gene delivery will often alter the state of the target cell and/or the host
- Changes in cell state (activation, metabolic stress, increased protein expression, promoter-driven signaling) may lead to “danger signals”

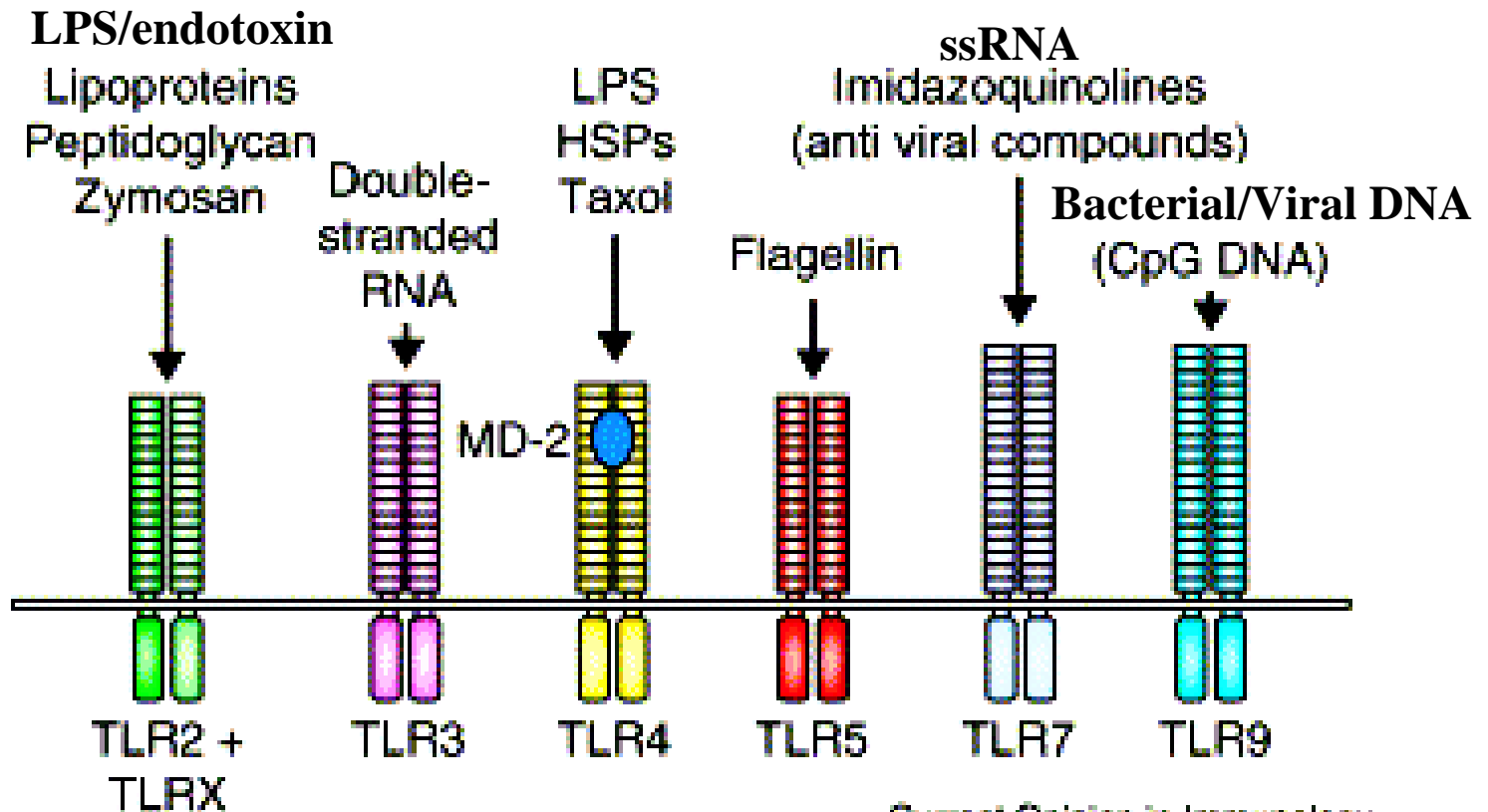
Immunity and Tissue Injury



Innate vs. Adaptive Immunity

- Innate immunity is the first line of response to acute injury and invasion
 - Primitive
 - Based on pattern recognition receptors
 - No memory
- Adaptive immunity represents a complex system that responds to specific antigens
 - Evolves
 - Determines Self vs. Non-self recognition
 - Memory

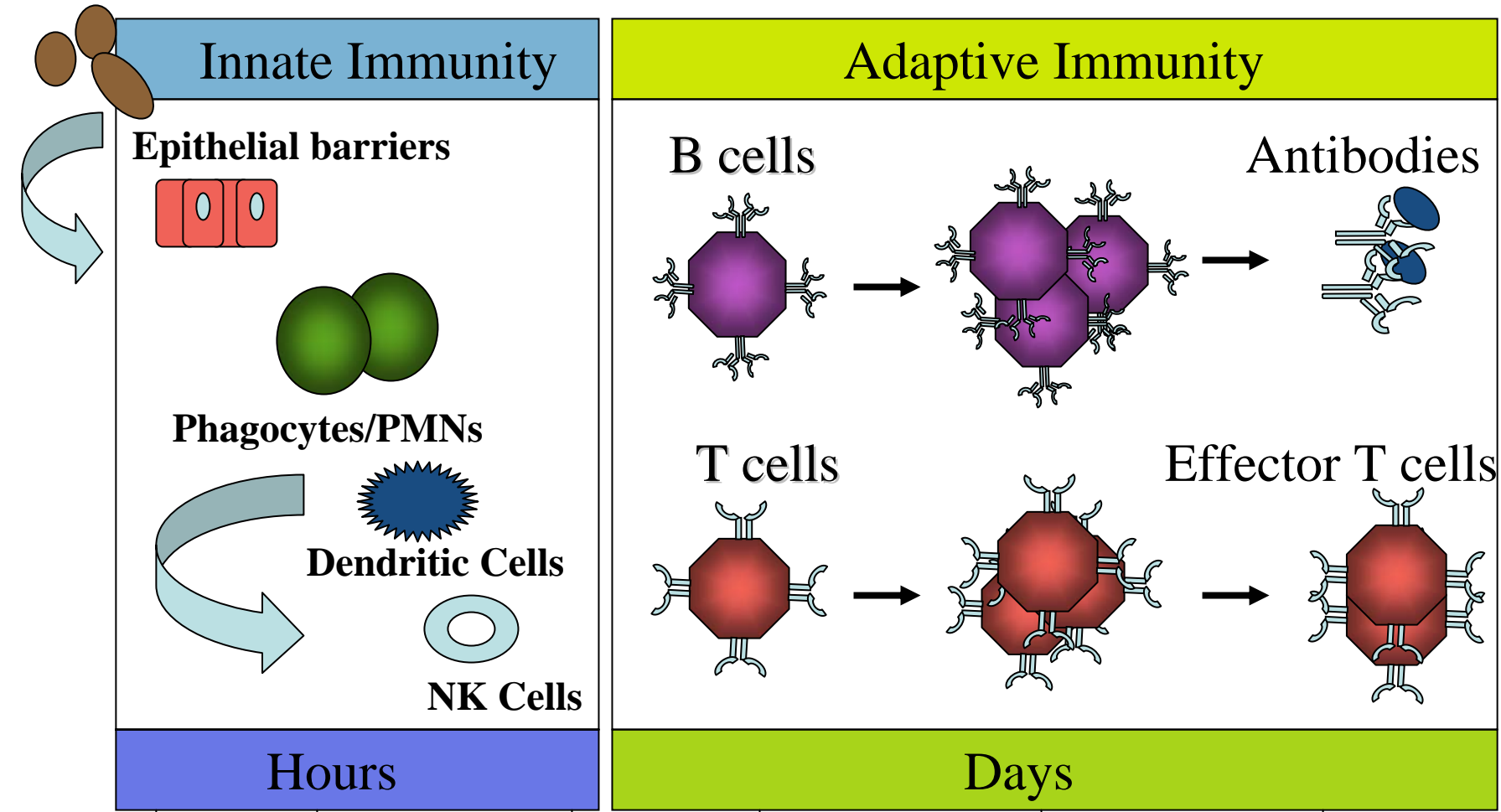
Toll-like receptors and their ligands



Innate Immune Receptors

- Toll-like Receptors 1-10
 - Endotoxin, dsRNA, ssRNA, CpG DNA, flagelin, mannose-alginate etc.
- CD14
 - Endotoxin, peptidoglycans
- CD36 + TLR2
 - Di-acyl lipopeptides and lipoteichoic acid
- DC-SIGN
- FMLP Receptor
- Dectin 1
- Scavenger Receptors
- Mannose Receptor

Pathogens/Cellular Injury

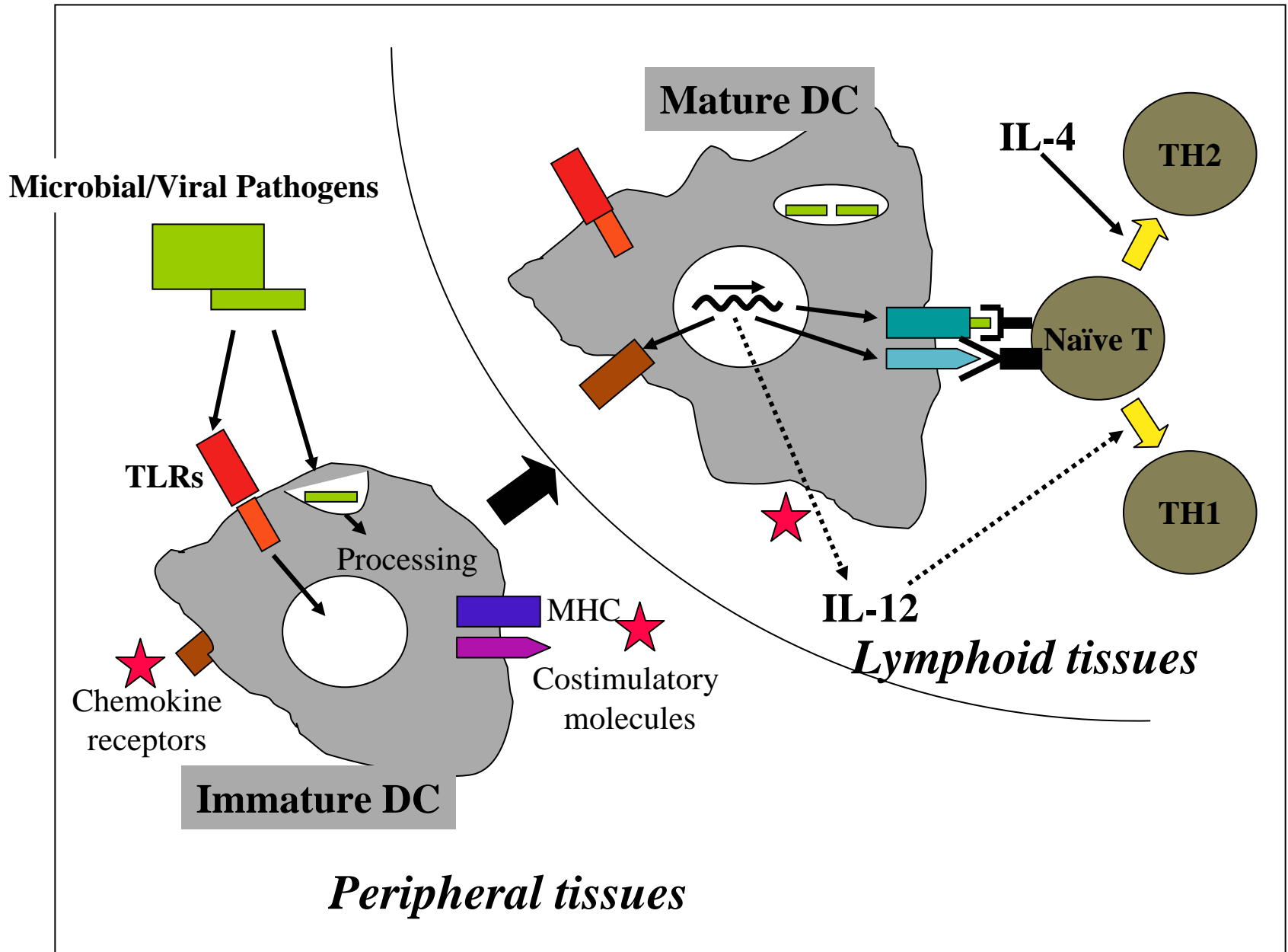


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1 3 5

Time after infection

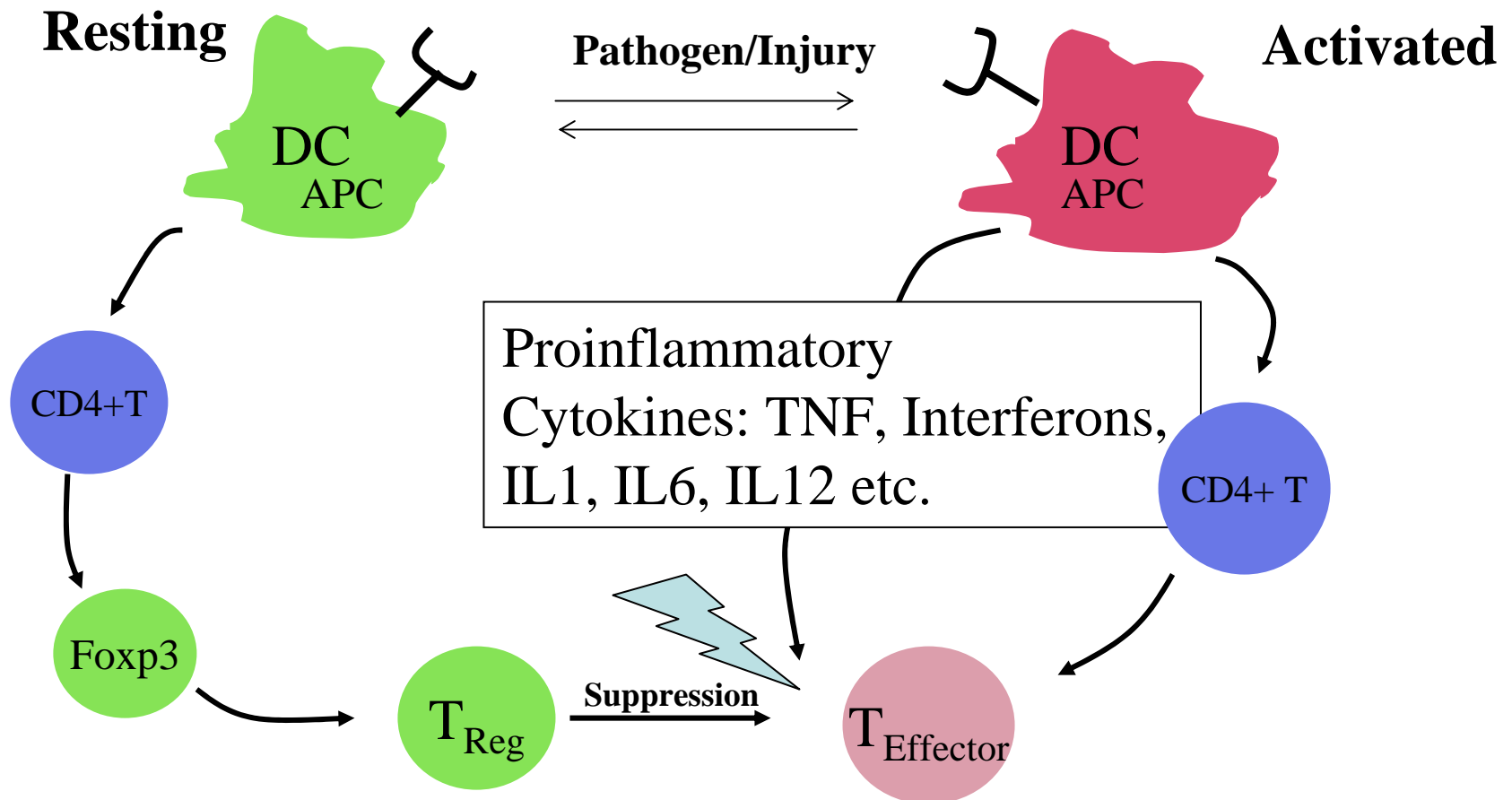
Link between innate and adaptive immunity



Innate Immunity is Good

- Activation of innate immunity in the context of therapeutic vaccines leads to enhanced adaptive immunity
 - Local
 - Systemic
- Bestowing a competitive advantage on gene modified cells could enhance selection of healthy over diseased cells

Link between innate immunity and immune regulation



Innate Immunity is Bad

- Any tissue injury created at a “transplant site” will trigger a cascade
- Viral proteins expressed by target cells are signals for destruction
- Significant alterations in cell state can target cells for destruction
- When innate immunity is triggered, adaptive immunity can follow

Directions Forward for Gene Therapy #1

- Basic research
 - The working “box” needs to be enlarged to include innate immunity
 - Much remains to be discovered about triggering and regulating innate immunity
 - Impact of different gene delivery strategies on tissue injury must be studied including dose
 - Impact of different gene delivery strategies on cell state must be studied
 - Different tissue compartments may have different rules
 - Innate immunity must be considered in new vector designs - not just viral genes but promoter selections
 - Potential of manipulating innate immune reactions must be studied - enhancing or inhibiting

Directions Forward for Gene Therapy #2

- Clinical Applications
 - Any strategy to limit tissue injury during gene delivery
 - Corticosteroids
 - Anti-inflammatory agents
 - Anti-cytokine antibodies (anti-TNF)
 - New generation of innate immune suppressors
 - For therapeutic vaccines, potential strategies to enhance dendritic cell activation (TLR agonists - imidazoquinolines, LPS equivalents, cytokines)
 - Expand the “box” for immune monitoring of clinical trials to include innate immune markers (cytokines, altered T or B cell activation, tissue injury)