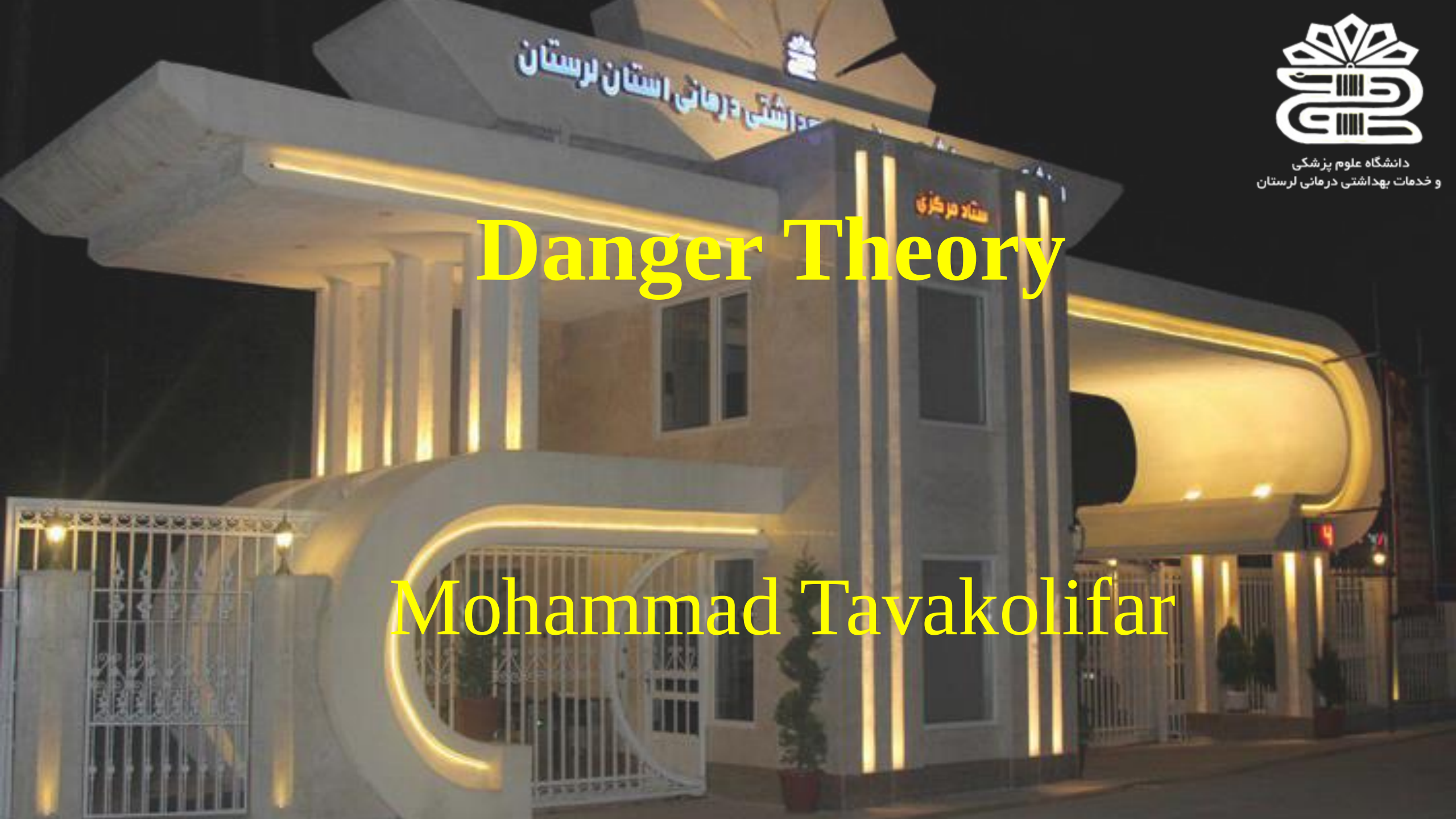

Danger Theory

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Outline

- History of the danger theory
- Explanation of the Danger Theory and the Concept of Danger
- Introduction to Damage Signals
- Critiques and Limitations of the Danger Theory

The self-non-self theory

- For 60 years, the dominant theory in immunology was the self–non-self theory.
- Immune response is triggered against all foreign entities.
- No immune response is triggered against the organism’s own constituents.

The emergence of the danger theory

- Matzinger suggested a rival theory, called the "danger theory".
- Like the Copernican Revolution.
- Immune responses are triggered by "danger signals," or "alarm signals," released by the body's own cells.

Criticisms of Danger Theory Theorists Towards the Self-Nonself Theory

- The central concept of “self” is ill-defined.
- 1) the sum of genome-encoded Ags.
- 2) the body
- 3)the total set of MHC/peptides
- 4) subset of MHC/peptides expressed on APCs

Criticisms of Danger Theory Theorists Towards the Self-Nonself Theory

- There are many exceptions. For instance, normal individuals produce Abs to self-Ags (such as DNA or keratin)
- why are B cells strongly activated by LPSs?
- Why is “complete” adjuvant, containing microbial products, required to elicit an immune response against soluble foreign Ags?

Infectious non-self theory

- Matzinger built upon Janeway's views.
- innate immune responses are triggered by "infectious nonself“.
- APCs recognize PAMPs.

The differences between the theories

- Janeway focused on the exogenous nature of the entities triggering immune responses.
- Matzinger asserts that immune responses are triggered by "endogenous cellular alarm signals from distressed or injured cells."

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The differences between the theories

Characterization of the entity			Theories		
Self/Non-self	**Danger**	**Pathogen associated molecular patterns (PAMPs)**	**Self–non-self theory**	**Infectious non-self theory**	**Danger theory**
Self	Not dangerous		No response	No response	No response
	Dangerous		No response	No response	Response
Non-self	Not dangerous	No PAMPs	Response	No response	No response
		With PAMPS	Response	Response	No response
	Dangerous	No PAMPs	Response	No response	Response
		With PAMPS	Response	Response	Response

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IS THE CONCEPT OF “DANGER” WELL DEFINED?

- "danger," "damage," "stress," "injury," "necrosis," and "inappropriate cell death"
- These terms are not synonymous.
- the concept of "danger" is anthropomorphic

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IS THE CONCEPT OF “DANGER” WELL DEFINED?

- Is organ transplant dangerous?
- Are allergens dangerous?
- It is much clearer if we interpret "danger" as synonymous with damage. The idea of "damage" has led to experimental investigations

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Damage theory

- “Immune responses are due to tissue damages, rather than danger.”
- It is clearer and more testable.
- damage theory” may be more appropriate.

Damage signals

- cellular stress, heat-shock proteins (HSPs), and necrotic cell death.
- Alarm signals may be due to an endogenous or an exogenous damage to tissues.

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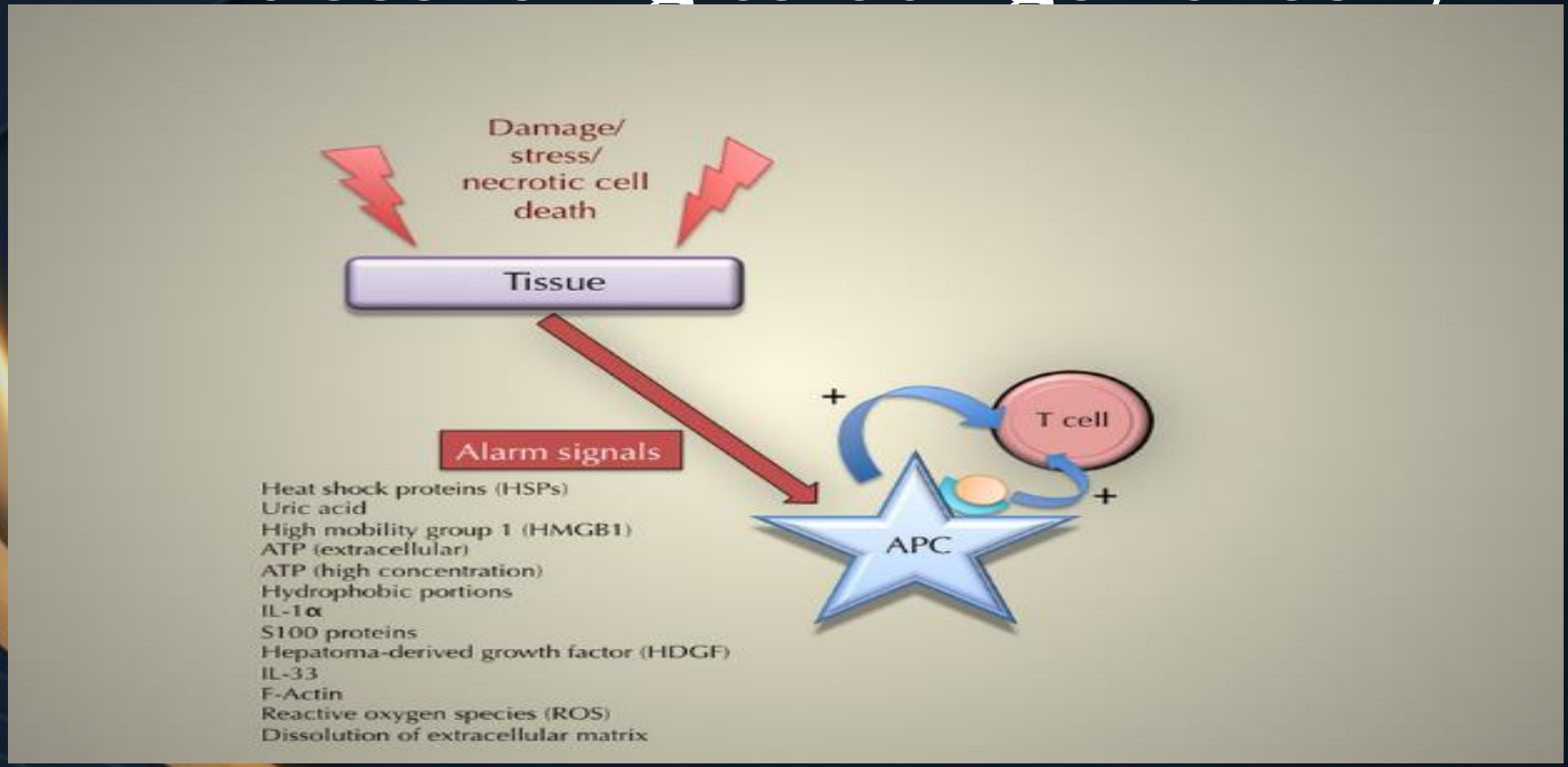
Triggering of an immune response according to danger theory



Cellular stress

- Stressed cell emits molecules that activate APCs.
- Without any foreign substances, dendritic cells may be activated by endogenous signals.
- not emitted by healthy or apoptotic cells.
- can function as natural adjuvants.

HSP

- Have a dual function
- Participate in the initiation of adaptive immune response.(allow exogenous antigen access to the endogenous antigen-processing pathway, i.e. they promote antigen cross-priming
- Modulate PAMP-induced immune stimulation.

HSP

- Endogenous danger signals in absence of pathogen.
- Some HSPs (HSP10 and HSP27) are“RAMPs” (resolution-associated molecular patterns)
- “DAMPERs,” because they tend to have a regulatory effect on immune homeostasis

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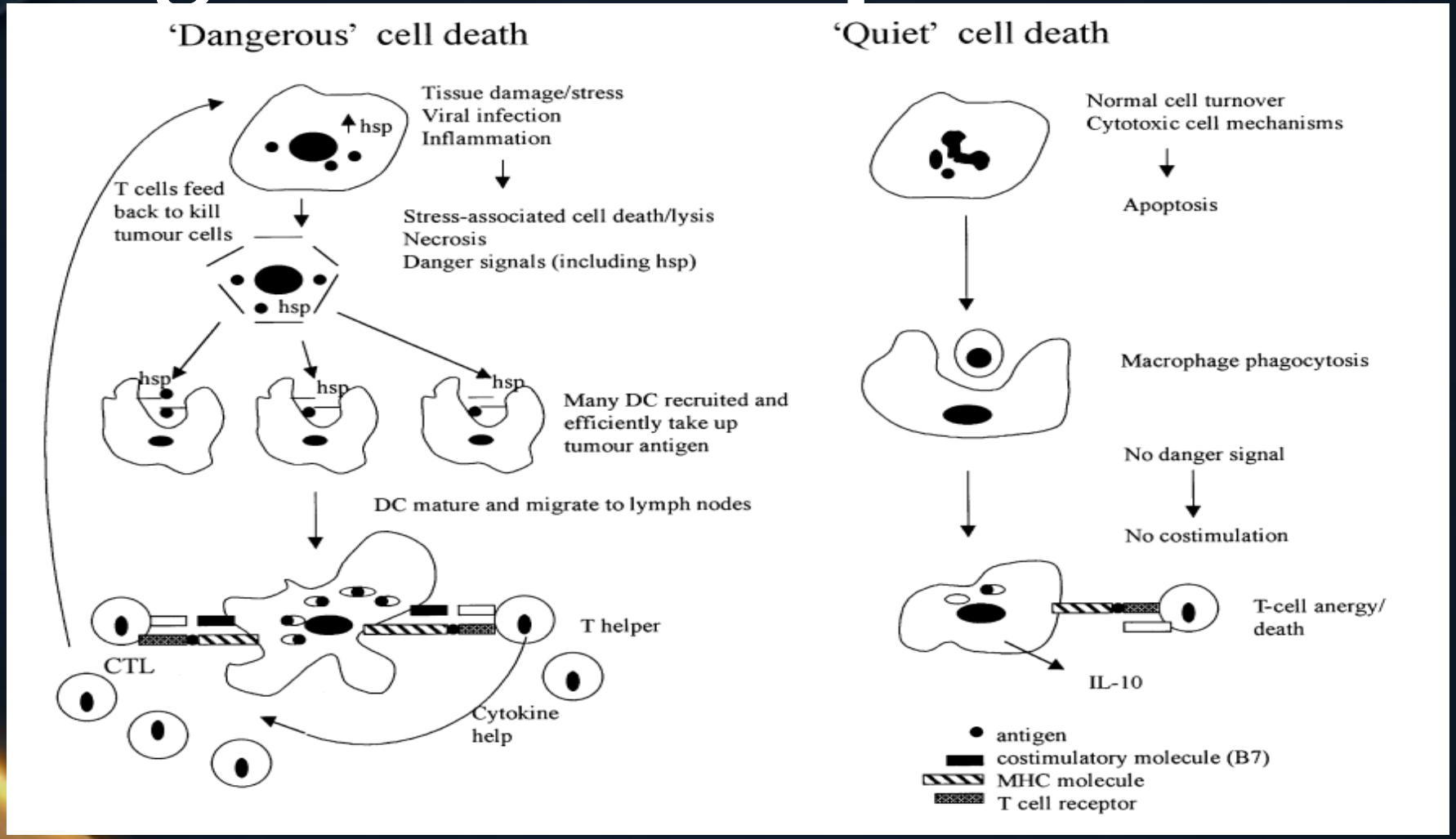
NECROTIC CELL DEATH

- In mice necrotic cell death can activate DCs.
- Release their intracellular contents, including DAMPs.
- “Hidden self model”

Summary of immune reactions to `dangerous' and `quiet' cell death



CRITERIA FOR A LEGITIMATE DAMP

- A DAMP should be active as a highly purified molecule.
- Biological activity of a DAMP should not be due to contamination with microbial molecules.

CRITERIA FOR A LEGITIMATE DAMP

- A DAMP should be active at concentrations that are actually present in pathophysiological situation.
- the selective elimination of a DAMP should ideally inhibit the biological activity of dead cells in vitro and in vivo.

URIC ACID

- Released by injured cells and stimulates dendritic cell maturation.
- when co-injected with antigen in vivo, significantly enhances the generation of responses from CTLs.
- Elimination of uric acid reduced the generation of CTL to an Ag in transplanted syngeneic cells and the proliferation of autoreactive T cells in a transgenic diabetes model

HMGB1

- Secreted actively by inflammatory cells.
- Released passively as a soluble molecule by necrotic cells.

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INFLAMMASOME

- Activate Caspase 1, and consequently the production of IL-1β.
- NLRP3 is a “sensor” of immune danger signals.
- “Sterile inflammation”
- Gout, Asbestosis and Silicosis

OTHER DAMAGE SIGNALS

- IL-1 α; S100 proteins; hepatoma-derived growth factor (HDGF); high concentrations of ATP;F-actin
- β-D-glucopyranosylceramide : activate iNKT
- IL-33:released from necrotic cells and that acts directly on antiviral CD8+T cells.

MODIFIED DANGER SIGNALS

- Endogenous proatherogenic danger signals
- Pathogenic role of modified LDL in the etiology of atherosclerosis.
- LDL-derived phospholipids and cholesterol crystals trigger TLRs and NLRs.

LOX1

- Multiligand receptor
- Oxidized LDL receptor
- Recognize C-reactive protein and C1q

The Possibility of Immune Responses Without Damage

- Some PAMPs can trigger an immune response with no accompanying damage.
- Activation of regulatory T cell is not supported by danger theory.
- Immune system is often at the origin of tissue damages.
- Why macrophages have activated in first place?

CANCER AND DANGER THEORY

- “There was no immune response to tumors”.
- “Proved its superiority to other theories”.
- The immune system does respond to tumors and eliminates(recent data)

CANCER AND DANGER THEORY

- Tumors are dangerous and may well send “alarm signals?” (save danger theory)
- Damage-based innate immune response to tumors in the fruit fly Drosophila melanogaster

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CANCER AND DANGER THEORY

- It cannot be excluded that immune response to tumors are due to emission of damage signals.
- Molecular modifications rather than damage.

DANGER AND GRAFTS

- Immune responses against transplants are due to surgical damages.
- Surgical autograft is not rejected.
- Rejection reactions between two protochordate colonies of Botryllus schlosseri

DANGER AND GRAFTS

- Based on clinical trials in kidney transplant patients:
- Reperfusion injury after ischemia can be reduced by antioxidants like superoxide dismutase, leading to lower rates of both acute and chronic rejection.

Symbiotic Exogenous Entities AND DANGER THEORY

- Are tolerated because they do not provoke damages.
- Gut immune system respond to bacteria, but in a highly controlled way.
- Bacteria can trigger strong immune responses if they change their location.

Limitations of the 'Danger' Concept

- The "Danger" concept focuses on cellular damage, but many immune signals, like LPS, bacterial DNA and viral RNA activate immunity without causing harm.

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Conclusion

Table 3 | Advantages and drawbacks of the danger (or "damage") theory.

Immunological question	Assessment
Criterion of immunogenicity	Satisfying
Importance of APCs in adaptive immune responses	
Immune responses to endogenous constituents	
Innate immunity	Not satisfying
Immune responses to tumors	
Immune responses to grafts	
Immune responses to symbiotic bacteria	

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