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Immunology and Immunogenetics Insights

The Immune System as Drug Target

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ABSTRACT: The immune system is perhaps the largest yet most diffuse and distributed somatic system in vertebrates. It plays vital roles in fighting infection and in the homeostatic control of chronic disease. As such, the immune system in both pathological and healthy states is a prime target for therapeutic interventions by drugs—both small-molecule and biologic. Comprising both the innate and adaptive immune systems, human immunity is awash with potential unexploited molecular targets. Key examples include the pattern recognition receptors of the innate immune system and the major histocompatibility complex of the adaptive immune system. Moreover, the immune system is also the source of many current and, hopefully, future drugs, of which the prime example is the monoclonal antibody, the most exciting and profitable type of present-day drug moiety. This brief review explores the identity and synergies of the hierarchy of drug targets represented by the human immune system, with particular emphasis on the emerging paradigm of systems pharmacology.

KEYWORDS: drug design, immune system, adjuvants, natural products, major histocompatibility complex, antibody, biologic drug

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Compared with, say, the nervous system, a system of similar complexity and importance, the immune ystem is a more diffuse, less discreet entity comprised of molecules and cells, as well as macroscopic organs. It is less centralized and less localized but is prone to the same cooperative, emergent behavior common to all systems comprising elements operating at different time and length scales. The immune system is both a bulwark against infection and a crucial homeostatic mechanism; thus, it protects the viability while maintaining the integrity of the host organism. Part of the de facto protective role of human immunity is to control and suppress chronic disease states and pathologies, as well as protect against the pernicious effects of infectious organisms. Despite, and yet because of, the immune system's protective role, it is also an expanding target for therapeutic and prophylactic drugs.

Illness has many sources, including life-threatening conditions arising from infectious, genetic, or autoimmune disease, as well as conditions impinging deleteriously on quality of life. Yet, there is seldom a clear distinction between disease causes. Genetic disease can result from Mendelian or from multifactorial inheritance. In Mendelian conditions—such as cystic fibrosis, thalassemia, Tay-Sachs disease, or tyrosinemia—an altered phenotype arises from mutations to a single dominant gene or to 2 recessive genes. In multifactorial inheritance—such as asthma, heart disease, and type II diabetes—mutations in many distinct genes, combined with a significant environmental contribution, give rise to disease. Identifying genes leading to Mendelian disorders has often proved outstandingly successful. By contrast, multifactorial diseases seldom yield clear-cut causative genes. Genome-wide association studies (GWAS) have begun to open a flood-gate of such susceptibility genes for multifactorial diseases,[1] but with knowledge has not come simplicity or understanding. The nature of inheritance in multifactorial diseases is probably so complicated that the interaction of genes, modifier genes, and causative multiple mutations (necessary for a changed phenotype to be seen) may continue to defy straightforward identification. Disease also arises as the homeostatic mechanisms of the immune system are subverted or fail, leading to autoimmunity and inappropriate immune reactions.

The immune system is thus a key target for drug intervention both when the system works and when the system fails; augmenting the functional immune system aids the fight against both chronic and infectious disease, while stymieing inappropriate immune responses can mitigate autoimmunity and the potentially catastrophic effects of the misfiring immune system. The immunity comprises the innate and the adaptive immune systems, both targets and potential sources of drug moieties.

While it is always possible to subdivide any complex topic in many relevant and interesting ways, it is fairly clear that this topic falls quite neatly into the following tripartite structure. First are pharmaceutical products that induce immune responses, immunization against pathogens, and tumors. These his would include, inter alia, adjuvants, DNA vaccines, and dendritic cell vaccines. Second are drugs that modulate immune responses against self-reactive autoimmune diseases. Such drugs might target mechanisms as diverse as tolerance induction, Th1/Th2 shift, anti-cytokine treatments, and nonspecific immune suppression. Third are drugs that stimulate the immune system to target nonimmunological diseases, which include prophylactic immunization against Alzheimer's, Parkinson's, and other chronic or degenerative disease states.

The immune system is both a target itself and a hierarchy of individual, identifiable targets of increasing size and complexity. As an emergent system, the immune system can be seen as something greater than the sum of its parts and capable of distinct, autonomous behavior at many levels. It can respond and be targeted in many ways, at many length scales, and on various time scales. Thus, a pathogen may attack the body by secreting individual small molecules such as siderophores,[2] by secreting proteins such as toxins, or by using supramolecular complexes such as type-IV secretion systems to puncture holes into the cytoplasm of eukaryotic cells. A pathogen may also attack the body by being engulfed as a whole cell by a whole cell, as is the case with TB bacteria,[3] or cooperatively, through quorum sensing, to attack larger scale structures. Likewise, the immune and associated systems produce small antimicrobial peptides. These systems also produce proteins, such as neutrophil gelatinase-associated lipocalin, to bind siderophores, and these systems also recognize bacterial components, triggering large-scale, highly-diverse immune responses, and so on.

For the last few decades, which follow a largely empirical, targetless prehistory, drug discovery has mainly, if not exclusively, concentrated on membrane-bound receptor proteins and enzymes as principal targets. This has led to a one-receptor-one-disease-one-drug paradigm that presupposes highly selective drugs. Although this view is now in flux, it remains compelling. Drugs take many forms, but the dominant triad comprise small molecules, protein biologics, and vaccines. Small molecule drugs may be wholly synthetic, such as cimetidine; natural products, such as taxol; or synthetic analogues of a natural product. After decades of futile high-throughput screening, drug design has returned to the natural product.[4] Analyses of natural products have found that they differ in several key properties from commercially available compound libraries. Natural products typically incorporate fewer nitrogens, aromatic rings, and rotatable bonds per compound than synthetic drugs yet contain more oxygens, more chiral centres, and more fused rings. This suggests natural products are characterized by rigid, nonflat, intrinsically three-dimensional structures. This may increase the chance of clinical success for candidate drugs, since compound unsaturation and chirality increases as drugs develop.[5]

Peptides are also regaining ground as potential therapeutic agents. Like small molecules, they can be designed using paradigms from rational drug design. Leveraging the power of computational chemistry in all its guises, we can within the immune context design novel, nonnatural sequences that might act as heteroclitic peptides, superagonists, antagonists, or blockers of MHC mediated T-cell responses. Doytchinova et al used a model of A2 binding to design superbinders with affinities up to 2.5 orders of magnitude greater than the most affine natural peptide sequences.[6] They were also able to alter systematically the amino acid identity of anchor positions showing that peptides with at least 10 residues other than canonical anchors can be bound at or above the affinity threshold concomitant with putative immunogenicity. The same design principles can be applied to any physical or biological property of peptides, allowing us to tailor their pharmacokinetics and immunogenic qualities in much the same way medicinal chemists have optimized small molecules for decades.

The immune system is replete with receptors, enzymes, and targetable receptors of all types. A particularly interesting, even exciting, example of protein target is provided by the so-called pattern recognition receptors (or PRRs) that mediate the recognition of pathogen-associated molecular pattern (or PAMP) by the innate immune system.[7] As we shall see, they are potential targets for small molecule adjuvants.[8]

Adjuvants potentiate immune responses, reducing the dosing requirements needed to induce protective immunity, particularly for weakly immunogenic subunit vaccines. Few adjuvants are licensed for human use. These comprise principally alum and squalene-based oil-in-water adjuvants. Yet there are many types of potential adjuvant, including proteins, oligonucleotides, drug-like small molecules, and liposome-based delivery systems. So-called small molecule adjuvants (SMAs) are the most underexplored extant adjuvants, even though many small molecules exhibit adjuvant properties. Extant SMAs include both complex biologically derived natural products and fully synthetic drug-like molecules.[9] Notable natural product SMAs include QS21; muramyl dipeptide; mannide monooleate, typically formulated as an oil-in-water adjuvant such as montanide ISA 720 and montanide ISA 51; MurNAc-L-Ala-γ-D-Glu-mDAP (M-TriDAP); and monophosphoryl lipid A (or MPL).

Fully synthetic drug-like small molecules are also adjuvants,[9] for example, bestatin (ubenimex or UBX), levamisole, bupivacaine, and 2-(4-methoxyphenyl)-N-methylethanamine (also known as compound 48/80). Yet easily the best explored of SMAs are the so-called imidazoquinolines, the best known of which are imiquimod, resiquimod, and gardiquimod. These target Toll-like receptors, that is, TLR7 and/or TLR8, inducing IFN, TNF, and IL-12 secretion. SMAs can also be discovered in a rational and systematic manner.[9] The best example is provided by the discovery of adjuvants acting as antagonists of the CCR4 chemokine receptor, which act via regulatory mechanisms of the cellular adaptive immune system. Inhibiting CCR4 receptors may give rise to adjuvantism as the receptor is expressed by regulatory T-cells (or Tregs) that normally suppress immune responses, inhibit maturation of DCs, and downregulate costimulatory molecule expression.[10] Inhibiting CCR4 function using an effective CCR4 antagonist, and thus blocking interaction of DC with Tregs at vaccination, is anticipated to exacerbate vaccine responses. By combining experimental validation with virtual screening, we have identified several potential adjuvants, acting through the apparent inhibition of Treg proliferation.[11,12] These molecules behave appropriately in a variety of in vitro assays, increase the levels of various correlates of protection in vaccinated mice, and even show some enhancement in related challenge models observations supported by independent analysis.[13] These molecules also show activity against potential cancer antigens.[14]

Turning to the adaptive immune system, this too can act as a drug target in addition to its role as the source of the fast growing and most robust of modern drug types: monoclonal antibodies. Small-molecule drugs, antibodies, and vaccines target adaptive immunity, and it can be hoped that in future other drug types, including cellular therapeutics such as dendritic cell vaccines, will also target the adaptive Immune system.

One the principal adaptive immune targets is provided by the trimeric MHC-peptide-TCR (pMHC-TCR) complex, a supramolecular complex at the heart of the cellular immune response.[15,16] For example, the pMHC-TCR complex is a therapeutic target in diabetes. Coadministration of glyphosine with insulin peptide B:9–23 induces IL10 production leading to prevention of diabetes in animal models.[17] Likewise, anti-insulin/MHC complex antibodies can block T-cell activation. Similarly, specific TCR antibodies can prevent autoimmune diabetes in rat models.

Small molecule drugs can block allele specific peptide presentation to T-cells, which is both a potential mechanism to exploit therapeutically[17,18] and a pathological mechanism leading to so-called adverse drug reactions.[19,20] Drug-induced hypersensitivity reactions—such as drug rash with eosinophilia, Stevens-Johnson syndrome, toxic epidermal necrolysis, and systemic symptoms—are associated with high mortality and morbidity. For many adverse drug reactions (ADRs), particularly cutaneous ADRs, there is a strong association between the reaction to certain drugs (including abacavir, allopurinol, carbamazepine, and other antiepileptic drugs) and particular HLA alleles, allowing for the prognostic prediction of ADRs.

It is worth pointing out, and indeed emphasizing, in this context and at this stage, that developing new therapies based on current immunological hypothesis as supported by animal models, can lead to disappointing clinical results—such as the interaction of John Cunningham (JC) virus, a type of human polyomavirus exhibiting genetic similarity to SV40 and BK virus, which causes progressive multifocal leukoencephalopathy (PML) in natural or induced immunodeficiency, with Natalizumab in patients with multiple sclerosis[21]—and even significant deleterious effects.[22]

Beyond isolated molecular targets, we can view the immune systems at many levels, each offering a more generalised target for drug action. This can be at the level of whole cells, such as professional antigen presenting cells, B-cells or T-cells, or at the level of whole organs, from lymph nodes upwards. Perhaps the clearest example of this is the idea of using drugs to direct stems to differentiate within the immune environment, as has been done in other areas,[23–25] and the potential of unwanted immunogenicity of stem cell therapeutics.[26,27]

Hand-in-hand with the idea of the immune system as a hierarchy of targets is the concept of polypharmacy directed at many immune targets.[28,29] Beyond combination therapies and the like, in recent years, a new paradigm of drug discovery has begun to emerge: so-called systems pharmacology or polypharmacology. Systems pharmacology (or polypharmacology) targets activity against a pathway or, more generally, a large and complex system or subsystem of a pathway, rather than activity against a single, isolated receptor. In our case, the system would be the immune system or a discrete subsystem within it. All drugs have side effects or off-site activity; thus, drugs can be designed to target many targets, and such drugs combined to form complex formulations simultaneously affecting many targets. Thus, much recent interest focusses on identifying ligands with clearly defined polypharmacology arising from the increased awareness of the multiple interactions of existing drugs and the likely improved efficacy of treatments, which engage at several points in biological systems. When commencing a multi-target drug discovery project, it is easy enough to search compound databases for starting points, seeking molecules that hit sets of homologous or distinct targets. Like one view of Chinese medicines, developing complex multi-potent drug combinations, possibly working at a subclinical level, would have a general yet beneficial effect in combatting both therapeutically and prophylactically chronic and infectious disease, since complex, refractory, and unsatisfying conditions probably require equally complex and unsatisfying multiple interventions.

The immune system is a potent cornucopia of new drug targets and drug-mediated mechanisms for treating both

chronic and autoimmune disease, as well as infectious disease, and also a fascinated and bountiful fountainhead of new chemical moieties of all kinds. We have highlighted that both old style small-molecule drugs and new therapies, such as SMAs and designed peptides, can be used to address such targets, heralding a new era of immunological drug discovery. Yet the immune system is also a Pandora's box, as it contains immense hope yet also brings forth the spectre of extreme immune reactions and ADRs, mediated by innate and adaptive immunity, to new drugs, both small-molecule and macromolecular, whether or not they target the immune system specifically.

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