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Start: 17/11/17

The body-reaction to an implant is called a foreign body reaction.

In the following I will shortly describe how the provisional matrix, formed immediately around the implant when it is placed in the body, is transformed into a fibrous capsule, and how specks of metallic gold introduced into the provisional matrix, i.e. in the implant-tissue interface or adhering to the implant surface, can modulate the process by inhibiting the local inflammation.

When an implant, e.g. a breast prosthesis, is placed in the human organism, proteins adsorb to all implant-tissue interfaces and a 'provisional matrix' is formed. Simultaneously, monocytes/macrophages adhere to the implant surface, and a chemical dialogue starts between the macrophages and the other cellular components of the inflammation. This acute phase of inflammation unfolds within the first two to four weeks and is followed by a more chronic phase.

The immediate 'blood-tissue-implant' interaction that produces the provisional matrix also ignites the acute inflammation and starts the formation of granulation tissue leading to the development of a fibrous capsule.

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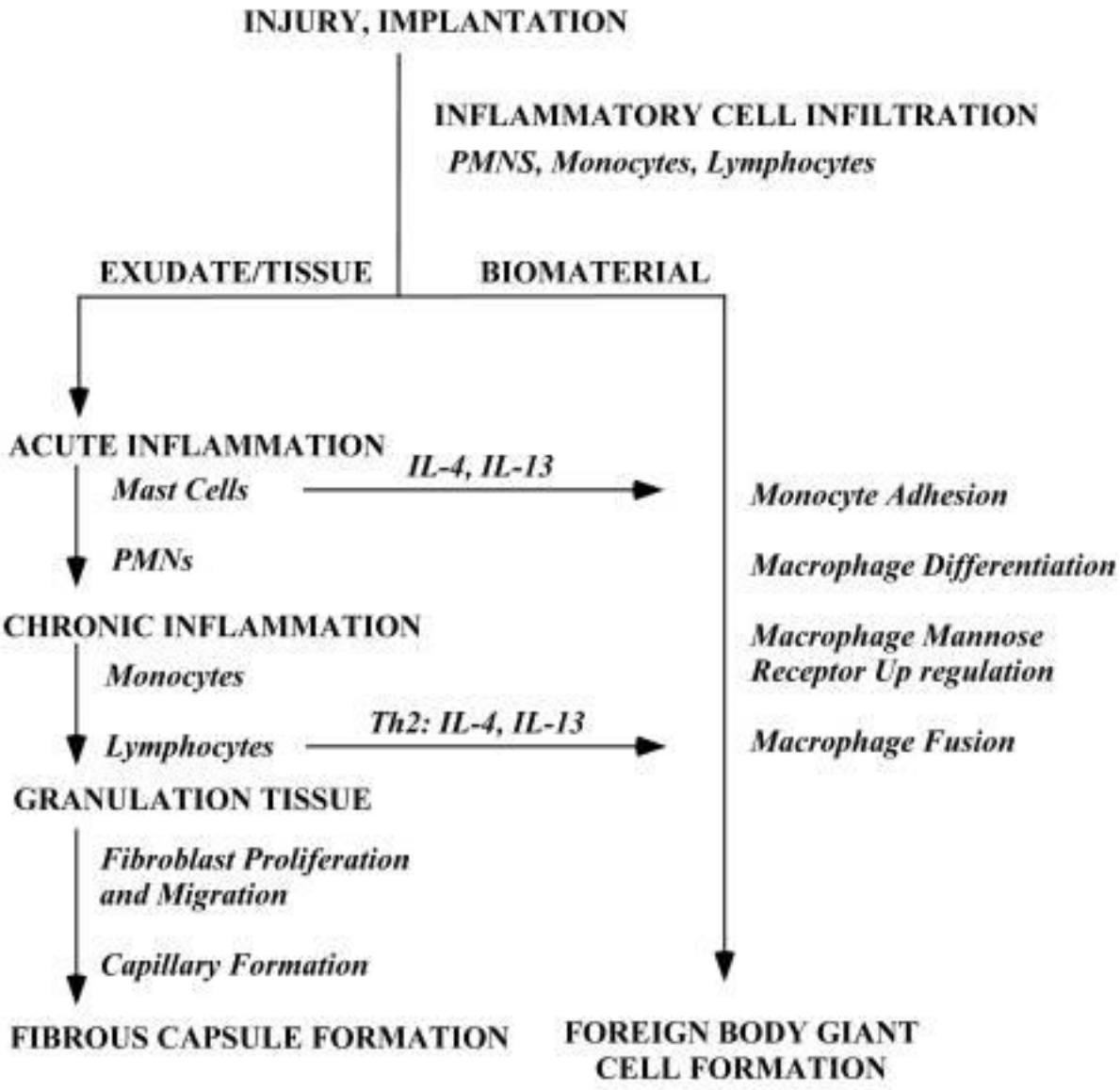

Diagram of the events involved in the inflammation and healing responses that take place in the provisional matrix. Note the potential importance of mast cells in the acute inflammatory phase and Th2 lymphocytes in the following chronic

inflammation. (Anderson et al. 2008).

The implant surface, in this way, does not only initiate the inflammatory responses, it also provokes thrombus formation and ignites extrinsic and intrinsic coagulation cascades, i.e. the complement system, the fibrinolytic system and the quinin-generating system.

These protein cascades may be intimately involved in the dynamic phenomenon of protein adsorption and desorption known as the Vroman Effect. The blood/ tissue protein deposition on the surface of an implant, the provisional matrix, is vital for promotion of the ensuing creation of a capsule. The presence of mitogens, chemoattractants, cytokines, growth factors, and other bioactive agents in the provisional matrix creates a dynamic soup of activating and inhibiting substances capable of activating macrophages and modulating their activity (Anderson et al. 2008).

Macrophage activation and cytokine secretion

Macrophages secrete an array of inflammatory mediators following activation. A resting macrophage becomes activated in response to an array of factors. A macrophage adhering to an implant surface is activated to become an M1 macrophage attacking the surface in order to dissolve it or isolate it. Subsequent cytokine secretion directs the inflammatory and later wound healing responses.

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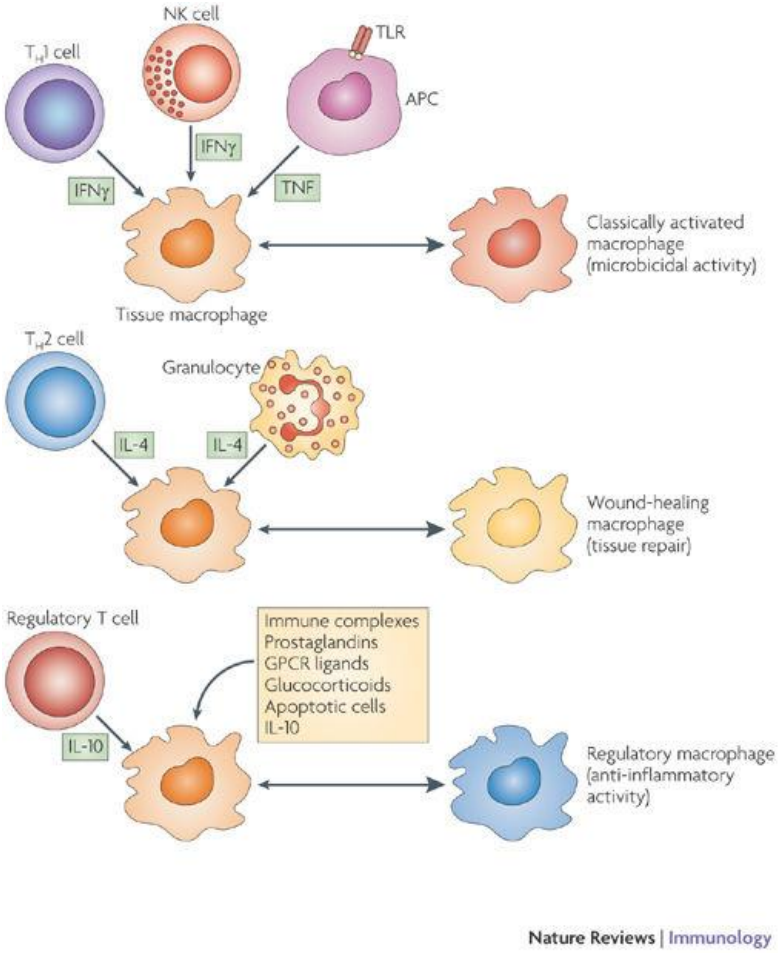
Classically activated macrophages, M1 macrophages, whose main function is the killing of intracellular pathogens and removal of foreign bodies, e.g. implants, upregulate pro-inflammatory cytokines, inhibit anti-inflammatory cytokines, and produce nitric oxide.



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Implant adherent macrophages are considered to be the main mediators of the foreign body response and to influence the leukocytes, i.e. neutrophils, monocytes, lymphocytes, fibroblasts and keratinocytes, by secreting soluble mediators.

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Macrophages are capable of secreting growth and angiogenic factors that are important in the regulation of fibro-proliferation and angiogenesis in the granulation tissue. Implant adherent macrophages secrete proteins that through fibroblasts modulate fibrosis and in turn the structure of the fibrous capsule that develops around the implant.

Although not well known, surface chemistry can impact macrophage behaviors such as adhesion, apoptosis, fusion, and cytokine secretion (Andersen et al. 2001).

Metallic gold's influence on the implant provoked foreign body reaction. When a pure gold implant is placed in the body, a normal foreign body reaction as just described will take place. I.e., a provisional matrix will build up and macrophages adhere to the gold surface. The macrophages are believed then to structure the provisional matrix where they adhere, creating a local 'dissolution membrane'. The macrophages then control the chemical events in the dissolution membrane and start liberating gold ions from the surface by a process coined 'dissolucytosis'.

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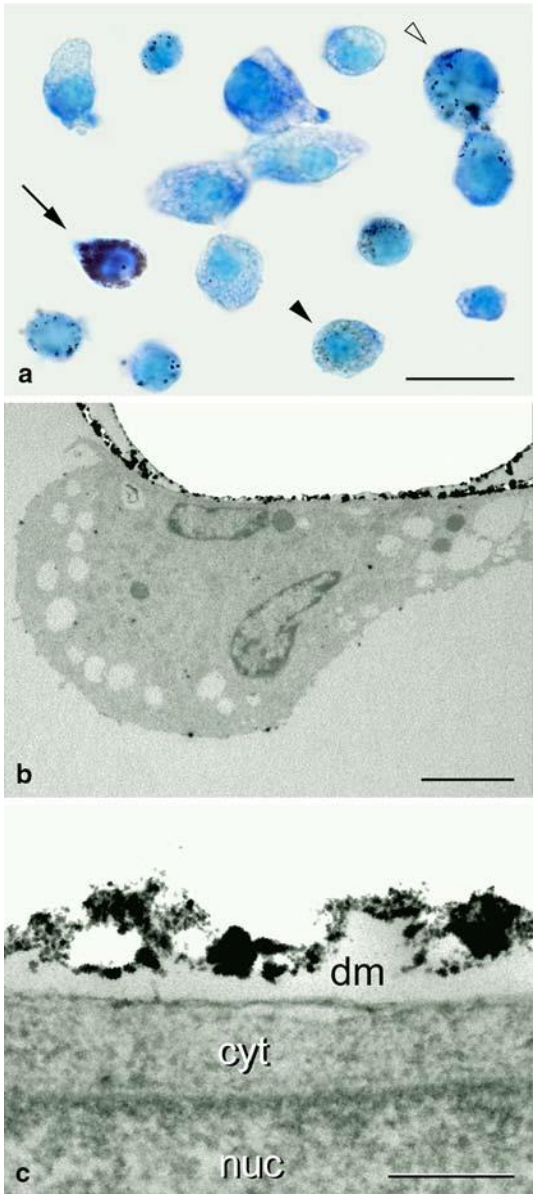

Fig.2 a Variations in gold load of macrophages. Light micrograph of AMG silver enhanced J774 cells packed with silver enhanced gold nanoparticles. (1) Heavily loaded cell (arrow). (2) Cell filled with tiny AMG grains (black arrowhead). Such gold-dusted cells were recorded already after 2 days of exposure. (3) Dissolucytes containing coarse AMG grains after 5 days of exposure (white arrowhead). The picture is a mosaic composed of J774 cells grown on gold surfaces for 2 and 5 days, respectively. Scale bar 20 lm. b Liberation of gold ions into the dissolution membrane. Electron micrograph of a macrophage and its dissolution membrane. The grid to which the cell was attached was removed during the tissue preparation. Notice the silver-enhanced gold nanoparticles within the membrane. Scale bar 3 lm. c Electron micrograph of the dissolution membrane to show the AMG grains at higher magnification. Dm dissolution membrane, cyt cytoplasma, nuc nucleus. Scale bar 200 nm

The gold surface seems to stimulate an oxidative liberation of gold ions by

acting as a pro-drug reliant on neutrophils and monocytes to produce hypothiocyanite, leading to the presence of cyanide ions in the dissolution membrane (Danscher 2002).

$$4\ Au + 8\ NaCN + O_2 + 2\ H_2O \rightarrow 4\ Na[Au(CN)_2] + 4\ NaOH$$

The released gold ions may exert their inhibitory effect on inflammation by binding to peptides and proteins of the inflammatory cascade or by binding to particular surface proteins of one or more of the cells that participate in the complicated processes of inflammation and repair .

The gold cyanide ions drift from the dissolution membrane further out into the intercellular space. After chemical binding to e.g. sulphydryl species, of molecules on/in the plasma-membranes they are phagocytosed by the different cells i.e. mast cells, macrophages and other cells farther away.

It has been proved that the bigger the surface of gold is, the more gold ions are released and the farther away gold loaded cells can be found (Danscher 2002; Larsen et al. 2007).

The accumulation of gold in lysosomes of local macrophages, fibroblasts and mast cells, where it is also found in the mast cell granules, shows that the nano-amount of bio-released gold ions ends up in cells close to the gold ion source (Larsen et al. 2007). After tissue sections have been radiated with UV light that reduces gold ions to metallic gold atoms, the bio-released gold ions now bound in lysosomes and mast cell granules can be visualized by

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Autometallography at light and ultrastructural levels (Danscher 1981; Danscher and Stoltenberg 2006).

The finding of macrophages and mast cells free of gold close to an implant shows that these cells are replenished over time.

The attacking macrophages being closest to the dissolution membrane are also the first to take up gold ions. The uptake of gold ions appears to down-regulate their cytokine signalling, thus slowing or even stopping the inflammatory signal cascade eventually leading to a stop of the inflammatory reaction.

The presence of gold ions in the secretory granules of nearby mast cells is believed to down regulate the release of the pro-inflammatory signal and histamine from the mast cells, and to be instrumental to the observed increase of oedema (Shalit et al. 1990).

Fibroblasts are a third target. It is hypothesised that these cells bind gold ions to their membrane proteins, take them in, and then processes them in lysosomes where gold ions, as mentioned above, can be located by Autometallographic (AMG) development after being reduced out by UV light to nanoparticles of gold atoms. (Danscher 2002; Danscher and Stoltenberg 2006).

The concentration of gold ions released from a given metallic gold surface is regulated by the intensity of the local inflammation. As the breast prosthesis is sterile and the application process is in accordance with the best practices

for sterility, the release of gold ions will be low. But if, for any reason, local inflammatory process are ignited the increased number of macrophages will cause a steep increase in the amount of gold ions. In turn the tiny attempts will die out.

In conclusion: Clinically effective levels of bio-released gold ions are created around implants that contain metallic gold in/on or close to its surface by macrophages. Although the concentration of released gold ions is low it has been found to be sufficient to turn off the local inflammation. Because the gold ions are relatively few they do not spread in the organism, but instead stay locally making the technique safe.

The trials to date indicate that the bio-release of gold ions will last lifelong, i.e. if a local inflammation might occur within or close to the capsule it will be turned of.

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