Harnessing the power of inflammation in immunoprevention and immunotherapy

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Inflammation: an ancient highly efficient defensive mechanism

Among the strategies developed for preserving their integrity and propagating the species, multicellular animals display an array of endogenous functions, which complete their behavioral defensive activities (e.g., avoidance, mimicry). Endogenous defensive functions imply the recognition and elimination of damaged cells within the organism (maintenance of structural and functional homeostasis) as well as the elimination/segregation of foreign bodies, such as microorganisms or particles. Homeostatic “cleaning” functions usually take place in a silent way, whereas elimination of foreign agents entering the body entails the activation of an inflammatory reaction.

In invertebrates, lacking the sophisticated and highly specific adaptive immune mechanisms (antibodies, T and B lymphocytes, based on gene recombination), innate responses are exclusively based on innate and inflammatory reactions. It should be noted that innate immunity nevertheless displays a substantial capacity of specific recognition and memory. The major protective activity is phagocytosis, brought about by different cell types scattered throughout the body tissues and fluids (these correspond to macrophages and neutrophils in human beings). Recognition mainly occurs through interaction with pattern recognition receptors (PRRs), membrane proteins that recognize molecular patterns characteristic of microbes (pathogen-associated molecular patterns - PAMPs-) or fragments released by damaged endogenous molecules (danger associated molecular patterns - DAMPs-). Following recognition, phagocytes ingest the foreign agents and degrade them with proteolytic enzymes, reactive oxygen species (ROS) and nitric oxide (NO). Granular cells (which, in humans, are the mast cells) release pre-formed or newly formed mediators, including lytic enzymes (such as lysozyme, which degrades microbes extracellularly), opsonic molecules (which bind on the microbial surfaces and facilitate their phagocytosis), chemoattractants (which attract phagocytes) and cytokine-like factors that can increase the killing capacity of phagocytes. In response to a substantial tissue damage, defensive reactions such as encapsulation and melanization can isolate the dangerous agents (e.g., microbes) from the rest of the body by surrounding them with phagocytes or by forming a melanin capsule around them and killing them by ROS. Among soluble defensive components, complement components have multiple roles, from chemotraction to opsonization and lysis. The majority, if not all, of these innate/inflammatory defensive reactions are maintained in human beings (Figure 1A).

In humans, inflammation has been known for hundreds of years only for its pathological consequences. In his treatise “De Medicina”, published before 47 AD, the Roman encyclopedist and physician Aulus Cornelius Celsus described fever and the four signs of inflammation: dolor (pain), calor (heat), rubor (redness) and tumor (swelling). The fifth sign of inflammation, functio mancipialis (functional integrity and only in rare cases they have pathological consequences). As an example, gut microbiota do not induce an inflammatory reaction in the gut because they are kept outside the body by mechanical/chemical (mucus) and cellular barriers (the tight mucosal epithelium). The apical surface of epithelial cells facing the gut lumen does not carry PRRs and, therefore, these cells are not activated in contact with bacteria. In the case of microorganisms able to cross the barriers and enter the subepithelial tissue, or in the case of bacterial entry due to damages in the gut wall, a defensive inflammatory reaction is initiated by macrophages present in the submucosa. As in invertebrates, a defensive inflammatory reaction includes recognition, phagocytosis and elimination of the invading microorganisms. This reaction can be “silent” and quick, without the need of activating a strong inflammatory reaction and a more complex defensive system (adaptive immunity). It is estimated that over 80% of invasion cases fall in this category. If the bacterial burden is high, and silent elimination is not sufficient, a much stronger inflammatory reaction will take place, with activation of innate cells (resident macrophages and mast cells and blood-derived neutrophils and monocytes), active phagocytosis, release of cytokines and chemokines, activation of complement, production of ROS and NO, intracellular and extracellular degradation of bacteria, and consequent initiation of adaptive immunity. In such reaction, most of the incoming neutrophils and monocytes die, and the affected tissue can suffer damage. The reaction stops with the elimination of bacteria, and the phase of tissue repair and re-establishment of homeostasis takes place. Despite immune cell death and tissue damage, this reaction is not pathological, as it resolves successfully without obvious symptoms or with transient symptoms. Pathological inflammation occurs only in rare cases, for instance when the initiating agent cannot be eliminated, or when the host immune system is not fully functional. This is the case of autoimmune, chronic inflammatory and neurodegenerative diseases, as well as allergies (including anaphylaxis and asthma) and the Shwartzman reaction. And it is also the case of the particularly severe cytokine storm in elderly people with respiratory viral infections (such as SARS-CoV-2). In these cases, inhibition of inflammation has a powerful therapeutic effect, with the use of classical anti-inflammatory drugs such as corticosteroids in chronic inflammatory and autoimmune diseases, or more recent anti-inflammatory biologicals such as TNF inhibitors, used in the treatment of rheumatoid arthritis, inflammatory bowel diseases and several other pathologies.

Inflammation in preventing diseases: the power of vaccination

Triggering an inflammatory reaction is a strategy largely used for improving vaccine efficacy (Figure 1B). At variance with vaccines based on whole microorganisms, very effective in inducing immunity but highly inflammatory and in some cases also toxic/unsafe, vaccines based on isolated antigenic proteins are much safer but less immunogenic, i.e., not very efficient in inducing long-lasting protective immunity. In 1925, the French veterinarian Gaston Ramon observed that vaccination against the diphteria toxoid (inactivated toxin) was much more effective when an inflammatory reaction was triggered at the toxoid inoculation site. He used a number of “helping” substances (adjuvants, from the Latin verb adiuvare = to help) to induce a beneficial inflammatory able to amplify the protective immune response, including bread crumbs, tapioca, saponin, starch oil, agar. The following year, 1926, the British physician Alexander Glenny used aluminum salts (alum) for inactivating the diphteria toxoid and generating an effective adjuvanted vaccine. At present, many vaccines still use alum as adjuvant, while more recent adjuvants encompass oil-in-water emulsions that complex the vaccine antigens in a particulate form, longer lasting and better detected by...
A. Innate immunity – inflammation

Macrophage

Innate immune cells
Phagocytosis/efferocytosis
ROS & NO
Proteolytic enzymes
Cytokines
Complement/chemoattractants
Encapsulation/melanization

Pathology (excessive/persistent reaction)
Healthy joint / Rheumatoid arthritis
Inflammatory cells
Bony, synovial, pannus

IL-6 inhibition
IL-1 inhibition
TNF inhibition

B. Inflammation in immunoprevention: vaccine adjuvants

Antigen processing and presentation

Activated macrophage

Phagosome

IL-12

Antigen presentation

MHC II

Inflammasome activation

Depot effect
APC recruitment

PRR activation

C. Inflammation in immunotherapy: anti-cancer strategies

Capillary

BCG

Cytokines
ROS, NO

DEPOT effect

Antigen

Activated macrophage

PAMP

D. Innate memory in inflammation-based immunoprevention and immunotherapy

Immunotherapy

Cytokines
ROS, NO

Macrophage

Activated memory macrophage

Inflammatory cytokines
ROS, NO

Figure 1. Exploiting inflammation for improving health

(A) Innate immunity/inflammation is a major homeostatic and defensive system, based on innate immune cells such as macrophages, soluble mediators (e.g., complement), and specific functions (e.g., phagocytosis, encapsulation). Persistent/excessive inflammation may have pathological consequences, as in the case of rheumatoid arthritis. Treatment with anti-inflammatory agents, such as anti-cytokine antibodies, can rebalance the reaction and improve the disease symptoms. (B) Exploiting inflammation for immunoprevention is mainly based on the use of adjuvants, which can promote antigen persistence in the tissue (“antigen depot effect”) and facilitate recruitment of antigen-presenting cells by inducing a localized inflammation and associated chemokine production. Adjuvants can engage and activate innate PRRs (TLR, NLR, RLR) on antigen-presenting cells such as macrophages, leading to gene upregulation and cytokine/chemokine production, thereby initiating an inflammatory reaction. Adjuvants can also activate the assembly and activity of the inflammasome, a cytoplasmic complex that activates different caspases leading to the cleavage/maturation of IL-1β, a major inflammatory and immunostimulatory cytokine, and the assembly of the gaseous D pore, through which mature IL-1β can access the extracellular space and exert its functions. Antigen processing occurs into phagosomes, after uptake facilitated by adjuvants, or in the cytoplasm (through the proteasome, not shown), and antigenic peptides are mounted on MHC molecules, exposed on the membrane of the antigen-presenting cells and “presented” to naïve T lymphocytes to initiate an adaptive immune response. (C) Immunotherapeutic anti-cancer strategies imply the targeted induction of an inflammatory reaction, as in the case of BCG therapy of superficial bladder cancer. Treatment with live bacteria such as BCG induce a local inflammation, with extravasation of innate cells (e.g., monocytes and polymorphonuclear leukocytes) and antigenic peptides are mounted on MHC molecules, exposed on the membrane of the antigen-presenting cells and “presented” to naïve T lymphocytes to initiate an adaptive immune response. (D) Innate memory (trained immunity), i.e., the ability of innate immune cells to engage in a more effective innate/inflammatory reaction if previously exposed to inflammatory agents, is being exploited for establishing a non-specific resistance to cancer and for improving vaccine efficacy and broadness. After previous exposure to bacteria or an adjuvant, recruited monocytes can become “memory” macrophages, long-lived quiescent cells that retain the imprinting of the past activation through epigenetic and metabolic changes. Upon a new encounter with a tumor cell or a pathogen, and the derived pathogen- and danger-associated molecules, memory macrophages are activated in a more efficient fashion, compared to the primary activation, due to the priming-induced changes in their reactivity. Innate memory responses are non-specific, i.e., more effective against challenges that can be different from the memory-inducing agent, making innate memory an excellent complement to antigen-specific adaptive immune memory. Abbreviations: BCG, Bacillus Calmette-Guérin; C3b, complement factor 3b; CR, complement receptor; FcR, antibody Fc receptor; H2O2, hydrogen peroxide; IL, interleukin; LPS, lipopolysaccharide; MHC II, class II major histocompatibility complex; Mo, monocyte; NLR, NOD-like receptor; NO, nitric oxide; O2-, superoxide anion; PRR, pattern-recognition receptor; RLR, RIG-like receptor; ROS, reactive oxygen species; TLR, Toll-like receptor.
macrophages and other antigen-presenting immune cells. The capacity of adjuvants to generate a local controlled inflammatory reaction is at the basis of their capacity to enhance the establishment of an effective adaptive immune reaction and protective memory against the vaccine antigens. The particulate form induces phagocytosis and macrophage activation. Very important in adjuvant inflammation is the activation of the inflammasome, a cytoplasmic protein complex with both sensing and enzymatic properties. Adjuvants can achieve inflammasome activation and cause the activation of caspase-1, the enzyme that matures a very important cytokine, IL-1β. IL-1β is considered a typical inflammatory cytokine, because of its powerful effects in activating inflammatory mechanisms in many cell types and its clear involvement in many inflammatory pathologies. However, it must be noted that IL-1β is not present in invertebrates, in which innate immunity/inflammation is the only immune defense system, and has evolutionarily appeared only in vertebrates, concomitant to adaptive immunity. This leads to hypothesize that the main role of IL-1β is bridging inflammation to adaptive immunity, acting as main mediator of inflammation-dependent amplification of adaptive immunity.

Inflammation in curing diseases: adjuvant immunotherapeutic approaches to cancer

Inflammation is a double-edged sword in tumor development. It is known that an inflammatory tumor microenvironment (TME), with production of chemokines and strong infiltration of macrophages, can promote tumor growth. The tumor-associated macrophages (TAMs) that enter a solid tumor for killing cancer cells are re-directed by the TME towards “healing” macrophages, the functional phenotype adopted in the late phases of an inflammatory reaction, when the reaction must be resolved and the damaged tissue reconstructed. These healing macrophages actually help tumor growth and expansion. Thus, current anti-tumor therapeutic approaches include modulating the inflammatory reaction in the TME, by re-directing TAMs to tumor killing. This can be done by targeting innate checkpoints (one is the IL-1 family receptor IL-1R8), inhibiting macrophage recruitment, blocking myeloid suppressor cells, and/or using activators of the innate tumoricidal functions.

The use of inflammation for curing cancer, the first type of immunotherapy, dates back over 3000 years, with physicians in ancient Egypt and Rome using infections for curing tumors. This practice was refined at the end of the 19th century, when William Coley standardized a cancer treatment based on infection with *Streptococcus pyogenes*, later replaced by the so-called Coley’s toxin, a mixture of different bacteria and bacterial toxins. The bacteria-based immunotherapy is still very promising nowadays and, in some cases, is the golden standard of anti-cancer therapy, as in the case of BCG in non-muscle invasive bladder cancer (Figure 1C). BCG, the Bacillus Calmette-Guérin attenuated strain of *Mycobacterium bovis*, is the only marketed vaccine for tuberculosis and is well known for its capacity to activate macrophages towards tumoricidal functions; its capacity to induce tumor regression is thought to rely on such activation. An important characteristic of BCG, shared by other live microbial vaccines/immunotherapeutics, is the ability to induce innate memory, the capacity of innate/inflammatory cells previously exposed to an inflammatory agent (e.g., an infection or a vaccine) to react better in response to a new challenge. At variance with the classical adaptive immunological memory, innate memory is non-specific, meaning that a better response can be triggered by different unrelated agents. The possibility to establish an innate memory able to raise an efficient inflammatory reaction against tumor cells is another promising direction of anti-cancer immunotherapy (Figure 1D).

Future perspectives

Inflammation is a very potent conserved protective immune mechanism. Because of its strong destructive capacity, many natural mechanisms (antagonists, inhibitory receptors, signaling blockers) act as checkpoints to control it and avoid excessive collateral damage. Indeed, an inadequate control of inflammation (mainly an insufficient capacity to resolve it) can lead to pathological consequences, as in the case of chronic inflammatory and degenerative diseases. The vast majority of transmissible and non-transmissible diseases, also including aging, encompass an anomalous inflammatory activation. Nevertheless, inflammation has been used since many centuries for improving resistance to diseases and curing cancer. We are now experiencing fast and vast technological developments and substantial advancements in knowledge, with the identification of innate/inflammatory immune checkpoints and mechanisms for raising protective innate immune memory active against infections and tumors. The deeper knowledge of the development and control of inflammation is now allowing us to control inflammation, so that we can fully exploit it to attain effective immunopreventive and immunotherapeutic power while avoiding pathological consequences.

REFERENCES


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DECLARATION OF INTERESTS

The authors declare no competing interests.