EDITORIAL

The dynamic interface of genetics and immunity: toward future horizons in health & disease

Understanding the genetic basis of immunological processes and their overall dynamics under the influence of population immunogenetics and host-microbe interactions has been at the core of health and disease research. Our understanding of these dynamics has recently undergone a paradigm shift with the application of high-resolution single cell or spatial omics technologies that have facilitated a deeper understanding of healthy or diseased immune milieu. At *Genes & Immunity*, we wish to revamp the journal to cater to these trends and bring together researchers working at these multidisciplinary interfaces of immunology and genetics, with the aim of advancing fundamental and translational knowledge while revealing new immunotherapy or biomarker modalities.

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The multidisciplinary research field at the interface of immunology and genetics is currently experiencing an unprecedented expansion and tremendous progress. In past, this field was largely focussed on classical immunogenetics research i.e., finding genetic regulatory systems behind different immune processes, explaining genetic basis of diversification of specific immune receptors (e.g., T cell receptors or TCRs and B cell receptors or BCRs), explaining genetic variations of specific immune loci, or explaining the genetic basis of immune lineage commitment [1–6]. However, technological advances such as next-generation sequencing, single cell or spatial -omics, and high-end imaging have allowed deep profiling of different immune cell subsets at an unprecedented resolution and scale [7–9]. Such immunogenomic, immuno-transcriptomic or immuno-proteomic big data is fundamentally altering our understanding of the immune system. Thus, not surprisingly, computational immunology is now considered a core part of the field. Moreover this approach is currently progressing toward usage of artificial intelligence methods like machine learning, deep learning, or neural networks for extracting immunologically meaningful knowledge from clinical or pre-clinical datasets [10–12].

In parallel to immunological 'big data' explosion, three equally important paradigm shifts have also co-transformed the interfacial field of immunology and genetics. Firstly, a large part of previous immunogenetic studies were restricted to either model organisms (e.g., whole-body genetic manipulations in rodents) or ex vivo cultures of human immune cells. However, the higher resolution of, and relatively affordable access to, different omics technologies and immune cell lineage-specific genetic manipulation approaches have allowed better mapping of in situ or in vivo immune cells. In particular, the omics technologies have allowed human immunological processes to be analyzed or annotated on an intra-subject or inter-subject level for various healthy or diseased states [13]. This progress was particularly useful for mapping the human-specific pathology of coronavirus disease 2019 (COVID-19) across the entire world's different human populations in a relatively short period of time [14, 15]. Secondly, while the influence of the immune system was previously considered to be restricted to few pathological contexts e.g., infection, autoimmunity, or transplant rejection [16], yet now this influence has been established to be relevant for diverse pathologies like cancer, cardiovascular disease, fibrosis, metabolic disorders, and even neurodegenerative maladies [16–22]. Finally, in the last decade the enormous potential of immunotherapy has finally been realized, thanks in-part to cancer immunotherapy [16]. Pioneering immunotherapies that agonize or antagonize different immune processes are changing the clinical therapeutic landscape in cancer, autoimmunity, allergy, inflammatory disorders, fibrosis, and transplantation [16]. These advances have also provided valuable clinical datasets that have enabled the correlation of biomarkers of immunological process with clinicopathological parameters of patients e.g., long-term survival, therapeutic response.

All the above trends are together starting to paint a 'network view' of our immune system (Fig. 1). It is now appreciated that both system-wide and local immunological, cellular, and molecular signals co-ordinate the activities of different immune cells and organize them into specific interaction hubs (Fig. 1). At the core of this organization lies the ability of our immune system to differentiate self-antigens from disease-specific antigens. Herein, self-antigens uphold immuno-regulatory signaling aimed at suppressing autoimmunity while disease-specific antigens facilitate pro-inflammatory signaling aimed at eliminating diseased cells to halt the progression of a particular pathology [23]. The above differentiation is further aided by the presence of danger signaling accompanying disease-specific antigens (Fig. 1) [24]. Specifically, infections or sterile immuno-pathologies (like cancer) might be accompanied by extracellular exodus of specific danger signals like pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) respectively [24–26]. Presence of such danger signals activates the antigen-presenting cells of our immune system (macrophages or dendritic cells) thereby allowing them to better prime the T cells for disease-specific antigens thereby initiating a more robust antigen-specific immunity and efficacious disease resolution [24].

The robustness of above processes is further facilitated by the occurrence of specialized immune cell interactions hubs depending on different organs representing organ-specific immune networks (Fig. 1). Indeed, specialized immune cell subsets are

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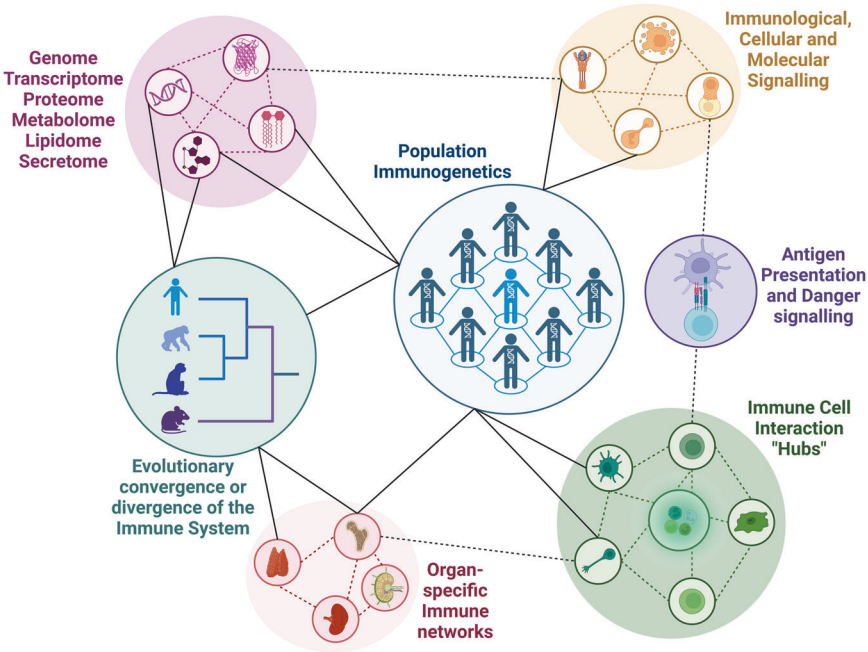

Fig. 1 The complex interface of genetics and immunity. A systems biology view of the immune system, integrating its various quantitative, qualitative, and dynamic aspects from the perspective of biomolecules, signaling pathways, cellular interaction hubs, organ-specific immune milieu, evolutionary trends, and population immunogenetics (Figure created using Biorender.com templates).

established to reside in different organs, where they perform organ-specific homeostatic functions e.g., skin-resident immune cells forming a barrier to extrinsic pathogens, gut-resident immune cells regulating the gut microbiome while avoiding opportunistic infections, or liver-specific immune cells that aid in liver's detoxification and lipid metabolism regulatory functions [16, 27, 28]. Such organ-specific immune networks are just beginning to be uncovered and a lot more work is required to fully decipher the organ-specific immune milieus.

Above immune processes are co-regulated by a complex interplay between different biomolecular layers i.e., genome/epigenome, transcriptome, proteome, metabolome, lipidome and secretome (Fig. 1). Various high-resolution omics tools have revealed the multi-factorial functioning of the immune system on the level of above biomolecular layers [7, 29]. These insights have facilitated our deep understanding of TCR/BCR repertoire, the affinity and potency of different antibodies, spatial organization of immune cell hubs in different organs, variations of proteomic and metabolite abundances depending on different pathological states, and the tight regulation of the composition of different immune cells' secretome [7, 30, 31]. While impressive, many of these insights remain largely fragmented across loosely connected datasets. Thus, one of the emerging challenges is to systematically organize the analyses of these biomolecular layers into integrated multi-omics and spatial frameworks that more intimately connect the different patients and/or pathologies to paint a more complete picture of the immune system and its signaling hubs [7, 32, 33].

To overcome the deficiencies of descriptive omics datasets, cause-effect analyses based on genetic manipulation or pharmacological inhibition remains the cornerstone of understanding the molecular underpinnings of different immunological processes. Such cause-effect analyses are best executed in vivo in model organisms (e.g., rodents, primates) and the efficacy of such approaches is determined by the relative evolutionary convergence or conservation of immunological processes between humans and such model organisms (Fig. 1) [34, 35]. However, the evolutionary divergences between humans and various model organisms pose a potent barrier to cross-species translatability of these insights [36]. While efforts are ongoing to overcome this barrier through genetic manipulation screens involving human organoid or tissue explant cultures, yet these tools may not fully recapitulate the systems-wide and organ-specific dynamics of different immune networks [37, 38].

The final frontier for the interfacial field of immunology and genetics is to integrate above massive amounts of knowledge and insights with human population immunogenetics (Fig. 1). It is well-acknowledged that the complexity of the immune system is further compounded by population-driven immunogenetic polymorphisms [39]. Such polymorphisms create subject-to-subject or patient-to-patient variations on the levels of various molecules e.g., human leucocyte antigen (HLA) and killer-cell immunoglobulin-like receptors (KIR) [39]. These polymorphisms, which are co-regulated by mitochondrial DNA, Y-chromosome, microsatellites, and single nucleotide variations (SNVs), create allotype and haplotype variations in human populations [39]. These immunogenetic polymorphisms heavily influence various processes mentioned above e.g., TCR/BCR repertoire, gut microbiome, metabolism, PAMP/DAMP sensing, and susceptibility/resistance to specific pathologies [39–42]. Unfortunately, these human population-specific features cannot be modeled in any rodent model especially owing to the highly inbred nature of typical rodent models (which tremendously reduces their immunogenetic diversity) and their maintenance in animal facilities with low microbial burdens (which negatively affects natural diversity of gut microbiome) [43, 44]. Finally, the distinct vaccination history and life-long microbial experiences of typical human populations creates a large microbial antigen-specific TCR/BCR repertoire that can confound differentiation of disease unspecific (bystander) vs. antigen-specific T or B cell features in descriptive omics datasets [45, 46]. This is because annotation of antigen specificity of TCR/BCR repertoires in humans remains a potent challenge [7].

Despite all the gaps in knowledge highlighted above, the evolutionary conservation between model organisms and

humans, as well as the high-resolution insights from omics datasets have successfully revealed various therapeutic and biomarker targets. Such modalities have been successfully utilized in human clinical settings e.g., vaccination or pharmacological interventions against different infectious microbes and immune-checkpoint blockade (ICB) immunotherapy in oncological contexts [47–49]. Despite these promising developments, such immunotherapies or anti-microbial interventions still encounter the setbacks of therapy resistance and/or lack of response, as well as serious adverse events [50, 51]. Thus, studying the fundamental immune mechanisms and their population-level variations hold the key for creating better immunotherapy strategies, and innovative treatment combinations. Similarly various immunologically relevant features have been successfully utilized as clinically approved biomarkers e.g., tumor mutational burden (TMB) or microsatellite instability (MSI) (both being potent sources of tumor-specific antigens) and PD-L1 levels as markers of immunogenic tumors highly likely to respond to ICBs [52]. However, the specific cut-off threshold of some of these biomarkers to reliably differentiate ICB responders from non-responders remains a challenge for current clinical practice [52].

Clearly, this is an era of thriving multidisciplinary research at the interface of immunology and genetics which has created a vibrant research community that is seeking new and innovative ways to collaboratively tackle above challenges. By better showcasing such research, the revamped *Genes & Immunity* aims to provide a unique forum that captures the breadth of this community, from fundamental research to translational and clinical studies. Through our pages, we hope to increase the knowledge around four key themes i.e., general immunology, immune-omics & biomarkers, translational & clinical immunology, and immunotherapy, and become a flagship journal for publications within these themes. Ultimately, our goal is to provide an evolving and transformative forum for researchers interested in the genetics of immunology. As we embark on this revamped vision, we thank our authors, editorial board members and referees as well as welcome our readers.

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ADDITIONAL INFORMATION

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