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Review Article

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Effects of Pathogen and Tumor Evasion Techniques on Immune Response in the Context of Critical Care

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Abbreviations: CD4/CD8: Cluster of Differentiation 4/8; CTLA4: CYTOTOXIC T-Lymphocyte Associated Protein 4; CTL: Cytotoxic Lymphocytes; DNA: Deoxyribonucleic Acid; DC: Dendritic Cells; EBV: Epstein-Barr Virus; CMV: Cytomegalovius; FOXP3: Forkhead Box P3; GAS: Group A Streptococcus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HSV: Herpes Simplex Virus; MHC: major Histocompatibility complex; MDSC: Myeloid-Derived suppressor cell; NK: Natural Killer Cell; PML: Progressive Multifocal Leucoencephalopathy; PDL1: Programmed Cell Death Ligand 1; PsA: Pseudomonas Aeruginosa; TAM: Tumor Associated Macrophages; TAF: Tumor Associated Fibroblasts; TGFB: Transforming Growth Factor Beta; Tim3: T-cell Immunoglobulin and Mucin-Domain Containing-3; SSPE: Subacute Sclerosing Panencephalitis; V(D)J: Variable Diversity Joining; NET: neutrophil extracellular trap.

Introduction

Immune responses are dynamically influenced by invading pathogens and by host immune quality. While basic science literature is abundant in recognizing the reciprocation of immune fight with pathogens, which develop assorted sophisticated techniques of evading and modulating the immune response, the embeddement, the translation of this information into clinical thinking is not routinely employed. The comprehension of the phenotype of the invading pathogen regarding the immune deviation enables to a certain extent to predict the character of the immune response. This article serves to highlight the aspect of immune evasion for clinical intensivists. The rarely implemented measurement of immune response may validate the evasion tactics as triggers of immune dysregulation, and more so potentially disclose a pre-existing immune deviation that is intrinsic to the host.

Overview

The constitution of sepsis, the most serious and generalized form of infection including the immune response, with profound clinical reverberations, is diverse [1]. There is uncertainty as to how to underpin such diversity clinically, how to interpret and how to customize therapy. Oblivious immune modulation without concluding the individual phenotype of sepsis, with emphasis on the particularization of the invading pathogen may not offer desired results. It is perhaps partly why so many large clinical trials attempting at monosyllabically influence the immune response during sepsis failed to bring benefit. Immune evasion, perceived in a broad term, denoting modulation, suppression and upgrading antibiotic resistance mechanisms is integral to microbial pathogenic mechanisms, it is a way of self-preservation against destruction so that active invasion can continue unharmed [2].

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Tumor Immune Evasion

Immune evasion is a popular and newly acclaimed mechanism of tumor growth and propagation. It is the redefinition of original dogma, which argued that self cannot be recognized and attacked. The tumor is perhaps more of a distorted self, presenting neoantigens which undergo recognition mechanisms similar to pathogenic and autoantigens. Cells that are exposed to constant provocation mutate, eventually transform, and become oncogenic. The ultimate outcome is the clinical conclusion of unfortunate, randomly occurring mutations, enhanced by toxic environmental pressures [3]. Transformation and oncogenesis are random events. DNA and retroviruses participating in viral oncogenesis, introducing further stimuli to already preexisting mutagens, particularly during chronic infection, are not primarily interested in oncogenesis, rather in host cell survival to secure ongoing reproduction. They usually carry or incorporate host prooncogens to their own genome, alternatively produce factors that stimulate cell survival and proliferation pathways [4] or produce epigenetic modifications [5]. Frame shift mutations, inducing tumors which are associated with cigarette smoke and irradiation, produce more neoantigens, than single nucleotide mutations, consequently eliciting a more potent immune response, increasing the likelihood of tumor specific or tumor associated antigen presentation and development of antitumor immunity.

The phenomenon of pathogen evasion uses conceptually similar strategies to tumor evasion and while tumor specific and associated immunity is a relatively recent concept, it offers important insights and triggers alternative questions regarding the behaviour of the immune system in general. Tumor elicited immunity is triggered upon neoantigen and damage associated molecule presentation on patient's individual MHCI and II molecules primed in sentinel lymph nodes with the aid of dendritic cells. Originally, the immune involvement in tumors was narrowed to immune cell tumors that arbitrarily undergo frequent gene recombinations, in the VDJ regions for instance, opening opportunity for mistakes culminating potentially in phenotypically diverse pathologies, autoimmunity [6] and immune cell tumors. Similarly, virus- associated tumors [7] representing about 12-20% of all viruses, add to the mutational burden. Among them EBV and CMV stand out for clinicians for widespread colonisation of the adult population, and association with increasing prevalence of lymphomas, gastric cancers, glioblastomas, etc [8-10].

The tumor elicited response begins with surveillance, continues with elimination and equilibrium. These are clinically dormant periods that ultimately build up to learned or induced evasion, signaling that a previously capable antitumor immune response becomes bypassed and exhausted [11]. This back-and-forth battle is accompanied with immune selection for tumors that are less immunogenic to safeguard survival. It is likely the balance of cytotoxic and regulatory cells and their activation equilibrium that defines the dormant stage (NK, CD8, Th1, MDSC, Foxp3, CTLA4). Tumors developed multiple ways to evade, slow and ultimately stop the immune response aimed at eliminating faulty cells. There are ways of impaired antigen trafficking to the cell surface, MHC downregulation [12] to evade CD4 helper and CD8 cytotoxic effectors, TAM and TAF associated impairment of NK cell functions [13]. Interferon gamma produced by cytotoxic T cells empowers tumors to PDL1 production and induction of T cell suppressive phenotype. Tumor associated fibroblasts produce a barrier that effector cells cannot breach. Tumors upregulate CTLA-4 to dampen T cells responses. Some tumors produce large amounts of regulatory cytokines: IL-10, and TGFbeta. As per common metabolites, lactic acid and ammonia contribute to immunosuppressive phenotype. Cancer cells may overexpress do not eat me signals, like CD47, to disable phagocytosis by macrophages. While CD8 and CD4Th1 presence is associated with improved outcome, Th17 association decreases survival.

Viral Immune Evasion

Virus infected cells are killed by CTL based on MHCI presented virus peptides. Many viruses disable peptide processing and presentation through proteasome and endoplasmatic reticulum pathways, or remove already attached peptides from MHC groove (adeno, CMV, HSV, HIV, EBV) [14,15]. Others create CTL escape mutants by presenting peptides that are not recognized as foreign (HSV, HBV). CTL escape, as opposed to antibody escape, doesn't propagate, because MHC composition is relatively unique to the individual. HIV induces FasLigand expression on the surface of CTL and reverse killing assumes. Certain organs are immune privileged in the body to avoid self-damage by killing (eyes, CNS, testes,). In the rare, irreversible sequel of measles infection-SSPE, measles virus particles persist, and within 5-10 years cause progressive, degenerative panencephalitis [16]. Some polyomaviruses can also persist for unknown reasons, and rarely complicate biological therapies. Antia4b1 integrin blockage disabling immune cells from entering the brain may cause progressive multifocal leuco encefalopathy. HBV may persist too, in 5% of adults and 95% of newborns, may lead to T cell exhaustion and decades later to hepatocellular cancer [17]. Parenteral entrance, bypassing barrier immunity is an effective evasion technique. Type I interferons serve as major, universal defense mechanisms for all viruses, including HCV [18]. HCV however developed several counterfeit mechanisms, using non-structural proteins to suppress interferon alpha production, hijacking several intracellular pathways. Chronic hepatitis C infection is characterized by predominance of exhausted CD8+Tim3+PD1+ cells, similarly to tumors [19].

Bacterial Evasion of the Immune Response

In the bacterial world, persistent cells had been described, albeit in tiny proportions in a quiescent form, with great resilience towards macrophage engulfment and antibiotics [20]. Many bacteria

possess sturdy capsules that serve as barriers to complement and antibody mediated opso-phagocytosis. GAS [21] owns a hyaluronic acid-based capsule that prevents opsonisation and serves a molecular mimicry substrate, also a M protein, that limits terminal complement MAC formation and pore forming. GAS virulence functions via toxins, such as streptolysin O leading to massive host cell apoptosis, including host immune cells. GAS is able to dismantle IgG molecules. Beyond these versatile tricks tackling the innate and adaptive immune response, bacteria may hide intracellularly, may form biofilms or survive dormant in persistent cells, to hide from antibiotics that do not have capability to penetrate cells. A hallmark example is Staphylococcus aureus, that forms biofilms on prosthetic surfaces, or if ultimately can not resist engulfment using quorum sensing mechanisms, it hides intracellularly particularly during chronic osteomyelitis and contributes to bone resolution [22]. Pseudomonas Aeruginosa (PsA) [23] is notorious for hiding beneath biofilms, extracellular polymeric substances, which are structures built by bacteria, a highly impermeable habitat to antibiotics and immune targeting. In these biofilms, PsA alters its own phenotype to become more resistant to killing, its persistence triggers ongoing inflammation and tissue damage. PsA in biofilms produce rhamnolipids, leading to neutrophil death. During sepsis, T cell phenotypes gradually become exhausted, characterized by high Tim-3, PD-1, and CTLA-4 expression, reminiscent of tumor associated T cell phenotypes [24,25] Certain bacteria deploy superantigens to circumvent antigen presentation, they bind to MHC directly and induce massive T cell activation and cytokine storm.

Neutrophils are the most abundant and significant immediate first line defense in bacterial infection. Arising and replenished from the bone marrow the transmigrate from blood to effect site based on chemotactic bacterial and host mediated inflammatory trigger, they phagocytose upon pattern recognition receptor, complement and immunoglobulin opsonisation, they kill by using reactive oxygen species, azurophilic protease enzymes and by NET formation [26]. NET formation is a suicide mission of neutrophils to tackle a huge variety of pathogens. It is a form of self-consuming event, with liberation of nuclear and cytoplasmatic content, entrapment of pathogens, and ultimately neutrophil cell death. Bacteria deploy various mechanisms to inhibit NET formation and function, inhibition of IL-8 production, by engagement with inhibitory SIGLEC receptors, NET degradation by DNAses (PsA), inhibition of reactive oxygen species formation (Klebsiella), aggregation of extracellular DNA and NET escape (Staphylococcus aureus) [27,28]. The concluding immune response may lack neutrophil stimulation, with impaired phagocytosis, and NET functionality, diminished transmigration, uninvited survival inside macrophages, mast cells, overall T or B suppression or inhibition of memory, and recall responses.

Conclusions

ICU patients frequently struggle with life threatening infections like sepsis due to underlying comorbid conditions or pre-existing immune dysregulation. Pathogens will perhaps never stop developing evasion mechanisms. They employ diverse mechanisms to evade, deviate and suppress the immune response. These sophisticated mechanisms, similarly to tumor escape, were developed upon selective pressure to enhance survival. Clinically it is impossible and irrelevant to scrutinize them, the concluding changes in immune response are however measurable to a reasonable extent. For clinical intensivists the priority is to recognize this aspect of disease pathogenesis as a fundamental step to understand pathogenesis and in the future perhaps to implement, targeted and measured therapies based on immune response dynamics and property. The potential measures of prevention are of utmost concern. It is particularly interesting to realize how certain features and logics are intertwined between autoimmunity, infection and tumor.

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Conflicts of Interest

None.

References

1. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, et al. (2016) Sepsis and septic shock. Nat Rev Dis Primers 2: 16045.
2. Nowacka AA, Sordo Vieira L, Petr V, Fageräng B, Würzner R, et al. (2025) The grand escape-how pathogens outsmart the human complement system. Immunobiology 230(6): 153126.
3. Galassi C, Chan TA, Vitale I, Galluzzi L (2024) The hallmarks of cancer immune evasion. Cancer Cell 42(11): 1825-1863.
4. Torres MKDS, Pereira Neto GDS, Cayres Vallinoto IMV, Reis LO, Vallinoto ACR (2025) The Impact of Oncogenic Viruses on Cancer Development: A Narrative Review Biology (Basel) 14(7): 797.
5. Bautista J, Lopez Cortes A (2025) Oncogenic viruses rewire the epigenome in human cancer. Front Cell Infect Microbiol 15: 1617198.
6. Alriyami M, Polychronakos C (2021) Somatic Mutations and Autoimmunity. Cells 10(8): 2056.
7. Qi L, Hu B, Cao C, Peng T, Xu M, et al. (2025) Viral oncogenesis and immune remodeling: Decoding the therapeutic potential of immune checkpoint inhibitors in virus-associated cancers. Biomed Pharmacother 191: 118515.
8. Wu X, Zhang Z, Zhang L, Daniels DJ (2025) Role of cytomegalovirus in glioblastoma development: promoter or culprit? Virol J 22(1): 194.
9. Sylvia Frisancho Kiss, Mária Gusková, Pavol Šust, Ivan Úradníček, Anna Šebová, Michaela Ciulisová, et al. (2025) A Case of Fulminant Guillain Barre Syndrome in Association with Acute Cytomegalovirus Infection. Progress in Medical Sciences Vol 9(1): 1-7.
10. Grech N, Dalli T, Mizzi S, Meilak L, Calleja N, et al. Rising Incidence of Glioblastoma Multiforme in a Well-Defined Population. Cureus 12(5): e8195.
11. Mittal D, Gubin MM, Schreiber RD, Smyth MJ (2014) New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol 27: 16-25.

12. Dhatchinamoorthy K, Colbert JD, Rock KL (2021) Cancer Immune Evasion Through Loss of MHC Class I Antigen Presentation. Front Immunol 12: 636568.

13. Vitale M, Cantoni C, Pietra G, Mingari MC, Moretta L (2014) Effect of tumor cells and tumor microenvironment on NK-cell function. Eur J Immunol 44(6): 1582-1592.

14. Silva JM, Alves CEC, Pontes GS (2024) Epstein-Barr virus: the mastermind of immune chaos. Front Immunol 15: 1297994.

15. La Rosa C, Diamond DJ. The immune response to human CMV. Future Virol 7(3): 279-293.

16. Griffin DE, Lin WH, Pan CH (2012) Measles virus, immune control, and persistence. FEMS Microbiol Rev 36(3):649-662.

17. Ghosh S, Chakraborty A, Banerjee S (2021) Persistence of Hepatitis B Virus Infection: A Multi-Faceted Player for Hepatocarcinogenesis. Front Microbiol 12: 678537.

18. Barik S (2023) Suppression of Innate Immunity by the Hepatitis C Virus (HCV): Revisiting the Specificity of Host-Virus Interactive Pathways. Int J Mol Sci 24(22): 16100.

19. Osuch S, Laskus T, Perlejewski K, Berak H, Bukowska Ośko I, Pollak A, et al. (2022) CD8+ T-Cell Exhaustion Phenotype in Chronic Hepatitis C Virus Infection Is Associated with Epitope Sequence Variation. Front Immunol 13: 832206.

20. Niu H, Gu J, Zhang Y (2024) Bacterial persisters: molecular mechanisms and therapeutic development. Signal Transduct Target Ther 9(1): 174.

21. Frisancho Kiss S (2023) Group A Streptococcus, the Story of the Perfect Warrior and the Lonely Defense. Crimson Publishers 14(3).

22. Lathram WA, Radka CD (2025) Intracellular survival of Staphylococcus aureus in macrophages during osteomyelitis. Virulence 16(1): 2553789.

23. Sahu A, Ruhal R (2025) Immune system dynamics in response to Pseudomonas aeruginosa biofilms. NPJ Biofilms Microbiomes 11(1): 104.

24. Frisancho Kiss S (2024) Monoclonal Antibodies in ICU Management of Sepsis, Matters of Affinity, Targeting and Specificity. Crimson Publishers 16(3).

25. Shepherd FR, McLaren JE (2020) T Cell Immunity to Bacterial Pathogens: Mechanisms of Immune Control and Bacterial Evasion. Int J Mol Sci 21(17): 6144.

26. Janssen L, Muller HS, Martins VP (2022) Unweaving the NET: Microbial strategies for neutrophil extracellular trap evasion. Microb Pathog 171: 105728.

27. Kobayashi SD, Malachowa N, DeLeo FR (2018) Neutrophils and Bacterial Immune Evasion. J Innate Immun 10(5-6): 432-441.

28. Touaitia R, Mairi A, Ibrahim NA, Basher NS, Idres T, et al. *Staphylococcus aureus*: A Review of the Pathogenesis and Virulence Mechanisms. Antibiotics (Basel) 14(5): 470.