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IMMUNE CHECKPOINTS AND BACTERIAL PERSISTENCE: REVIEW OF EMERGING CONNECTION IN CHRONIC INFECTIONS

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ABSTRACT
The persistence and immune evasion of microbes have continued to be a major health challenge worldwide since chronic bacterial infections persist in many parts of the world. The role of immune checkpoint molecules like PD-1, CTLA 4 and LAG-3 in cancer and viral infections is extensively studied, and their importance in bacterial pathogenesis is becoming appreciated. These routes lead to regional immune impairment, permit the establishment of long-lasting reservoirs and obstruct eradication. The review discusses the immunological immunoregulatory functions of immune checkpoints during chronic bacterial infections, which focus on *Salmonella Typhi Helicobacter pylori*, and biofilm-forming pathogens. The comparison of checkpoint activity in bacterial and viral environments is made where differences in expression patterns, reversibility in functional effect, immune compartment are noted. Recent findings indicate that the checkpoint molecules are not only the brakes of the immune system, but also the contributors of microbial persistence in host tissues. Combined checkpoint inhibitor and antibiotic-based therapeutic approaches have therapeutic potential within preclinical models. Clinical use is however limited by a lack of human data, unpredictable immunopathology, and a need to develop reliable biomarkers that can guide therapy. The pathogenic particularities of checkpoint signaling Virus comprehending the peculiarities of checkpoint signaling is critical to safe and effective treatment design in bacterial infections. This review combines the mechanistic considerate of this area, translational barriers, and opportunities and proposes constructs where targeting immune checkpoints can be used as adjunct therapy in bacteria persistence.

KEYWORDS: Immune checkpoints, Antibiotic therapy.

1. INTRODUCTION
The persistence of chronic bacterial infections despite inhibitory effect on host immune system and chronic infection of tissues by bacteria has continued to pose a great health threat to the global population. Even pathogens that are known as *Salmonella Typhi Helicobacter pylori*, and *Borrelia burgdorferi*, have developed strategies to evade elimination in the presence of immune surveillance as well as antimicrobial therapy. These chronic infections cause high morbidity and treatment failure as well as resistant infection to antibiotics.[1,2] Historically, such immune checkpoints, as programmed death-1 (PD-1), cytotoxic T- lymphocyte lymph node-associated antigen 4 (CTLA-4), and lymphocyte activation gene-3 (LAG-3), would be investigated in the context of cancer and chronic viral infections, where they would inhibit T cell responses and avoid tissue destruction caused by immune effectors.[3] Nonetheless, there is an expanding body of evidence that indicates that comparable immune inhibitory pathway can be abused by bacterial pathogens to facilitate immune evasion and sustain life long within a host.[4,5] The recent reports have demonstrated that PD-1 and PD-L1 are upregulated during chronic infections with bacteria, especially in research on patients with tuberculosis and *H. pylori*-induced gastric infection, and they contain active host immune inhibition.[6,7] The modulation of T cell exhaustion, cytokine secretion and macrophage functions by this type of checkpoints, represents one of the potential ways by which bacteria establish an immunosuppressive environment.[8] The connection of immune checkpoint to bacterial persistence is an interesting frontier of the host-pathogen interaction dynamic that is underrepresented in research at this time. The functional aspects of the immune checkpoints in bacterial infection might provide fresh treatment options. Cancer immune checkpoint inhibitors (ICIs) have clinical application and could provide an opportunity to target persistent pathors. Their usage in the setting of infectious diseases, however, is still questionable because of the possibilities of immune reactivation and concomitant pathology.[9]

This review gathers existing evidence in developing an immune-checkpoint pathway and bacterial persistence in chronic infection environments. It is an amalgamation of current discovery within immunology, microbiology, and translational studies and an analysis of the effective implications of such to the therapeutic intervention approach.

2. THE OVERVIEW OF IMMUNE CHECKPOINTS

Immune checkpoints are inhibitory pathways that are involved in central control of self-tolerance and regulation of immune activation so as to avoid tissue damage of the host. These regulatory pathways entail co-inhibitory receptors that are mostly expressed in T lymphocytes including programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated express 4 (CTLA-4) lymphocyte activation gene 3 (LAG-3), and cell immunoglobulin and mucin-domain containing-3 (TIM-3). Such receptors bind to corresponding ligands on antigen presenting cells or tissue resident cells to inhibit the signaling in T-cell receptors, inhibit secretion of cytokines, and inhibit proliferation of cells.[9] PD-1 binds to PD-L1 and PD-L2 to kill the T-cells with exhaustion, especially when there is a situation of chronic antigen exposure. This mechanism was well characterized in cancer and long-term viral infections where it leads to long-term immune suppression.[10] CTLA-4 in turn disrupts the co-stimulatory effects of CD28, binding to CD80/CD86 and has its dominant influence in early stages of T-cell activation in the lymphoid organs.[11] Other checkpoint receptors like LAG-3, TIM-3 contribute synergistically with the PD-1 to enhance functional exhaustion in T-cells population. LAG-3 interacts with the major histocompatibility complex class II molecules, which regulate the activity of T cells and dendritic cells, whereas at the same time TIM-3 interacts with such ligands as galectin-9 and phosphatidylserine and is involved in the regulation of the Th1 responses as well as in the phagocytosis of apoptotic cells.[12,13] The recent efforts have expanded the applicability of these pathways to other adaptive immunity systems. Immune checkpoints have been described to be expressed on innate immune subsets such as natural killer cells, dendritic cells, macrophages, and myeloid-derived suppressor cells. These data indicate extended immunomodulatory roles both in physiologic and pathologic conditions.[14] Immune checkpoint blockade has proved highly effective in cancer therapy, especially in the ability to reinstate T-cell activities. An analogous inhibitory environment can exist in chronic bacterial infections where continual experience of antigens and immune adjustment is combined.[2]

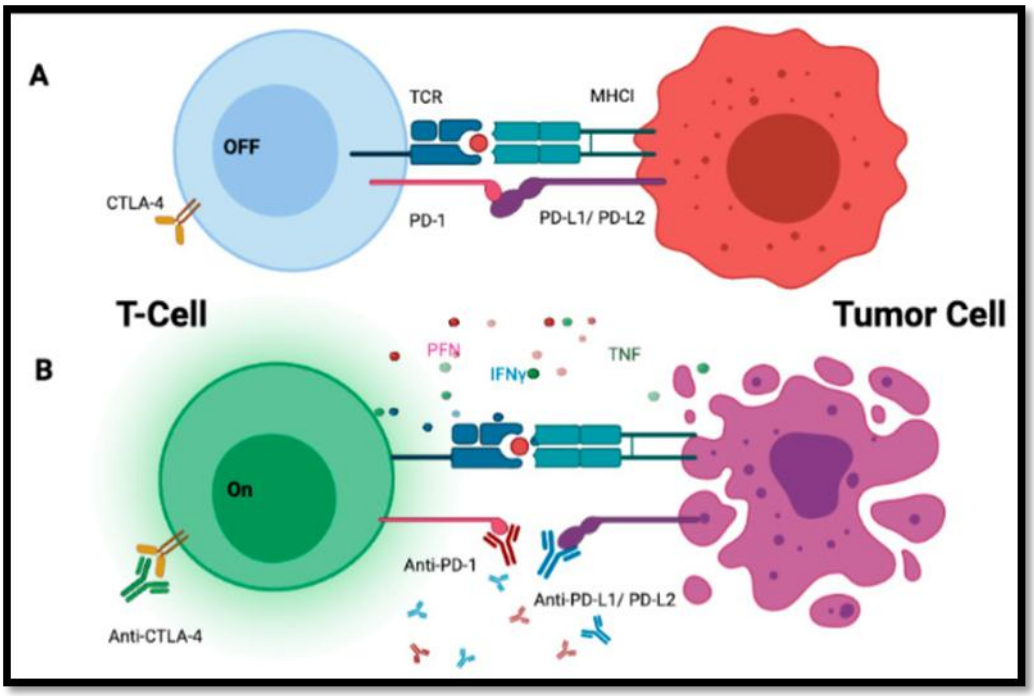

Figure 1: shows the effects of CTLA-4 and PD-1 as inhibitors of the priming and the effector stages of T-cell activation, and how inhibition of these pathways potentiates normal immune responses to persistent antigens.[10]

3. PERSISTENCE IN CHRONIC INFECTIONS OF BACTERIA

Persistence in bacteria is a level during which a small portion of bacteria response to the destruction of antimicrobial pressure and immune attack not as a result of resistance but as a consequence of occurring genetically. This phenotype promotes long term infection, failure to treat, and recurrence especially in immunocompromised hosts. The persistence is completely unlike the resistance; whereas point mutations in the strain of resistant changes can be acquired and inherited, dynamic phenotype changes in

persisters help them to survive in the adverse environment.[15] There are some pathogenic bacteria species with high persistence factors that relate to chronic infections, *Salmonella Typhi* can go into the static non-replicative, metabolically changed state in granulomas, which restricts the destruction and recognition of the granulomas and immune cells.[16]

Helicobacter pylori is a gastric pathogen which employs intracellular localization, defective antigenicity and immune evasion mechanisms to cause prolonged colonization of the gastric mucosa.[17] To evade the immune system and maintain lasting establishments in tissues, *Borrelia burgdorferi*, a causative agent of Lyme disease, uses antigenic variation, immune suppression and motility-related dissemination.[18] Besides these intracellular and evasive mechanisms, extracellular bacteria e.g., *Staphylococcus aureus* and *Pseudomonas aeruginosa* grow into biofilms (structured bacterial colonies that are covered by a protective coat).

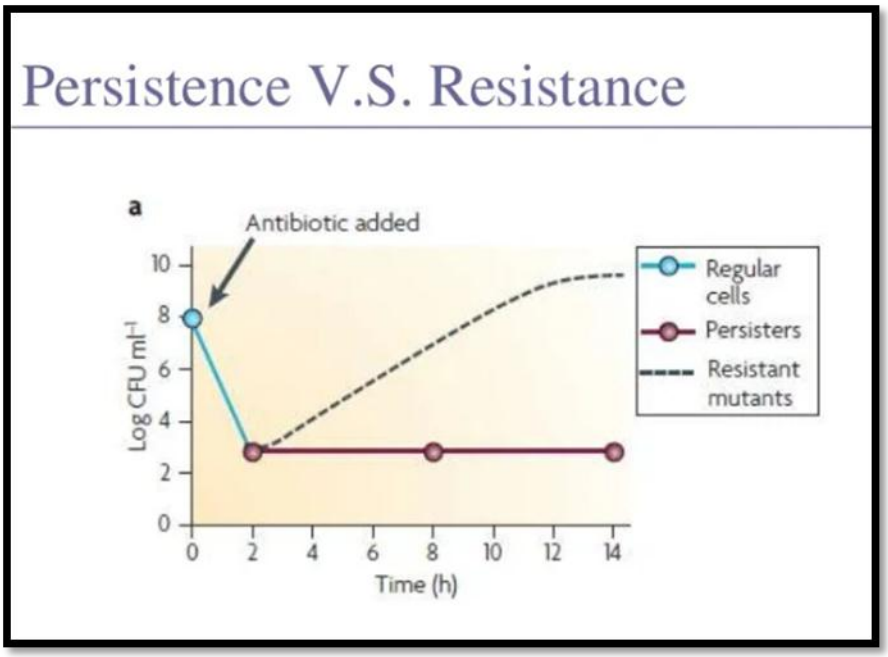

Figure 2: A graphic comparison between bacterial resistance, based on survival and regrowth of resistant strains, and persistence, based on inheritable phenotypic tolerance involving survival of a stable subpopulation to antibiotics shows the difference between these two phenomena.[18]

Biofilms enhance nutrient gradients, limited penetration by antimicrobials, and low rates of metabolism, which together cause survival in tissues and medical devices.[19] Immunologically, there is a higher incidence of dysfunctional or tolerogeneous immune response induced by persistent bacteria. There can be obstruction in the process of antigen presentation, exhaustion of T-cells, and cytokines are used to tend towards anti-inflammatory phenotypes. Such conditions resemble the microenvironments seen in cancer and in chronic viral infections and it is possible that immune checkpoint pathways contribute to the maintenance of bacterial persistence.[20] The immunological pathways that facilitate the persistence such as the checkpoint pathways can also give therapeutic approaches to clear the recalcitrant bacterial reservoirs. Interaction between survival mechanisms of microbial pathogens and the immune systems of their hosts offer a difficult but yet saving horizon in the study of infectious diseases.[21]

4. IMMUNE CHECKPOINTS AND CROSSTALK IN THE BACTERIA PERSISTENCE

New findings suggest that immune checkpoint signaling can strengthen bacterial survival by dampening host immune defense to favor pathogen survival in both the short- and long-term repertoire. Higher expression of checkpoint receptors on T cells and other immune subsets, including PD-1 and CTLA-4, are routinely manifested in chronic bacterial infections similar to the phenomenon seen with chronic viral infections and neoplasms.[22] In pulmonary tuberculosis, an increased expression of PD-1 has been found on CD4 + and CD8 + T cells obtained by the peripheral blood and the granulomatous lesions. Such upregulation is attributed to poor cytokine response, reduced proliferative potential, and exhaustion of T-cells, inability to kill *Salmonella Typhi* in spite of antigen stimulation.[23]

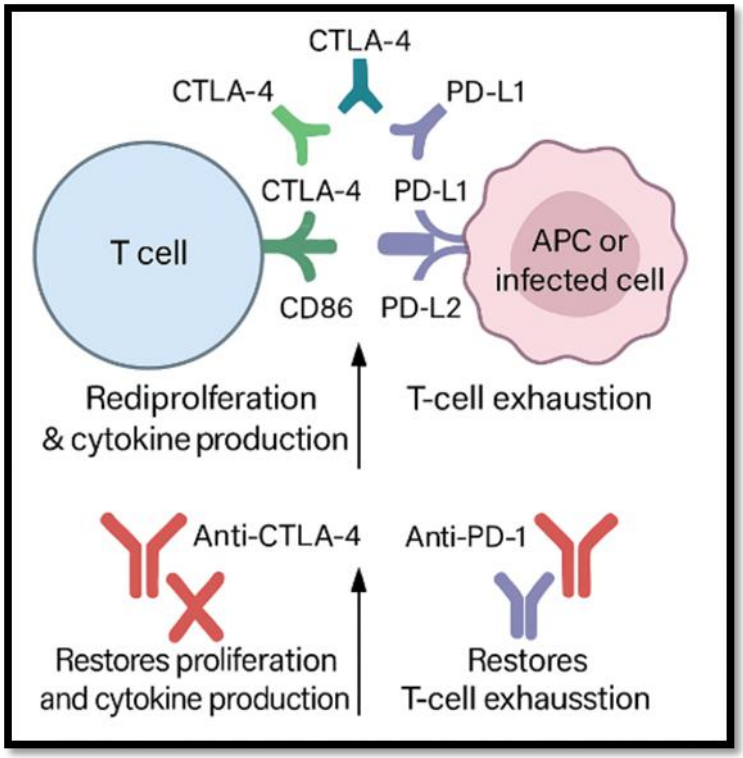

Figure 3: Inhibition of T-cell immune Checkpoints through CTLA-4 and PD-1 Signaling in Chronic Bacterial Infection.[24]

In addition, PD-1/PD-L1 blockade in mouse strains has led to increased clearance of bacteria, yet this is also associated with immunopathology as a consequence of unregulated inflammation.[24] Presence of increased PD-L1 has been noticed also in *Helicobacter pylori*-infected gastric mucosa infiltrating immune cells and epithelial cells. This term is associated with the decreased local T-cell activity and raised bacterial colonization, which implies that *H. pylori* is able to promote immune checkpoint circuitry to suppress the host reactions.[25] In Lyme disease, the presence of Borrelia burgdorferi has been linked with an upregulation of PD-1 and TIM-3 on T cells in murine and human patients with chronic infection. These alterations are associated with the slow removal of bacteria and prolonged joint inflammation.[26] In addition, bacterial pathogens that form biofilms like *Pseudomonas aeruginosa* are known to create suppressive cytokine environment further propagating the expression of checkpoints on the immune cells at the site of infection.[27] The above findings all contribute to a paradigm that bacterial pathogens can engage immune checkpoint signaling to create an immune suppressing microenvironment to survive despite ongoing immune attack. This leads to abnormal immune functioning that impairs effective clearance of the pathogen and which can lead to chronicity and relapse.[28]

5. IMMUNE CHECKPOINT BLOCKADE IN CHRONIC BACTERIAL INFECTION: THERAPEUTIC IMPLICATIONS

The idea of the therapeutic modulation of the immune checkpoints has redefined treatment approaches in oncology but their implementation in the scenario of chronic bacterial infections is still being explored. Evidence collected in experimental studies indicates the possible improvement of immune effector activity against chronic bacterial pathogens through transgression of immune checkpoints. However, the translation of the method in clinical practice is limited by the issue of the immune-mediated pathology and the worsening of the disease.[29] Experimental use of PD-1 or CTLA-4 blockade in mouse model of tuberculosis, has shown better clearance of intracellular infection, characterized by a rise in T-cell proliferation and in the synthesis of interferon-gamma. However, aggravated pulmonary inflammation is also observed in some experiments and that common signaling through checkpoints is dualistic and serves to balance control of microbes and protection of tissues.[30, 31] PD-1/PD-L1 inhibition has been effective to reinstate T-cell response and decrease bacteria load in preclinical models of Helicobacter pylori gastric infections. Nonetheless, this has the potential of improved gastric inflammation or injury and this requires careful analysis prior to implementing in the clinic.[32] Antibiotics are being studied as combinatorial approaches against immune checkpoint inhibitors (ICIs). The reasoning applied to such regimens is based upon reawakening of the immune effector pathways through addressing bacterial viability with an intent to produce a sterilizing immunity and lower rate of relapses.[33] Concepts have also been similar to infections by Borrelia burgdorferi and biofilm-related infections like Pseudomonas aeruginosa, where ICIs could work alongside antibiotic penetration/clearance host

responses.[34,35] Although in controlled conditions the approach has shown promising results, the absence of human clinical trials, the difference between responses in various host immune systems, and the possibility of immune hyperstimulation are significant obstacles. Potential approaches to achieve immunotherapeutic efficacy without the side effects would be based on biomarker-directed dosing and geographical modulation of the checkpoint.[36]

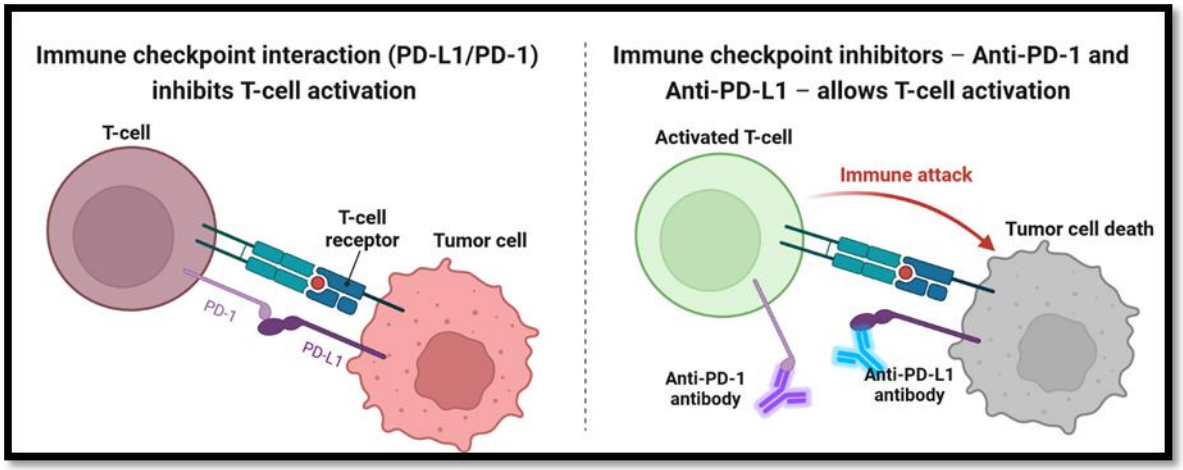

Figure 4: ICB reawakens T-cells and with the addition of antibiotics could induce improved eradication of bacteria causing chronic infections.[31]

6. IMMUNE CHECKPOINT KNOWLEDGE GAPS AND STRATEGIC POINTS IN IMMUNE CHECKPOINT TARGETED ANTIBACTERIAL THERAPY

Though the previous works have signalled some promise of immune checkpoint inhibitors (ICIs) in boosting hosts to their infections with persistent bacteria, some obstacles have not been clear. The immunological milieu of chronic infections by bacteria is variated and determined by the type of the pathogen, host genetics, location of infection and concomitant inflammation. This paradigm makes it difficult to discover ideal targets of immunomodulation and forecast clinical responses.[37] In bacterial infections, in contrast to cancer, where checkpoint blockade is frequently targeted toward focal immune exhaustion in the tumor microenvironment, there are reciprocating relationships between systemic and tissue-based immunity. Additionally, expression of checkpoint molecules in the context of infection is not restricted to T cells, but is integrable to the innate immune subsets such as dendritic cells, macrophages and myeloid-derived suppressor cells further complicating therapeutic manipulation.[38] Safety is a large issue. The increased activation of the immune system can lead to a non-specific effect on the tissue with the erosion or paradoxical aggravation of the infection especially with immune-privileged sites infected, like the central nervous system or lung parenchyma. Cases of development of tuberculosis after PD-1 blockade in cancer patients emphasize the importance of a cautious risk evaluation.[31] The other question yet to be answered entails the time and duration to checkpoint modulation. Early intervention can potentiate bacterial clearance whereas late targeting could worsen pathology caused by the immune system. The situation is that there are no biomarkers yet that could stratify patients based on either immune checkpoint expression patterns or profiles of T-cell exhaustion.[39] Additionally, majority of the available data are based on murine models. A translation study and controlled clinical trial as an evaluation of efficacy, safety, and biomarkers in humans are highly needed. ICI targeting may be further enhanced by preparation of tissue-specific or pathogen-specific ICI or combination approach with local administration to reduce toxic activity in other organs.[40, 41] The existence of knowledge gaps points out towards the multidisciplinary perspective that encompasses immunology, microbiology, pharmacology, and systems biology to perfect therapeutic approaches. These gaps are crucial to overcome the safe use of ICIs in the context of infectious diseases as well as to prevent the so-called unintended immunological effects.

7. COMPARATIVE IMMUNOLOGICAL IMPLICATION OF CHECKPOINT REGULATION IN BACTERIAL AND VIRAL INFECTIONS

Despite an abundance of investigations characterizing the immune checkpoint pathways (like PD-1 and CTLA-4) in chronic viral infection, the role of the immunological checkpoints in bacterial persistence show similarities and unique differences. In chronic viral infection with HIV, HBV, or HCV, continuous antigen-mediated stimulation causes a pattern of progressive T-cell exhaustion with sequential loss of effector functions, enhanced PD-1 expression and inhibited proliferation.[42] The role of these checkpoints is to restrain immune-mediated tissue damage at the sacrifice of compromised clearance of the virus. On the other hand, systemic T-cell dysfunction is rarely seen in chronic bacterial infections which mostly manifest with localized immune suppression. Expression of the checkpoint receptors is equally dysregulated, specifically upregulated in many

instances as well, though patterns of upregulated expression tend to be more heterogeneous and their functional impact context-dependent by tissue site, bacterial load and host genotype.[43] As an example, in tuberculosis, PD-1 expression is associated with the activity of the lesion, and spatially focused expression to granulomatous structures, meanwhile in Helicobacter pylori infection, PD-L1 is considerably up-regulated on epithelial cells to paralyze local T-cell reactions.[44, 45] The second difference is the reversibility of the checkpoints. Blockade of PD-1 in viral environments has been consistent in reinstituting antiviral responses. But in the case of bacterial infection, checkpoint inhibition produces a less predictable response with models both demonstrating increased clearance of the bacteria as well as immunopathology or a paradoxical worsening of the disease.[46] Moreover, physical barriers, found in bacterial pathogens, include the use of biofilms, which do not depend on the immune checkpoints to inhibit the access of immune cells. This is opposed to the viral latency, in which immunity evasion is molecular and intracellular. Such stratification makes the checkpoint modulation impact in bacteria more complicated and requires the special treatment regimens.[47] The different functions of the immune checkpoints in bacterial and viral infections highlight the need to consider pathogen-specific design of immunotherapeutic strategies and the requirement of having context-specific approaches to targeting the checkpoints.

Restrictions on the existing evidence

Although the past decade has witnessed an increased interest in immune checkpoint pathways as regulators of chronic bacterial infections, the available evidence has multiple gaps in them. The majority of functional data are based on murine models, and, despite their usefulness, do not entirely reproduce either human immunobiology in general or granuloma formation, the expression of epithelial checkpoints, and myeloid cell dynamics specifically.[48] Human translational studies are few and more often observational with less mechanistic resolution and/or uniform methods of immunophenotyping. Also, standard immune profiling of checkpoint markers has no consensus in bacterial infections. Further complicating the interpretation is variability in sampling sites (e.g., peripheral blood versus infected tissue), immune status is different in the patient and differences in strain. Depending upon the chronicity of the infection, organ niche or host comorbidities the expression of PD-1, CTLA-4 or other checkpoints can be very different.[49, 50] Notably, the existence of predictive biomarkers of response to immune checkpoint inhibitors in infectious disease is not developed. Unlike cancer, there are no such frameworks established in the cases of chronic bacterial infections, such as PD-L1 expression, tumor mutational burden, and T-cell infiltration guiding the therapy in oncology.[51] Lack of substantiated indicators impairs the logical selection of patients and exposes them to the possibility of immune overreactions or treatment failure. Lastly, there is a paucity of clinical evidence on checkpoint blockade, mostly observed as incidental encounter in patients with latent or subclinical bacterial infection in oncology. Such cases are very helpful but are not substitutional to prospective trials that specifically aim to determine safety and efficacy in infectious settings.[52] To overcome such limitations, specific research should be directed towards human cohorts, integrative immunogenomic analysis and controlled interventional studies that should take into account the complexity of host-pathogen interaction.

Translational considerations

Immune checkpoint modulation in bacterial infection is already looking like a promising, but insanely subtle mode of therapy. In infectious diseases, the indications and predictive biomarkers are very unspecific compared to oncology, making the use of checkpoint inhibitors very hypothetical and speculative. Potential translation of preclinical results into clinical intervention involves a systematic re-assessment of dosing, the time at which to do the intervention, selection of patients and co-therapy formulation.[53] Expression of checkpoints in chronic infections tend to be compartmentalized where only a localized increase of expression takes place as opposed to the overall system-wide increase. It means that widespread use of checkpoint blockade may have unintended consequences of immune activation in innocent bystander tissues causing collateral inflammation or reactivation of latent infections. More potent carriers that are much safer and more effective due to targeted, or localized, delivery may be possible, e.g., inhaled preparations in the case of pulmonary TB or gastric specificity of the system in the case of *H. pylori*.[54] Moreover, unless the therapy is well timed, co-administration with antibiotics should be synergistic with immune modulation. It may be beneficial to employ checkpoint inhibitors only after establishing some level of bacterial clearance to stimulate immune system clearance of protective reservoirs, rather than incurring the cytokine storm syndromes.[55] The other important factor is the host variability. Immune checkpoint profile is dependent on age, the presence of comorbidity, the background immunogenetics, and their history of antigen experience. T-cell exhaustion markers, cytokine signature, and checkpoint co-expression should be used in personalized immunological profiling used to design and stratify clinical trials.[56] The importance of closing this divide between the laboratory and clinic will rely on the formation of effective human cohorts, new-generation immunomonitoring technologies, and interdisciplinary co-operation. With the accurate coupling of immunology, infectious disease biology, and translational science alone can the immune checkpoint medication can develop into successful auxiliary in the treatment of long-term bacterial infections.

CONCLUSION

Immune checkpoints e.g PD-1, CTLA-4, and LAG-3 show an emerging role in the process of developing the host reaction to the chronic bacterial infection. Although

long regarded only as a characteristic of cancer and viral maintenance, it has recently been shown that check point controlled immune modulation has become relevant as a survival mechanism of several bacterial pathogens, such as *Salmonella Typhi* and *Helicobacter pylori*. This review highpoints the operational similarities and differences of checkpoint dynamics bacterial versus viral settings. Checkpoint upregulation can be a localized phenomenon in sub-populations or sub-environments in the case of bacterial infections, thus playing a role in immune suppression, persistence and therapeutic failure-however in spaces and times different to those of chronic viral disease. New preclinical evidence is evidence that checkpoint blockade can stimulate antimicrobial immunity, especially when it acts in concert with conventional antibiotics. Translation to clinical practice is limited, however, by limited human data, lack of predictive biomarkers, and safety issues of hyperactivation of the immune system. The way forward will depend on how far infection-specific immune profiling, checkpoint delivery strategies are developed, and well-designed clinical trials. It is only with the aid of such precision-based tactics that immune checkpoint modulation can be exploited in a useful way in the fight against chronic bacterial infections.

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