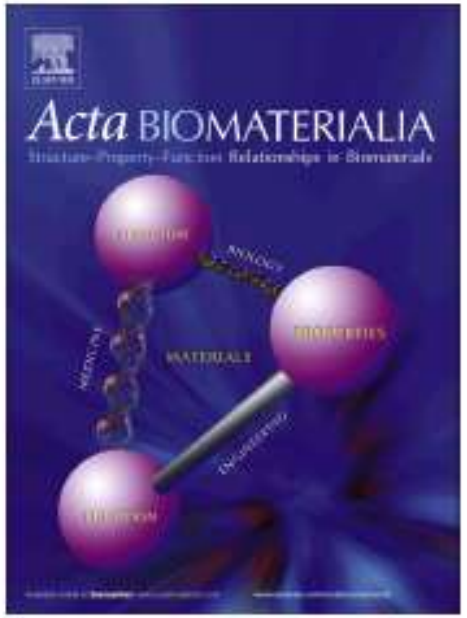

The Inflammasome in Host Response to Biomaterials: Bridging Inflammation and Tissue Regeneration

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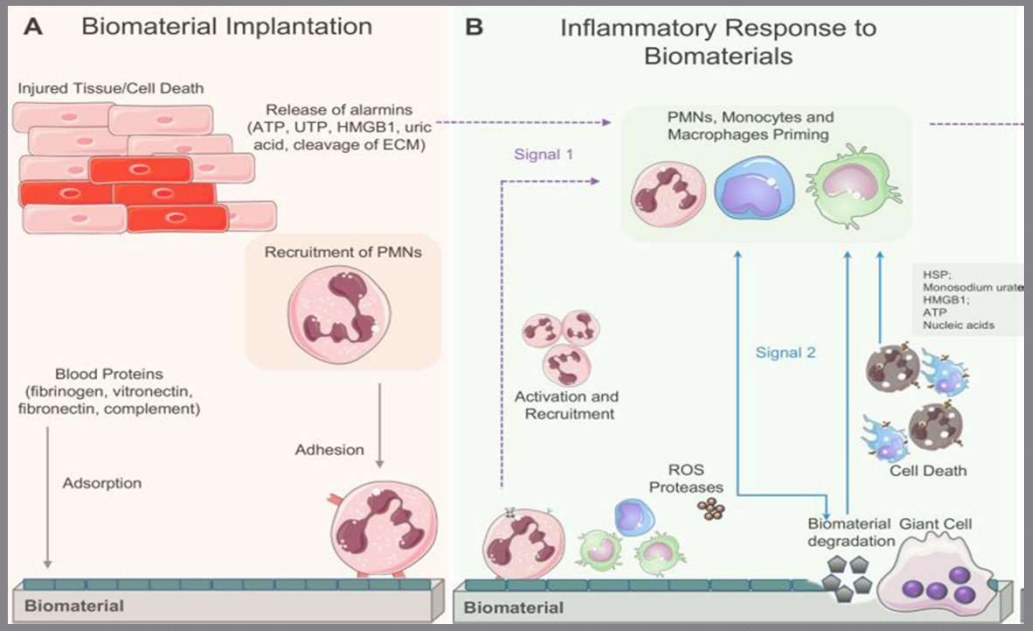
The Inflammatory Responses to Biomaterials

- Acute response to tissue injury directed at limiting damage to body.
- Deposition of a collagenous fibrous capsule around the implant which affects the biomaterial stability.

Tissue Responses:

1.Blood-material interactions
2.Release of danger signals by injured cells
3.Acute inflammation
4.Chronic inflammation
5.Foreign body reaction



Resolution of Inflammation

- Inflammation is a response to pathogen invasion, infection and also to tissue injury
- Resolution of inflammation is an active process that is highly regulated
- Specialized immunoresolvents have a fundamental role in the termination of inflammation triggering pathways that signal the termination of the acute phase of the inflammatory response
- These mediators include a group of endogenous molecules: resolvins, lipoxins, protectins and maresins
- Chronic inflammation and fibrosis will occur if inflammatory resolution fails

The New Trend in Biomaterial Development

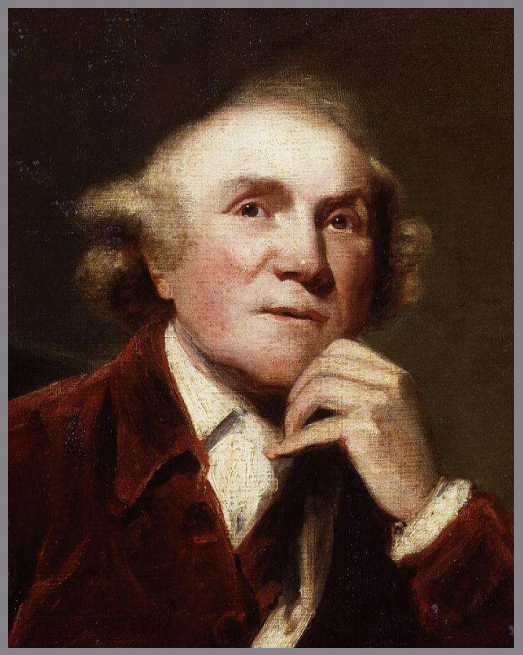
- During several decades biomaterial engineering was dedicated on the development of passive biomaterials to minimize the host response.
- But it has now been understood that allowing specific biological responses is beneficial for both biomaterial integration and performance.

Biomaterials development has change:

Immune-Evasive → Immune-Interactive

to allow the modulation of the inflammatory response improving healing and regeneration.

The New Trend in Biomaterial Development

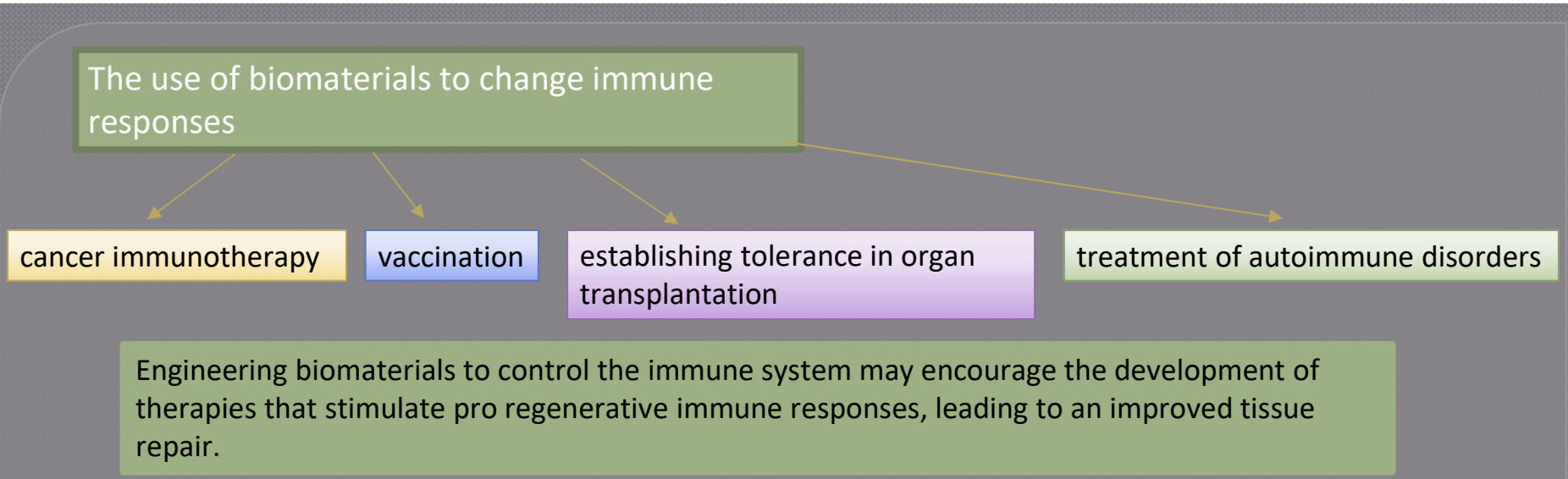


- "Inflammation in itself is not to be considered as a disease but as a salutary operation consequent to some violence or some disease."

  –John Hunter, Surgeon

- Traditionally, the immune system has been viewed by biomedical engineers as an enemy to the adequate design of biomaterials, as a coordinator of the host response that decreases the duration and function of implants.

- However, interest is increasingly growing on engineering biomaterials to wisely control the immune system by enhancing or suppressing immune reactions.

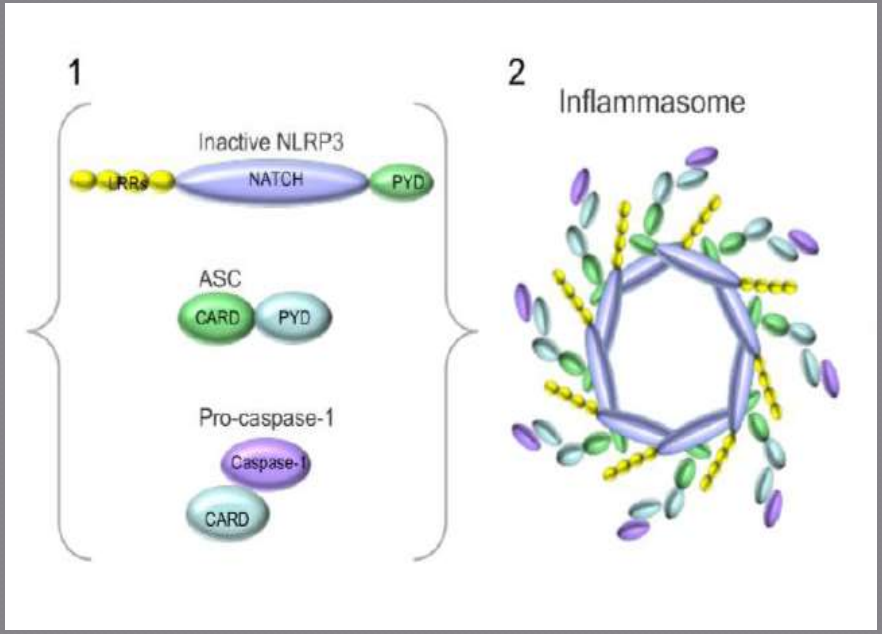


Engineering biomaterials to control the immune system may encourage the development of therapies that stimulate pro regenerative immune responses, leading to an improved tissue repair.

Immunomodulatory biomaterials created with different strategies:

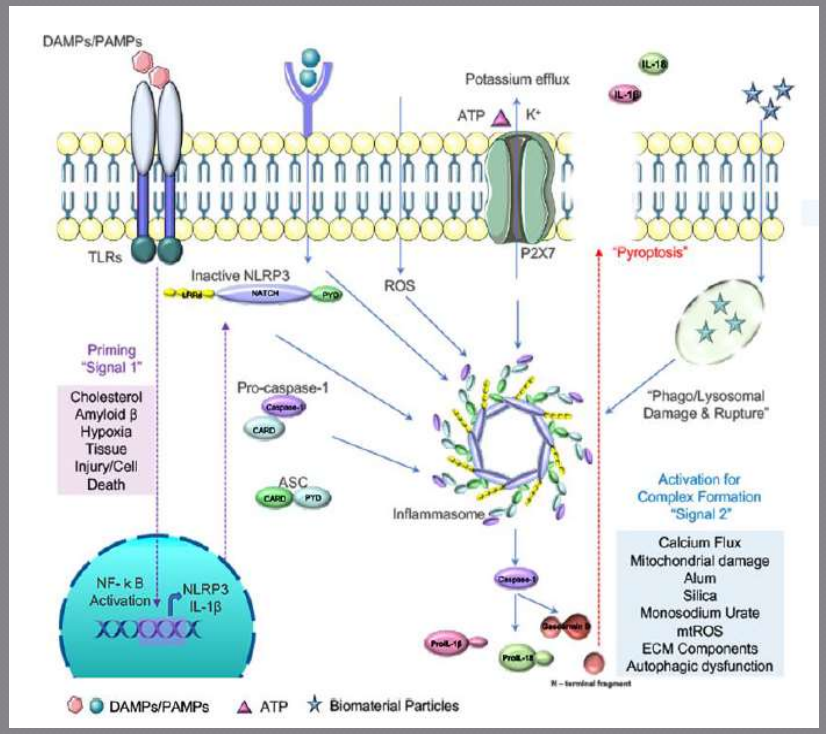
- Tuning of the chemical properties of biomaterials,
- Changing the physicl properties of the materials,
- Incorporation of bioactive molecules,
- Decellularization of extracellular matrix,
- Cell therapy methods

What is the Inflammasome?



- Inflammation is initiated on the recognition of signs of acute damage or disturbances of the steady state and mainly mediated by the production of soluble factors like cytokines.
- Inflammasome is derived from the word inflammation – to reflect the function of this complex - and the suffix “some” from the Greek “soma” that means body, which is generally used to define several molecular complexes such as liposome or ribosome.

The Importance of the Inflammasome in the Innate Immune Response

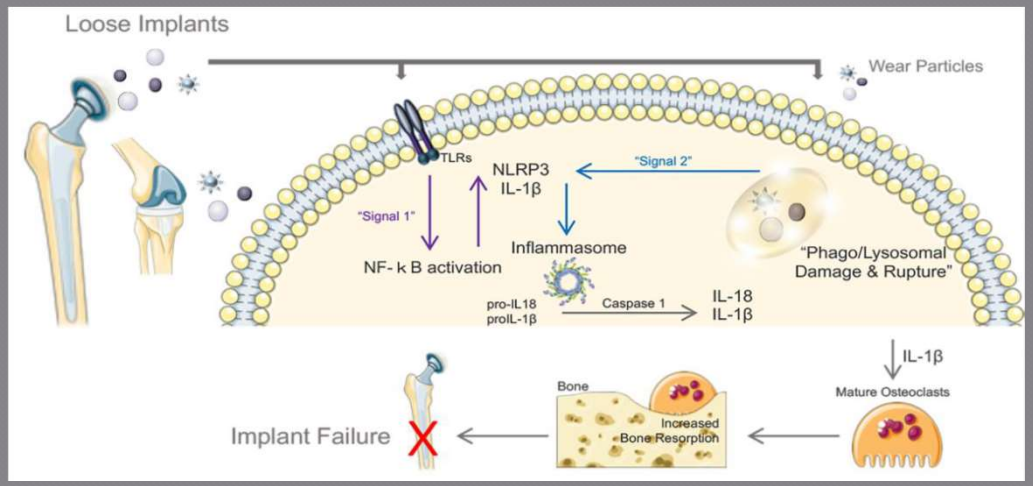


- A selection of germline-encoded pattern-recognition receptors are a major component of the inflammasome activation complex along with other receptors. Once in the presence of a certain stimuli, the relevant receptors oligomerize to become a caspase-1-activation scaffold, which eventually induces the inflammatory response.

The Inflammasome in the Inflammatory Response to Biomaterials

- The implantation process of biomaterials causes injury to cells and as a result, can release hazard signals that can activate the NLRP3 inflammasomes.
- Activation of inflammasomes by implanted biomaterials is still a research subject.
- Studies have shown that inflammasomes participate in interactions between cells and biomaterials and the progression of the foreign body response using NLRP3, ASC, NLRC4.

- NLRP3 inflammation is associated with a biological response to wear debris from joint replacements.
- The usage of joint replacements results in the formation of wear debris, and process is directed towards periprosthetic tissue destruction and implant loosening.
- The wear debris act as a danger signal in the tissues around loose implants. This induces activation of the NLRP3 inflammatory pathway, these pro-inflammatory mediators in the joint fluid lead to differentiation, and bone resorption dominates the osteogenesis at the bone-implant interface and eventually leads to loosening of the implant.



The Inflammasome as a Bridge between Inflammation and Regeneration

- The immune system is of primary importance in orchestrating a correct repair process, and since inflammasomes are involved in the innate immune response, it is expected that they have a key role in tissue repair/regeneration.
- Activation of inflammasomes not only induces the inflammatory response, but also plays an important role in regulating extracellular levels of specific proteins
- As a result of studies on KO and WT mice, it has been observed that NLRP3 inflammation contributes to the early inflammatory phase and is extremely important for effective healing.
- In a study on the liver, NLRP3 revealed that signal deficiency impairs liver regeneration and it was concluded that NLRP3 signaling is required to improve liver regeneration after inducing the inflammatory response.
- Modulation of NLRP3 activity is an important goal for developing effective strategies for biomaterial integration, which poses a major challenge in biomedical research and clinical medicine.

Concluding Remarks and Future Perspectives

- The engineering of biomaterials that not only fulfil all the needed requirements of the past but that can also modulate the immune system, both innate and adaptive responses, is now a major goal of several studies.
- The use of biomaterials that stimulate the establishment of a proregener ative microenvironment at the implantation site is clearly an emerging and promising field of research.

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