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Review Article



The effect of cross-reactivity on trained innate immunity

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Abstract

Trained immunity is a new concept of innate immune memory which gives enduring protection through developing adaptive features against foreign reinfection, through many studies, when any pathogen invades the human body a series of metabolic alterations occur and lead to epigenetic reprogramming of various transcriptional innate immune pathways due to different types of endogenous and exogenous antigens which have similar epitopes that trigger cross-protective immunity which is represented by the heightened trained innate immune response to various reinfections due to cross-reactivity of these similar epitopes of various antigens by trained innate immune cells specially (monocytes and macrophages), this concept has been used previously unintentionally and currently can be used as potential therapeutic strategies for immunological management of various diseases such as cancer, coronavirus disease 2019 (COVID-19) and other diseases by use different vaccines due to non-specific effects of vaccines, such as BCG vaccine effects on different diseases.

Keywords: Trained Immunity, Epigenetics, Cross-Protection, Immunotherapy, Non-Specific Vaccines.

Introduction

Trained immunity is a new concept of innate immune memory that gives enduring protection through developing adaptive features against foreign reinfection, by functional reprogramming epigenetics of innate immune cells by endogenous and exogenous stimuli which gives a heightened immune response to reinfections but short-term protection. Innate immunity is “broad spectrum” resistance, containing different types of barriers and inflammation-related serum proteins but in the issue of trained immunity, what matters to us is the cellular components of innate immunity, which consist mainly of NK cells, monocytes, macrophages, antigen-presenting cells (dendritic cells), granulocytes (neutrophils, eosinophils and basophils) and mast cells (Daha, 2011), these cells circulate through the blood circulation and reside in tissues watching for potential problems, to respond as well as communicate with other immune cells if an issue

arises. Upon entrance of pathogenic microbes, the instant recognition of these microbes occurs by a cellular pattern and soluble pattern (chemokines, cytokines, pentraxins, defensins, the complement system, and presumably other, yet to define, mediator systems) of the innate immune system and could mount resistance to reinfection.

Nowadays, microscopic pathogens, especially viruses, are attacking us from all sides, so we have to understand the role of trained innate immunity in combating such pathogens. Immunity is the capacity of the immune system to protect the human body from infectious diseases through its reaction to an enormous number and variety of foreign antigens, and the innate immune response is the first line of defense that immediately responded by the following components:

1. Barriers such as Skin and mucosa, secrete proteins and enzymes.

2. Effector cells such as Granulocytes, Monocytes/macrophages, Dendritic cells and those who do the following; Phagocytosis, cytokine production, protein and enzyme secretion, destruction of pathogens), Natural killer (NK) cells (Lysis of infected and tumoral cells, activation of macrophages through cytokine production). Innate lymphoid cells (Mediate immune response and regulate tissue homeostasis and inflammation), Endothelial/epithelial cells (Microbial recognition, cytokine production).
3. Antimicrobial peptides that destruction of invading pathogens such as Defensins (a major family of host defense peptides expressed predominantly in neutrophils and epithelial cells) have an essential role in innate immunity as a protective component against viral, bacterial and fungal infections (Xu and Lu, 2020).

Soluble mediators

Cytokines (TNF- α , IL-1, chemokines, IFN- α , IFN- γ , IL-12, IL-15, IL-10, TGF- β), chemokines, interferons, etc (which are proteins produced by innate immunity cells such as macrophages, neutrophils, NK cells and some endothelial and epithelial cells produce some cytokines) that attract and recruitment the innate immune cells in the blood circulation to support them in eliminating the inflammation in that area.

Series proteins

Complement system that act through opsonization, destruction of pathogens, and T lymphocyte activation.
Collectins and C reactive protein which act also through the opsonization of pathogens and complement activation
Coagulation system which causes a localization of damage of infected tissue upon exposure to a second stimulus.
Enzymes such as lysozyme.

Cellular receptors

1. Toll-like receptors (TLRs): Recognize a variety of microbial components (Netea et al., 2020).
2. Nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs): Sense bacterial components present in the cytoplasm.
3. C-type lectin receptors (CLRs): Recognize sugar moieties of bacteria and fungi
4. Rig-I-like Receptors (RLRs): Sense viral RNA

Innate immunity cells

The innate immunity cells are classified into three groups

1. Phagocytic cells (eg, neutrophils, monocytes, macrophages)
2. Innate lymphoid cells (eg, natural killer cells; which constitute 5 to 15% of peripheral blood mononuclear cells lack

antigen-specific receptors; however, recent evidence suggests that could develop long-lasting and antigen-specific memory to haptens and viruses (Peng and Tian, 2017) and γ ζ T cells.

3. Polymorphonuclear leukocytes (neutrophils, eosinophils, basophils).

These cells are not associated with a specific tissue; therefore their functions are independent by identifying and eliminating pathogens, and cannot reproduce on their own, but are the products of multipotent hematopoietic stem cells in the bone marrow.

These cells during reinfection induce increasing a subsequent of the protective innate immune responses to the same or unrelated challenges, through upregulation of genes by epigenetic (Epigenetic mechanisms play an essential role in the organization of gene expression depending on the body's response to environmental stimuli (Heitmueller et al., 2017) without changes of the original DNA sequence, through reprogramming myeloid cells by stable epigenetic changes and lead to increasing of innate immunity cell number, which plays an essential and vital role in immune-mediated diseases (van der Valk et al., 2016), although, the innate immunity has the capacity to give wide immunological protection, through its barriers and induce its cells at this area of inflammation that do their work in addition to producing substances of certain proteins, and occur a series alterations in metabolic mechanisms in glycolysis, TCA cycle, and fatty acid metabolism, which modulate several enzymes activity that associated with epigenetic remodelling processes through methylation and acetylation of these genes that related with the innate immune response.

Innate immune memory

An increasing of evidence through epidemiological data that use of live vaccines such as the BCG vaccine, smallpox vaccine, measles vaccine, and oral polio vaccine have beneficial, non-specific protective effects against other infections by inducing trained immunity cells (Netea et al., 2020).

Innate immune memory lacking genetic information but the epigenetic has the effect through reprogramming of innate immune cells that contain special receptors known Pattern Recognition Receptors (PRRs) which can distinguish molecules frequently found in pathogens (pathogen-associated molecular patterns—PAMPs) or molecules released by damaged cells (the Damage-Associated Molecular Patterns—DAMPs) (Amarante-Mendes et al., 2018), and the subsequent challenges with the same or unrelated stimuli lead to modulate the second protective innate immune responses and that is through number increasing of the innate immune cells especially phagocytosis cells through upregulation of genes to enhance the clearance of microbes (Boraschi and Italiani 2018), this was proven by in vivo experiments in experimental mice by injecting them with PAMPs such as β -glucan, peptidoglycan, oligodeoxynucleotides, flagellin, etc which

induce protection against infection with *Staphylococcus aureus*, *Toxoplasma*, and *Escherichia coli* meningitis, *Streptococcus pneumoniae* and rotavirus respectively (Netea et al., 2016) through recognizing the ligands of pattern recognition receptors in mice, and also in other studies which use innate immune cytokines to provide trained immune protection by immunometabolic changes and histone post-translational modifications which enhance production of pro-inflammatory cytokines (Cavalli et al., 2021), as an example of injection of one dose of recombinant IL-1 before infection give protection against mortality by *Pseudomonas aeruginosa* to mice (Van der Meer et al., 1988; Riksen and Netea, 2021).

The innate immune cells have pattern recognition receptors (PRRs) which sense and engage diverse pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP), through the engagement of PRRs. Innate immunity gets training, knowledge and memory through exposure to different types of antigens, which contain epitopes that may be similar to the epitopes of some pathogens, in addition to the surrounding environmental factors lead to innate immunity trained with memory during future exposure to other pathogens (through reprogramming of innate immune cells by epigenetic reprogramming of transcriptional pathways and metabolic reprogramming), allowing quantitatively and qualitatively modified innate responses cells to next time-delayed heterologous stimulation and may cause either a hyper-inflammatory state or an immunological tolerance (Netea et al., 2020).

The continuation of epigenetic modifications of innate immune cells leads to the training of these cells on two levels central innate immune memory (bone marrow precursors and in circulating immune cells) and peripheral innate immune memory (tissue macrophages) which heightened preparedness to non-specific re-respond to reinfection with pathogens and this a clear through using BCG vaccination which provides non-specific effects against different diseases through generating trained immunity (Netea et al., 2020; Divangahi et al., 2021) and the memory of this type of immunity is short-duration due to the continuous regeneration of central and peripheral innate immune cells (Divangahi et al., 2021).

The BCG vaccine consider an attenuated vaccine from *Mycobacterium bovis* and the special characteristic of *Mycobacterium* species is the thicker wall than other bacteria, this wall has a complex lipid outer layer, lipids and lipopeptides which are important in an invasion and virulence (Benedictus et al., 2020) and these components are powerful modifiers of the innate immune response (Chandler and Ernst, 2017) and adaptive immune response (Benedictus et al., 2020) and due to abundant hydrophobic, waxy, mycolic acids, and major essential lipid components, which has adjuvant activity (Kubota et al., 2020), so this bacteria use in this vaccine due to it have a good amount of different antigens such as crude antigens (glycolipid antigen, plasma-membrane antigen), and purified antigens (TPX, TRB-B, ESAT6, CFP10, 85B, MPB64, MPB70, MPB83, MPT63, MPT64, KatG, MPT51,

ESAT-6, MTC28, 14kDa protein, 38kDa protein, MBP59, CFP-10, TbdP, LAM, and Ag85 etc. (Alito et al., 2003; Meikle et al., 2009; Tanner et al., 2019; Kubota et al., 2020; Benedictus et al., 2020) that act as PAMPs that stimulate the receptors of the innate immune cells and these antigens give cross-protection from *Mycobacterium tuberculosis* and other pathogens infection, so the BCG vaccine, which was mentioned in many studies that showed its broad ability to generate broad-spectrum immunity against different pathogens such as *Candida albicans*, *Schistosomamansoni*, malaria, leprosy, influenza A virus, respiratory syncytial virus (RSV), herpes simplex virus type 2, COVID-19 virus and *Staphylococcus aureus* (Covián et al., 2019; Netea et al., 2020; Koneru et al., 2021) while fungal ligand β -glucan give protection against different types of pathogenic microorganisms (Kim et al., 2011; Marakalala et al., 2013; Murphy et al. 2021).

Conclusion

Conclusion Trained immunity is considered an alternative innate response to another unrelated challenge, due to epigenetic reprogramming of various transcriptional innate immune pathways due to different types of endogenous and exogenous antigens which have similar epitopes that trigger cross-protective immunity which is represented by the heightened trained innate immune response to various reinfections due to cross-reactivity of these similar epitopes of various antigens by trained innate immune cells especially (monocytes and macrophages), and this concept has been used previously unintentionally and currently can be used as potential therapeutic strategies for immunological management of various diseases such as cancer, coronavirus disease 2019 (COVID-19) and other diseases by use different vaccines due to non-specific effects of vaccines, such as BCG vaccine effects on different diseases.

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