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Potentials of Innate Immune Memory IIM

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Abstract: Innate Immune Memory IIM is a twist functional mode of innate immune cells. In the present opinion paper, It is being; conceptualized, immune mechanism explored and potentials explained. IIM is of central and peripheral nature, impart specific long term adaptation for innate immune cells in bone marrow and in peripheral organ tissue microenvironment with marked immune functional plasticity. The IIM stimulants are; infection, microbial macromolecules, vaccination and inflammogen. Mechanisms behind which are; Noncoding RNA, gene circuit regulation, epigenetic reprogramming, circadian rhythm regulation and metabolic shift from oxidative to glycolytic pathways in the innate immune cells. IIM have both protective and pathogenic potentials. The spectrum its functional activities ensembles; Vaccine confer shared immune protection against heterologous infections, an add on immune effect to past infection and past vaccination responses. Though in an unexposed population to second pathogen exposure, it can be synergistic with adaptive immune responses. IIM resilient respiratory and urinary bacterial infections in immune compromised patients. Its role in autoimmune diseases is context dependent. In some AD it promotes pathogenesis and in others its protective. Showcase analysis for human microgial cell, ageing mice and human BCG vaccination models for elucidation of IIM and suggestion for an IIM project for human typhoid. IIM stands as an encouraging scientific base for vaccine production programs and immunotherapeutic targets.

Keywords: Bacteria, circadian rhythm, epigenetic reprogramming, gene circuit, vaccine.

INTRODUCTION

In a chronological way of thinking, immunologists so far concerned with the theme of “immunity”. They hold the bifurcated ramification of immunity as innate and adaptive immunity [1]. The paradigm of innate immunity in the classical immune sense characterized as; general, non-specific, memory less, gene encoded and acts in first exposure to the stimulating insults as microbes, inorganics, cancer cell. That had been the notion of 50’s, 60’s and early in 70’s [2]. Though in late 1999’s there had been, a new holding to the non-specificity changed to a limited specificity confirmed by protein associated with phagocyte cell membrane that have the role of a model of negative contour of a microbial membrane surface located chemical macromolecular patterns termed as membrane associated pathogenicity associated patterns [3]. Parallel to this finding there have been ensemble in the immune specificity timeline, it had been found that some cellular microstructures and/or mediators (cytokines, complement, acute phase reactants) of the innate immunity took part in adaptive immune response events in one hand and cellular macromolecules or mediators(cykines/antibodies) took part in innate immune events. This kind of cellular helping effects known as immune cross-road functions [4]. Based on scientific current observations, immunologists suggest and then prove the paradigm of innate immune memory

IIM [5, 6, 7]. The major characteristics of this IIM in comparison to other immunities are briefed in Table -1. The objective of the present opinion paper was to elucidate the immune potentials of IIM.

Table-1:The Four Recently Classes of Immunity.

Features	Innate	Innate immune memory	Immune cross-roads	Adaptive
Genetic encodement	Genetic	Genetic and epigenetic	Genetic	Genetic
Onset stimulant	Microbe	Microbe	Microbe	Microbe, proteins
Duration	Short	Long term	Relatively long	Lon term
Specificity	General, partly specific [TLRs]	General, Stimulus impart specific [TLRs]	Specific and non-specific	Specific, antigen dependent
Memory	Memoryless	Conditional memory	Memory, memory less	Memory
Protectivity	General	General	Vhichle of protectivity events	Mostly protective
Role in vaccine	Early events	Promising role in vaccine strategies	?	Essential role
components	Humoral, cellular, barrier tissues	Cellular and cytokines	Complement fraction, antibody, cytokines	Humoral and cellular
Role of cytokine and chemokines	Take part in	Take part in	Take part in	Take part in
Role of antibodies	Natural antibodies	No role	Take part in	Take part in
hypersensitivity	Immediate	immediate	Immediate and delayed	Delayed
autoimmunity	Initial cellular immune reactions	promotive	?	Essential
preimmunity	Early events	Early, late	?	Essential
microbiome	Bidirectional role	Bidirectional role	?	Bidirectional role

CONCEPTUATIONS

Innate Immune Memory IIM dented to the functional capacity of innate immunity to exhibits the features of active immune memory. This sort of memory is faster and more stronger responses upon second exposure to heterologous pathogens mainly. Unlike adaptive immune memory that depend onto microbial antigen specific re-arrangement and the activation events in T and B lymphocytes. Innate immune memory IIM is antigen agnostic and mediated by epigenetic and metabolic reprogramming. IIM holds the paradigm of long term functional reprogramming for; macrophages, monocytes and natural killer cells following the second exposure to certain microbial stimulants. Such stimuli can lead to an enhanced antimicrobial non- specific response to subsequent homologous or heterologous infection, infestation and/or vaccination. Its either of disease protective or disease promotive potentials. It may mediates cancer defense and improve vaccine efficacy. Maladaptation to IIM may contributes in induction of chronic inflammation, auto-inflammation and autoimmunity [7, 8, 9]. IIM is of central and peripheral nature. The central occurs in bone marrow where hempoietic stem cell and progenitor cells are trained. While the peripheral IIM happened in peripheral organ tissue micro-environment of lung and brain [10].

MECHANISMS

To elucidate the IIM mechanistic themes, workers have been put-forward number of interpretation mechanisms such as genetic, epigenetic and allied mechanisms;

Genetic Epigenetic and Allied Mechanisms

The initial infection, infestation or vaccination stimuli leads to a stable changes in nuclear chromatin architecture of the innate immune cells. The main chromatin changes was in histone 3, lysine 4 trimethylation. H3K4me3 and acetylation of histone 3 lysine 27, h3K27ac. The methylation and acetylation of gene expression products remain at the promoter site of the inflammatory genes keeping them primed for rapid transcription upon re-stimulation [[8, 10] Non-coding RNA contributes in evolution of IIM [7]. The impact of regulatory gene circuits onto IIR are recently discovered to regulate the evolution of genetic events of the innate immune memory [7]. Innate immune memory is under regulation of circadian rhythm [11]. The innate immune cell metabolism is of aerobic oxidative nature on innate cells they will shift to aerobic glycolytic pathway. The glycolytic metabolites like fumarate and mevalonate support the functional events of the epigenetic machinery ensuring the maintenance state of IIM [8, 12], Table – 2.

Table-2: IIM operating Mechanisms

Biological Nature of operating mechanisms	Mechanisms	References
Epigenetic	Epigenetic reprograming	[4]
Metabolic	Metabolic reprograming	[4]
Genetic	Gene regulatory circuits	[7]
Genetic	Circadian rhythm	[11]
Genetic	Noncoding RNA	[7]
Immune	Gut microbiome-immune-neuronal axis	[12]

MAL MEMORY FUNCTION OF IIM

Persistent innate immune training by an endogenous stimuli with oxidized low density lipoprotein LDL or high salt diet augment atheroseclerotic response, diabetes and neurodegerative disease like ALZheimer's. While exagurated innate immune training may contribute in maintaining hyperinflammation condition and contribute in immune-pathgenesis enents leading to autoimmune diseases [13, 14, 15].

IIM OMINI SPECIFICITY VERSUS STIMULUS IMPART SPECIFIC

IIM have been as non or omni-specific memory exhibited by innate immune cells post to second exposure to the stimulus [8, 10] Though workers in 2025 [O'Farrell et al16] were proving that IIM is in fact stimulus impart specific. In an experimental settings human monocytes were separated and cultured macrophage derived. These macrophage were subjected primary and secondary IIM stimuli. The period between primary and secondary stimuli were six days. IIM probing parameter were inflammatory cytokine production and single RNA imaging. Both cytokine production and single RNA imaging demonstrate stimulus specific pattern of response to re-stimulation at single cell level. Inflammatory transcription factors ITF were detected by differential licensing of macrophages it was found that ITF is associated with encoding specificities in chromatin. IIM showed a stronger responses to secondary stimuli that are more similar to the initial stimulus. They suggested that stimulated macrophages experienced a functional role in of these stimulus specific memories rather than universal innate immune memory. These findings demonstrate that different stimuli induce an impart specific memories that generate distinct training macrophage phenotypes.

POTENTIALS

The logical and proved concepts and evolution mechanisms of IIM were found in a spectrum of potentials as; microbiome communication, interaction with pre-immunity, infection, impact in vaccination and in autoimmunity as in the following paragraphs.

MICROBIOME

The link between innate immune memory IIM and microbiome is in form of bidirectional communication via cross-talk mechanisms. Changing in the microbiome forming populations modulate the intensity of IIM. Some stimulators for IIM may alter any of the specific microbiome members or their metabolites. Such alteration can induce alternative IIM phenotype formation. These IIM phenotypes own the potentials of pathogen clearance and maintenance of immune homeostasis [17]. There were a functional patterns that links gut microbiome and IIM [12]. To interpret the “Microbiome-IIM link”, Yang et al [16], suggest three in hold possible mechanisms that may be in hold as; Non-coding RNA, microbiome-immunity-neuronal-axis and genetic variants. In an experimental setting in which mice model was treated with dextran sulfate sodium DSS. The DSS treatment disrupt mucosal barrier and lead to translocation of E. fecalis to bone marrow. Such translocation lead to epigenetic reprogramming of bone marrow progenitor cells to evolve IIM state. The IIM expressing progenitors showed an enhancing inflammatory responses [18].

PRE-IMMUNITY

Pre-immunity is specific variable grades, initial pre- existing immunity to past infection or past vaccination in any human population inhibiting certain geographic niche. In non-exposed human populations the levels of systemic and tissue resident memory cells have been minimal as the level of their natural inducing microbiome members. Though the central and peripheral innate and adaptive immune memory pre-existing in past infected or past vaccinated populations are of low or reasonable levels. The primary and secondary and secondary immune priming early in the immune response events, IIM may have possible add-on effect leading to more potent memory response in the innate arm and late in the immune response events adaptive arm mounted. This will leads to an augmented innate arm and boosting in adaptive immune memory to the inducing immunogen [, 19, 20, 21, 22].

INFECTION

Viral infection occurred in the human cellular tropism sites in which virus invade and replicate within the cells, triggering antiviral immune responses and production of type 1 interferons along with pro-inflammatory cytokines. TLR, RLRs on the surface of the phagocytic cells recognize the viral PAMPs in viral nucleic acids, innate immune cells activated and undergoes epigenetic and metabolic reprograming and adopt IIM state then secret pro-inflammatory cytokines and type 1 interferon, activating the antiviral mechanisms and coordinating adaptive immunity to produce antibodies by B cells and/or cytokines by T cells [23].

Human bacterial infections, LPS, peptidoglycan, and lipo-teichoic of the infecting bacteria constitute the PAMPs of the bacterial pathogenic invasion. In the onset of the infection the pathogen recognized by the TLR or RLR of the innate immune cells such recognition induces epigenetic and metabolic reprograming of these cells in which they adopt IIM state and produce pro-inflammatory cytokine and chemokines made them of enhanced anti-bacterial functions and promote the clearance of the pathogen [23, 24, 25]. In human fungal infections, Β- glucans, mannan and chitin are the fungal PAMPs that are involved in activation of dendritic cells and neutrophils. The activation lead to epigenetic and metabolic reprogramming in the myeloid cells that adopt IIM state leading to secretion of pro-inflammatory cytokines and chemokines with enhanced anti-fungal function and promote the clearance of the fungal pathogen [23]. IIMis induced through activation of pattern recognition receptors and the action of cytokines on hemopoietic progenitors and stem cells in bone marrow and innate leukocytes in the peripheral circulation. The trained phenotypes is induced and sustained by epigenetic modification that reprogram transcriptional patterns and metabolism. These modifications augment antimicrobial functions like that of leukocyte expansion, chemotaxis, phagocytosis and microbial killing, to facilitate an augmented host response to infection [25], Table-3

Table-3: Nature of IIM infection recognition events and functions [23].

Features	Virus	Bacteria	Fungi
PAMP/microbe surface	Nucleic acids	LPS, petidogylcan, lpo-tiechoic acid	Β-glycan, mannan, chitin
PRP/ innate immune cell	TLR, RLR, NLR on NK cells	TLR, RLR, NLR on CDs, macrophages	TLR, RLR, NLR on DCs, Neutrophils
Recognition outcomes	Pro-inflammatory cytokine and chemokines, antiviral effects	Pro-inflammatory cytokine and chemokines, anti-bacterial effects	Proinfammatory cytokine and chemokines, anti-fungal effects
IIM functions	Viral resilience	Bacterial resilience	Fungal resilience

VACCINATION

The immunological potentials of vaccines are; infection protection and cross protection, prevents hypercytokinemia, abite exacerbation of pre-existing conditions, reduce susceptibility to natural pathogens and reduce secondary bacterial complications [26]. The inductive IIM state in innate immune cells hold the background for development of novel vaccine strategies that are planned to deliver broader and long lasting protection against various pathogens. This can be through the development pan specific vaccine epitopes just like that of BCG. Currently, IIM is being promising in a number of vaccine technology topic such as; vaccine histancy, limited efficiency variants vaccines for protection against unknown pathogens. Trained immunity offers new chances for immunomodulatory therapy for infectious and immune mediated diseases, by modulating pathogens involved in initiation of IIM state. It ca n be possible to enhance the host defense against wide range of pathogen, especially those that are difficult to target by conventional vaccines. Therapeutic targeting for the IIM molecular and cellular events of innate immune cells offer new strategies for treatment of inflammatory, auto-inflammatory and autoimmune diseases. Such therapeutic strategies can adjust polarization of macrophages between pro-inflammatory M1 and auto-inflammatory M2 state which is useful in managing allograft rejection [23, 26, 27, 28, 29]. Adjuvants can induce IIM in innate immune cells [30].

HYPERSENSITIVITY

If the inducing microbial antigen bears an immediate type allergenic epitope within its antigenic composition it will mount eosinophilic inflammatory response in first and second exposure as an IIM mixed response with other innate immune cells. But if it is of semi-delayed or delayed nature it will appears in the adaptive response as delayed hypersensitivity that evolve as activated macrophages and T cell subtypes responses along with inflammatory cytokines and chemokines. The different type of allergies are mediated by effector and memory cells. In case of type I hypersensitivity, B cells, a pre-requisite for activation of adaptive immune cells, is the activation of innate immune cells. The resulting inflammations is essential not only for initiation but also for elicitation of allergies. Innate immune system, tissue stress and damage response orchestrate inflammation [31].

AUTOIMMUNITY

It seems that there no definite evidence behind the IIM-autoimmunity connection paradigm. The matter is within the limited within levels of hypothesis, suggestions and laboratory animal finding variations. Tobi et al. [31] state that recent autoimmune disease works suggested that the innate immune system underlies the autoimmune disorders. Arts et. al. [14] have been stated as; we hypothised that in an appropriate activated IIM can played inductive role in induction and maintenance of autoimmune and auto-inflammatory disorders. Mucosal trained immunity based vaccines may relive infection in autoimmune disease patients in which both IIM and adaptive immune responses synergized to assist immune protection of infections in AD patients [21]. The enhanced responses of IIM in the macrophages could contribute to develop and maintain autoimmune and auto-inflammatory diseases [32, 33]. In an experimental setting of RA prone phenotype of the genetic mouse model, B -glucan can be employed to initiate the disease. Parallel to these findings B-glucan induced IIM can derive generation of osteoclast mediating inflammatory bone erosion in RA and bone loss in periodontitis, hence, the inductive potentials of IIM in autoimmune diseases is a disease context dependent and suggest a cross-talk between induction of IIM and susceptibility to autoimmune diseases [34]. V gamma4T cells an innate lymphocytes that express markers of conventional T cells severs as critical pathogenic role in mouse models of autoimmune diseases [4, 35, 36, 37].

TOLERANCE

Tolerance is a state of reduced or abolished responses to an inducing antigen in human and experimental laboratory animals. Tolerance is central genetic encoded and peripheral acquired. The dose limits for toleragens are either low or high dose tolerance. Tolerance is a matter of adaptive immune T and B cells. Tolerisation of lymphocytes need continual presence of toleragen facing the lymphocytes. The tolerisation mechanisms involved; T reg. function, anergy, and/or clonal deletion. Though innate immune cells may exhibit a type of tolerance as; BV2 cell culture were stimulated by either B cell activating factor or Bacterial LPS. Two stimulation programs were made. First, BAF as priming stimulus followed by LPS re-stimulation and the second was by first priming LPS followed by second LPS re-stimulation. The first program lead to an enhanced inflammatory stimulus indicating IIM. While the second program showed reduced inflammatory response suggesting tolerance state. First LPS stimulus lead to aerobic glycolysis while the second LPS stimulus does not induce aerobic glycolysis. Hence the first LPS priming and its induction of aerobic glycolysis was an essential step in the induction of innate immune tolerance [38].

INNATE IMMUNE MEMORY IIM VERSUS ADAPTIVE IMMUNE MEMORY AIM

Immune memory, classically known within the continuum of the cellular events of adaptive immunity. Though in the three lasting decades of th21ist century, natural IIM have been evolved, proved in man and animals and experimental induced in laboratory animals. In this context it is invite-able to coin a comparative view to both of the immune memories, Table-4.

Table-4: A comparative view to IIM and AIM.

Features	IIM	AIM
Antigen dependence	Independent	Dependent
Cells involved	Macrophages, dendritic cells, NK Innate lymphocytes subsets	B and T lymphocytes
Cell receptors involved	TLRs. RLRs, NLRs and CD markers of innate lymphocyte subsets	TCRs, BCRs
Induction/Activation	Primary and secondary stimuli	Primary and secondary booster antigen doses
Mediator involved	Inflammatory cytokines and chemokines	Cytokines, paired signal transduction
Memory Reaction intensity	Intense	Intense
Memory reaction onset and mediator secretion duration	Short duration	Short duration
Memory action duration	Relatively long	Long
Memory Reaction outcomes	Recall active immune and Tolerance [glial cell model]. Mal-training induce immune mediated diseases	Recall active immune and Tolerance. Allergenic and auto-reactive responses lead to immune mediated diseases

Immune Specificity	Stimulus impart specific	Stimulus specific
Effect of ageing	Both aged and young have same immune response	Ageing lead to immune decline

MICROGLIAL CELL MODEL; A SHOWCASE ANALYSIS [38]

Introduction

The mononuclear cells of the nervous system are the microglia. Microglia have two main memory response state, innate immune memory and tolerance. Following the microglial challenge, it retain immune memory. Though the differences between immune memory and tolerance mechanism are rather unclear.

Program

The stimulating agents were BAFF and LPS. The cell culture line was BV2 cell line. Two treatment were planned. First BV2 stimulated by BAFF the second stimulus was LPS. While the second treatment was the primary stimulus by was LPS and the second stimulus was by LPS.

Findings

The first treatment has shown enhanced responses indicating of priming as IIM. The second treatment has shown reduced suggesting tolerance.

Conclusion

The main difference between the two treatments was the induction aerobic glycolysis by LPS as in treatment one. While LPS re-stimulation, microglia were unable to induce aerobic glycolysis.

Memory Analysis

BFAA and LPS induce IMM in microglial cells in their cultures. While Primary stimulus and re-stimulus with LPS induce tolerances state.

AGEING MICE; A SHOWCASE ANALYSIS [23]

Introduction

Aging markedly increase the incidence and severity of human persons of age 65 and above for 65% of sepsis cases. IIM found enhancing resistance to infection by modulating aging immune system; Laboratory mice may extrapolate aging effect in human beings.

Program

Two groups of mice young10-12 weeks old and aged 18-28 week old were subjected to primary and re-stimulating B-glucan to evolve IIM and P. aeruginosa as infecting agent.

Three parameters were used to match IIM in primed mice groups as; P. aeruginosa bacterial clearance, leukocyte B and inflammatory cytokine production. The parameters for bacterial clearance were; bacterial phagocytosis and RNA sequence analysis for the gene expression.

Findings

It was found that B gulcan stimuli induces IIM in second exposure with an end point as; enhanced leukocyte B, increased bacterial clearance to the infecting agent, increase in phagocytosis and respiratory burst, distinct gene expression patterns, decreased cytokine production and suppression of pathways cell division both in aged and young mice groups. Compared to aged was being with enhanced gene ontology, respiratory aortic aneurysem, connective tissue deposition wound healings.

Conclusion

IIM can be effectively induced in aged mice which may provide an encouraging insights into potential strategies for enhancing infection resistance in elderly.

Memory Analysis

IMM in aged mice model prevents the declining effects of ageing in this mouse model.

SHOWCASE ANALYSIS OF HUMAN VACCINATION MODEL [39]

Introduction

BCG vaccine in vaccinee induce innate immune response in form of innate immune memory that may mediate shared immune protection against heterologous infections. Human innate and adaptive immune cells display oscillations in count and functions through out the day. BCG vaccinee express both IIM and adaptive immune responses.

Program

The program ensembles two study groups, the pilot and the test proper groups. The pilot includes 18 volunteers were vaccinated with BCG at 6 pm ang 36 were vaccinated at 8 to 9 am. At two weeks post vaccination and at three months after vaccination. Peripheral blood were collected from both of vaccinee groups and mononuclear cells separated then cultured. M. tuberculosis was the first stimulus and S. aureus was the second stimulus both for checking periods. The test proper group includes 302 volunteers and the vaccination and stimulating modes were as in pilot group. The cytokine IL1B, TNFalpha and IL6 for innate and IL2 for adaptive cytokine determinations.

Findings

Morning have been showing high innate inflammatory cytokine IL1B, TNFalpha, IL6 and adaptive IL2 cytokines compared to evening vaccination in pilot and early morning late in morning vaccinee compared to evening vaccine in test proper vaccinee.

Conclusion:

Both of IIM and adaptive immune memory were high in morning that in evening vaccinee.

Memory Analysis

BCG induces IIM and AIM in human vaccinee and in macrophage culture. Circadian rhythm enhances the IMM ad AIM in human and in macrophage response in culture at morning and early morning vaccinations. Evening BCG vaccination reduced by circadian rhythm influences both inhuman and in cell culture.

SUGGESTION FOR HUMAN STUDY PROGRAM

A population of 25 apparently normal volunteers and 25 test proper volunteers vaccinated with typhoid 2a vaccine in two shots first stimulus then15 days, the second stimulus. Post to second stimulus, Cell free culture filtrate of S. typhi were used to stimulate peripheral blood collected mononuclear cell separated and cultured in appropriate cultured cell line. Inflammatory cytokines IL1B, TNF alpha, IL6 for innate cells and IL2 for lymphocytes. Results will be analyzed for evidence of IIM in test proper as compared to control group.

CONCLUSION

IIM is an impart-specific immune memory effective in the second exposure, plastic in nature and functionally multipotent. It is genetically encoded and epigenetically induced. The mechanisms behind which are; epigenetic and metabolic reprograming, imply the action of noncoding RNA, circadian rhythm controlled, gene regulatory circuit regulated and microbiome-immune-neuronal –axis function related. It is non-antigen dependent, inflammatory cytokine mediated. IIM is involved in infection pan-protection and resilience of bacterial infections in immune compromised patients. Its malfunction associated with immune mediated diseases both in man and experimental laboratory animals. It is of promising potentials in vaccine production programs and as an immunotherapy targets.

REFERENCES

1. Hoffmann, et. al. 1999. Phylogenetic perspective I innate immunity. Science. 284:1313.
2. Parslow, T. G.; Stites, D. P.; Terr, A. T.; Imboden, J. B. 2001. Medical Immunology 10th ed. Lange Medical publications, McGraw-Hill, NY.
3. Katsikis, P. D.; Palendran, B.; Schoenberger, S. P. 2007. cross-Roads between innate and adaptive immunity. Adv. Exp. Med. Biol. 540. Spriger, California.
4. Vijay, K. 2018. Toll-Like receptors in healthy and inflammatory disease; Past, present and future. Int. Immunopharmacol. 59:391-412.
5. Netea, M. G.; latz, E.; Mills, K. H.; O'Neill, L. A. Innate immune memory:a paradigm shift in understanding host immunity16(7):675-679, doi10. 1038/ni. 3178.

6. Incalcaterra, S.; Andres, J. D. 2020. Trained immunity at a glance; A review on the innate Immune memory and its potential role in infection, disease and new therapeutics strategies. Adv. J. Gadu. Res. 8(1):68-81.
7. Alexopoulous. L.; Irla, M. 2025. Toll-like receptors(TLR) in the trained immunity era. eLife14:e106443. doi. 10. 7554/elife106443.
8. Qu, J.; Guo, X; Wang, X. et. al. 2025. The significance of trained immunity in cancer. Front. Immunol. 2025. 1665099.
9. Mhlanga, M. M.; Fanucchi, S.; Ozturk, M. et. al. 2025. Cellular and molecular mechanisms of innate memory responses. Ann. Rev. Immunol. 43; 615-640.
10. Ajit, J. 2025. Expanding horizons of trained immunity:implications in Cancer and pathogen resistance. Prim. J. Immunol. 3. 100006. doi. 10. 70389/Pij. 100006.
11. Vuscan, P.; Kischkel, B.; Joosten, L. A.; Netea, M. G. 2024. Trained immunity; general and emerging concpts. Immunol. Rev. 323:164-185.
12. Yang, B.; wu, J.; Hou, T.; Liu, S. 2025. Memory misfire:the gut microbiome-trained immunity circuit in inflammatory bowel diseases. Int. J. Mol. Sci. 3; 26(19)9663. doi. 10. 3390/ijms. 26199663.
13. Kaufmann, E.; Sohrabi, Y.; Dominguez-Andres, J. et. al. 2025. Evolving our understaniding of trained immunity. eLife14:e106029. doi. 10. 7554/eLife. 106029.
14. Hajishengallis, G.; Chavakkis, T. 2024. Central trained immunity and its impact on chronic inflammatory and autoimmune diseases. J. Allergy. Clin. Immunol. 154:1113-1116. doi. 10. 1016/jaci. 2024. 06. 003.
15. Arts, R. J. W.; joosten, L. A. B.; Netea, M. G. 1018. The potential role of trained immunity in autoimmune and auto-inflammatory disorders. Front. Immunol. 9. 298. doi. 10. 3389/fimmu. 2018. 00298.
16. O'Farrell, A.; Niu, Z.; Li, J. et. al. 2025. Innate immune memory is stimulus specific. bioRxiv. Priprint. doi. 10. 1101/2025. 01. 22. 634275.
17. Pellon, A.; Palacios, A.; Abecia, L. et. al. 2024. Friends to remember: Innate immune memory regulation by the microbiota. Trend. Microbiol. 33(5):510-520. dii. 10. 1016.]/j. tim. 2024. 12. 002.
18. Robes-Vera, I. et. al. 2025. Microbiota translocation following intestinal barrier disruption promots mincle-mediated training of myeloid progenitors in the bone marraw. Immunity, S1074-7613(24):00577-6. doi. 10. 1016/j. immunol. . 2024. 12. 012.
19. Ruiz, D. F. Z. 2025. development of microbiota specific T cell s during systemic autoimmunity3776. J. Immunol. 214; Supplement- 1. doi. 10. 1093/jimmu/vkf. 283. 1540.
20. Kang, A.; D'Agostino, M.; Afkhami, S. et. al. 2025. resident memory macrophages and trained innate immunity at barrier tissues. eLife, 0:e106549. doi. 10. 7554/elife. 106549.
21. Zhang, H. et. al. 2026. Expert reaction to study in mice on a vaccine for various pathogens. Science. aea1260. doi. 10. 1126/sciens/aea. 1260. Science Media Center.
22. Candelas, G.; Villegas, A.; Sanchez-Ramon. S. 2024. Mucosaltrained immunity based vaccine:cutting recurrent infcetions in autoimmune patients on immunosuppression. J. Allergy. Clin. Immunol. 154(5): 1120-1122.
23. Bahl, A.; Pandey, S.; Rakshit, R.; Kant, S.; Tripathi, D. 2025. Infection-induced trained immunity:atwist in paradigm of innate hot defense and generation of immunological memory. Infection Immunity93(1):1-25. doi. 10. 1128/iai. 00472-24.

24. Hao, D; Caja, K. R.; McBride, M. A. et. al. 2025. Trained immunity enhances host resistance to infection in aged mice. J. L. B. 117(4):qiae. 259/7932571.
25. Sherwood, E. R.; Burelbach, , K. R.; McBride, M. A. et. al. Innate immune memory and the host response t0 infection. J. Immunol. 208(4):785-792. doi. 10. 4049/jimmunol. 2101058.
26. Arunachalam, A. R. 2024. Vaccines induce homeostatic immunity, generating several secondary benefits. Vaccines12. 396. doi. 10. 3390/vaccines/12040396.
27. Ziogas, A.; Netea, M. G. 2022. Trained immune memory and heterologous protection against infections. Trend Mol. Med. 28(6):497-512.
28. Martin-Cruz, L.; Beneto-Villalvilla, C. :Angellina, A. et. al. 2024. Trained immunity-based vaccine for infection and allergic diseases. J. Allergy. Clin. Immunol. 154:1085-1094. doi. 10. 1016. =/jac. 2024. 09. 009.
29. Baydemir, I.; Dulfur, E. A. , Netea, M. G. et. al. 2024. Trained immunity-inducing vaccines:Harnessing innate immune memory for vaccine design and delivery. Cli. Immunol. 261:1-10. doi. 1016. /j-cim. 2024. 109930.
30. Pasco, S. T.; Martin-Ruiz, I; Arauja-Aris, S. et. al. 2026. Challenge specific modulation of responses to adjuvant-induced innate immune memory. Immunol. 177:254—269.
31. Martin, S. F.; Esser, P. R. 2022. Innate immune mechanisms in contact dermatitis. Hand Book Exp. Pharmacol. 268:297-310. doi. 10. 1007. /164-2021/482.
32. Tobi, M.; Spencer, P. Tobi, Y. Y. et. al. 2025. The role of innate immune system in autoimmune and other inflammatory diseases. Preprint. doi. 10. 20944/preprints2025. 11. 0351. vol. 1.
33. Funes S. C.; Rois, M.; Fernandez-Fierro, A. et. al. 2022. Trained immunity contribution tpo autoimmune and inflammatory disorders. Front. Immunol. 13:868343. doi. 10. 3389/fimmu. 2022. 868343.
34. Schulter, T.; Elsas, Y. V.; Priem B. et. al. 2025. trained immunity; induction of an inflammatory memory in disease. Cell Research. 35:792-802. doi. 103/s41422-025-1171-y.
35. Haacke, N. :wang, H.; Yan, S. et. al. 2025. Innate immune memory of osteoclastogenesis promotes inflammatory bone loss in mice. Dev. Cell. 60:1854-1870. doi. 10. 1016. /devcel. 2025. 02. 001.
36. Abreu, H.: Rainer, D; Chiocchetti, A.; Cappellano, G. 2026. Trained immunity in autoimmunity: friend, foe, or therapeutic target?, Biomed. 14, 526. doi. 3390/biomedicines. 1430526.
37. Mora, V. P.; Loaiza, R. L.; Soto, I. A. et. al. 2023. Involvement of trained immunity during autoimmune responses. J. autoimmunity. 137. doi. 10. 1016/j. jout. 2022. 102956.
38. Twriss, M.; MacVicar, B.; Cernia, A. V. 2023. Modelling microglial innate immune memory in-vitro:understanding the role of aerobic glycolysis in innate immune memory. Int. J. Mol. Sci. 24, 8967. doi. 10. 3390/ijms. 241058967. .
39. de. Bree, L. C.; Mourits, V. P.; Koeken, V. A. C. M. et. al. 2020. Circadian rhythm influences induction of trained immunity by BCG vaccination. JCI. 130(10); 5603-5616. doi. 10. 1172/jci. 133934.