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Molecular and Genetic Inflammation Networks in Major Human Diseases

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Abstract

It has been well-recognized that inflammation alongside tissue repair and damage maintaining tissue homeostasis determines the initiation and progression of complex diseases. Albeit with the accomplishment of having captured most critical inflammation involved molecules, genetic susceptibilities, epigenetic factors, and environmental exposures, our schemata on role of inflammation in complex disease, remain largely patchy, in part due to the success of reductionism in terms of research methodology per se. Omics data alongside the advances in data integration technologies have enabled reconstruction of molecular and genetic inflammation networks which shed light on the underlying pathophysiology of complex diseases or clinical conditions. Given the proven beneficial role of anti-inflammation in coronary heart disease as well as other complex diseases and immunotherapy as a revolutionary transition in oncology, it becomes timely to review our current understanding of the inflammation molecular and genetic networks underlying major human diseases. In this Review, we first briefly discuss the complexity of infectious diseases and then highlight recently uncovered molecular and genetic inflammation networks in other major human diseases including obesity, type II diabetes, coronary heart disease, late onset Alzheimer Disease, Parkinson disease, and sporadic cancer. The commonality and specificity of these molecular networks are addressed in the context of genetics based on genome-wide association study (GWAS). The double-sword role of inflammation, such as how the aberrant type 1 and/or

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BZ, XY and IMW conceived the idea. BZ, CF, XY, YZ and IMW collected the data, BZ, XY, CES, CF, YZ and IMW wrote the manuscript together. All authors read, edited and approved the final manuscript.

Additional Information

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type 2immunity leads to chronic and severe clinical conditions, remains open in terms of the inflammasome and the core inflammatome network features. Increasingly available large Omics and clinical data in tandem with systems biology approaches have offered an exciting yet challenging opportunity toward reconstruction of more comprehensive and dynamic molecular and genetic inflammation networks, which hold a great promise in transiting network snapshots to video-style multi-scale interplays of disease mechanisms, in turn leading to effective clinical intervening.

Keywords

complex disease; inflammation; immune response; systems biology; genome-wide association; gene coexpression network; gene regulatory networks; gene signature; gene networks; obesity; diabetes; coronary heart disease; Alzheimer Disease; Parkinson disease; cancer

Introduction

A vast majority of human diseases fall into the complex diseases categories, which are caused by a combination of genetic, epigenetic, and environmental exposure, most of which yet to be identified elaborately. Most common life-threatening and life-quality-impact diseases or clinical conditions, including obesity (OB), Type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), Alzheimer's disease (AD) and Parkinson's disease (PD), and cancer fully meet the criteria of the definition of complex disease, which in general does not obey the standard Mendelian patterns of inheritance but can be studied by a means of genetic predisposition such as genome-wide association study (GWAS).

The progress of these complex disease phenotypes depends largely on environmental exposure and lifestyle. Thus, the interplay between gene products/by-products and environmental exposure at the molecular level is a general scenario underlying complex diseases. Naturally, such interplays invoke inflammation, which comes from the Latin "*inflammo*", meaning "*I set alight, I ignite*". Inflammation, part of the body's immune response, is beneficial initially but can become self-perpetuating as more inflammation is created in response to the existing inflammation. If not stopped, it becomes chronic inflammation, which is linked to complex diseases, e.g., plaque in AD and genome instability in tumor cells.

Vertebrates including humans deploy two types of immunity to defend themselves against two distinct types of 'insult', namely, the type 1 – invasion of rapidly replicating microorganisms, such as bacteria, viruses, protozoa and fungi, and the type 2 – breach of the protective barriers of the body by physical trauma. For the first scenario, an antimicrobial type 1 immune response characterized by the T helper 1 (TH1) cell-associated cytokines interferon-γ and interleukin-12 (IL-12) is invoked, and is directed and enhanced through cytokines that are produced by TH1 and TH17 cells of the adaptive immune system; however, there is a risk leading to the induction of highly toxic antimicrobial products which are capable of damaging consequences for the host tissue. The Type 2 immunity involves innate immune cells, such as basophils, eosinophils, mast cells, M2 macrophages (also

known as alternatively activated macrophages) and group 2 innate lymphoid cells, with TH2 cells functioning as the central mediators of the adaptive immune response[1].

In-depth one-gene-one-protein-one-lab research has been offering great insights into such links. Encouragingly, recent technological advances have led to the generation of large amount of high throughput and high dimensional molecular data to study inflammation in a more systematic and comprehensive way[2-4]. Forward genetics discoveries have dissected pivotal genetic components, e.g., Mendelian disease genes[5] and GWAS[6] susceptibility genes. Both catalogs could provide meaningful targets for detailed molecular genetic explorations. Likewise, genome-wide expression studies (GWES) have revealed many molecular phenotypes that are directly linked to disease phenotypes[7]. Moreover, nuanced model based molecular studies that leverage diverse types of large scale molecular data have become available for modeling tissue-specific regulatory networks and pinpointing key regulators and have advanced our in-depth understanding of molecular mechanisms underlying disease progression[8]. These efforts have been driving an emerging network biology of complex diseases, in which pro-inflammatory response is of primary importance. Network biology aims to holistically reconstruct interactions, associations, or causal relationships among a large number of variables such as genes and proteins in biological processes, systems, or pathophysiologic states. As such, network biology has the potential to identify novel key variables and interacting pathways underlying a biological function, system or state under examination. As an example, the recently uncovered genome-wide genetic and transcriptomic data from brain tissues and demonstrated that an inflammation/microglial enriched subnetwork is most causally linked to AD and further validated that its key driver *TYROBP* was involved in amyloid-β (Aβ) turnover and neuronal damage[9]. Similarly, a causal role of a similar inflammation/macrophage enriched network in association with obesity and diabetes has been established and a number of key drivers of the network have been validated *in vivo*[4,10,11]. Further, the study of the transcriptome of nine different tissues from eleven disease models revealed a shared inflammatome signature that appears to play causal roles in multiple diseases[12].

Infectious diseases remain a significant threat to human health and a major cause of death, especially in developing countries. The top three most challenging infectious diseases including AIDS, malaria and tuberculosis generate more than 235 million new cases and cause more than five million deaths per year [13]. Although effective therapeutics have been developed for the top three infectious diseases, there are issues in prevention, drug resistance and availability. Similar situations exist for other infectious diseases caused by respiratory syncytial virus (RSV)[14], cytomegalovirus (CMV)[15], dengue virus[16], *Clostridium difficile* and *Staphylococcus aureus*[17]. Since the etiology of infectious diseases are known from the pathogen perspective, it has been crucial to elucidate the core component of the inflammation system by rigorous study infectious diseases especially with a means of focusing on host-pathogen interactions.

Here we review the mechanisms of inflammation in major human diseases including infectious disease, OB, T2DM, CHD, AD, PD, and CA in the context of molecular networks with identification of several big challenges in understanding the inflammation networks in complex diseases.

Recognition of pathogens by the innate immune system

The innate immune system plays an essential role in controlling pathogen infection and initiating specific adaptive immune response by recognizing microbial pathogen-associated molecular patterns (PAMPs) such as viral-/bacterial-nucleic acids and bacterial cell wall components [18]. Five main families of host germline-encoded pattern-recognition receptors (PRRs) have been identified including C-type lectin receptors (CLRs), nucleotide oligomerization and binding domain (NOD)-like receptors (NLRs), Pyrin-HIN (PYHIN) domain containing receptors (e.g. AIM2), retinoic acid inducible gene-I (RIG-I)-like receptors (RLRs), and Toll-like receptors (TLRs) [19]. These innate receptors closely interact with one another and many other signaling pathways (e.g. MAPK, NF-kB and IRFs[20]) including a recently found connection with autophagy, an eukaryotic pathway induced by PRRs to eliminate intracellular microorganisms[21]. An association between genetic variants in the regulatory region of parkin gene (*PARK2*), a ubiquitin ligase, and susceptibility to intracellular pathogen infection was established earlier[22] and more recent data suggested that parkin actually plays a key role in mediating autophagy of Mycobacterium tuberculosis and perhaps other intracellular pathogens since mice deficient in PARK2 are sensitive to various intracellular bacterial infections[23].

Close interactions between PRRs are further substantiated by the two-signal model mediated by TLRs and NLRs for the production of two of the most important pro-inflammatory cytokines, *IL-1β* and *IL-18*. In this model, TLR agonists stimulate transcription whereas NLR agonists activate the inflammasome to release active *IL-1β* and *IL-18*[24]. For examples, *TLR2* signaling has been shown to activate inflammasome and release *IL-1β* and *IL-18* in infection by RSV [25] and *Francisella novicida*[26] infection, respectively. In the former case, *NLRP3* gene expression was induced by RSV infection and two additional signals, potassium (K+) efflux and reactive oxygen species (ROS) were required subsequently to promote inflammasome activation for *IL-1β* secretion. Negash AA et al. [27] found that HCV viral RNA induces TLR7 signaling and a potassium efflux to promote *IL-1β* secretion via a *NLRP3*-containing inflammasome. By performing RNA sequencing analysis of liver from chronic hepatitis C patients and HCV-infected THP-1 macrophage cell line, they were able to show that intrahepatic IL-1β production by macrophage modulates gene expression networks of proinflammatory mediators and is the key driver of liver inflammation.

In addition to detecting pathogen infection by PRRs, cells also express multiple antiviral restriction factors which could block virus replication at different stages and in response, many viruses develop a plethora of mechanisms to evade host detection[28]. For examples, two genes or open reading frames (ORFs) encoded by varicella-zoster virus (VZV), *ORF47*[29] and *ORF61*[30], have been shown to interfere with the host innate immunity by inhibiting the activation of IRF3. Recently expression of many antiviral restriction factors such as *ADAR-1, APOBEC3, IFITM1/3, SAMHD1*, Tetherin and *TRIM5* were all down-regulated in VZV-infected MRC-5 cells (Wang IM et al. unpublished results). The type I interferon (IFN) family plays a key role in protecting cells from viral infection by stimulating hundreds of interferon-stimulated genes (ISGs)[31]. A lentiviral over-expression system was adopted to test the ability of more than 380 ISGs in inhibiting the replication of multiple important viruses and the results indicated *IRF-1, RIG-I/DDX58, MDA5/IFIH1*,

and *IFITM3* as being broadly acting inhibitors against multiple viruses whereas *DDX60, IFI6, IFITM2, OASL, TREX1* and *IFI44L* possess more targeted antiviral activity[32,33]. Consistent with the above finding, Goulet et al.[33] showed that a synthetic *RIG-I* agonist activated inflammatory and interferon-stimulated genes including IRF3, IRF7 and *STAT1* in human lung epithelial A549 cells and protected mice from a lethal challenge with H1N1 influenza virus at the picomolar range. This *RIG-I* specific effect offered partial protection from influenza-challenged mice in the absence of IFN signaling. Interestingly, a genome-wide RNAi screening using a similar lentiviral expression system described above identified a new negative regulatory role of virus-mediated innate immunity for the WNT/CTNNB1 signaling pathway[34]. The information could be used for selecting broad-spectrum antiviral agents for preventing inflammatory diseases caused by viral infection.

Immune dysfunction caused by chronic viral infection

Chronic infection by viruses such as anellovirus, circovirus, adeno-associated virus (AAV), polyomavirus, different types of herpesviruses including HHV-6, HHV-7, varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) is common in humans. Some viruses infect more than 90% of the population surveyed and estimated at 8-12 chronic infections in each person[35]. Most chronic infections mentioned above do not result in discernible disease, at least in healthy hosts but others such as papilloma virus, HBV, HCV and HIV could create a persistent low grade inflammation or immune dysfunction which predisposes susceptible hosts to other ailments including cardiovascular disease, type 2 diabetes[36] and cancer[37]. Most discussion in this section will focus on HIV since it's one of the best characterized examples of chronic viral infection. Evidences accumulated from the past decade indicated that although AIDS-related symptoms are well under control and patients' life expectances significantly prolonged since highly active anti-retroviral therapies (HAART) became available, patients' overall well-beings are still at risk with several complications reminiscent of aging. This is due to the latently-infected HIV which maintains a low-level systemic inflammation. To achieve a better life span and quality, novel treatment approaches targeting this chronic inflammation need to be in place[38].

Several key immune signaling pathways involved in shaping a normal physiological state are disrupted during viral infection. In the HIV-infected hosts, IFN signaling (and ISG genes), cell cycle and proteasome gene networks were perturbed but the transcriptome could be reverted in a way comparable to that of uninfected subjects with HAART treatment. By combining genome-wide gene expression and single-nucleotide polymorphism (SNP) data, it was found that expression of 190 genes was driven by cis-acting genetic variants or expression SNP (eSNP) and among them, one of the ISGs, *OAS1* was associated with viral load[39]. OAS1 is involved in the innate immunity against viral infection; genetic variants in OAS1 have previously been shown to associate with controlling West Nile virus infection [40] and clinical outcome of dengue virus infection [41].

Non-human primate (NHP) species such as sooty mangabey and African green monkeys are natural host for simian immunodeficiency viruses (SIV) and remain asymptomatic upon viral infection even in the presence of high viremia. In contrast, SIV-infected rhesus macaques, like HIV-infected humans, have depleted CD4+ T cells; elicit generalized

immune activation and develop AIDS[42]. Sooty mangabeys have substantially reduced levels of innate immune response upon SIV infection and their plasmacytoid dendritic cells (pDCs) produce significantly less type 1 IFN in response to SIV in vivo and TLR7/TLR9 ligands *in vitro*[43]. Comprehensive transcriptome analysis of human rapid progressors (RPs) and nonprogressors (NPs) upon HIV infection showed a clear resemblance of RP gene signature to symptomatic SIV-infected rhesus macaques whereas NP signature was more similar to that of asymptomatic SIV-infected sooty mangabeys[44].

Veazey et al. [45] first indicated that gastrointestinal tract was enriched with CD4+ T cells but there was a profound and selective depletion of this cell population in rhesus macaques within days after SIV infection. It was later discovered that in both chronically HIV-infected human and SIV-infected rhesus macaques, circulating microbial products such as lipopolysaccharide (LPS), an agonist for TLR4, was significantly increased and correlated to levels of innate and adaptive immune response [46]. These microbial products were derived from the gastrointestinal tract in a process called microbial translocation [47] due to damage in the gut epithelium caused only by the pathogenic infection since the process did not occur in nonpathogenic SIV infection of sooty mangabeys and could be partially reversed by antiretroviral therapy. Mucosal Th17 cell plays a key role in maintaining the integrity of gut epithelial barrier [48] but it's number is reduced and function altered during HIV infection [49]; however, in SIV-infected rhesus macaques, these abnormalities could be corrected by *IL-21* treatment [50]. Using next-generation sequencing (NGS) in SIV-infected rhesus monkeys [51] and high-resolution bacterial community profiling in HIV-infected humans [52], it was found that pathogenic (but not nonpathogenic) SIV infection was correlated to a significant broadening of the enteric virome with 32 previously undocumented viruses confirmed by independent assays. In this case, no association was evident between the family-level of bacteria and pathogenic SIV infection [51]. In the HIV-infected patients, markers of chronic inflammation, T cell activation and disruption of mucosal immunity was associated with enriched Proteobacteria and depleted Bacteroidia members and the level of dysbiosis was proportional to two established disease progression markers, tryptophan catabolism and *IL-6* [52]. The different result

Functional virus-specific T cells are generated during the early stage of infection but they gradually lose their immune competence when the infection becomes chronic – a process termed T cell exhaustion [53]. Several mechanisms for modulating immune response during chronic infections have been proposed based on results from high through-put genome-wide analysis. Gene expression of CD8 T cells derived from mice chronically infected with lymphocytic choriomeningitis virus (LCMV) was compared with normal functional CD8+ T cells and CD8+ T cells from acutely infected mice [54]. The results indicated that expression of several inhibitory receptors including *PD-1, CTLA-4, 2B4, CD160* and *LAG-3* were up-regulated by the exhausted T cells. In vivo administration of antibodies blocking the interaction of *PD-1* with its ligand, *PD-L1* decreased LCMV viral load and restored T-cell function of cytokine secretion, cell proliferation and cytotoxic capacity. Other significantly modulated pathways include T cell receptor signaling, cytokine signaling and chemotactic pathways as well as down-regulation of several metabolic and bioenergetics pathways. The finding was then extended to HIV-infected patients [55] and HCV-infected chimpanzees [56]. *PD-1* was significantly up-regulated in CD8+ cells from HIV-infected humans and its expression level was positively correlated to viral load and negatively correlated to CD4+ T

cell count. Blocking *PD-1/PD-L1* interaction increased HIV-specific CD4 and CD8 function and improved disease outcome [55]. In HCV-infected chimpanzees, *PD-1* blockade could reduce HCV viremia but the effect was more significant in animals with a broader T cell response to HCV.[56] It was proposed that *PD-1* immunotherapy could also be applied to treat other chronic viral infections such as hepatitis B virus and in fact, several anti-*PD-1*-related clinical programs are being actively pursued to treat multiple types of human cancers including melanoma, colon and lung cancer[5758].

The profound change in the immune system caused by chronic pathogens such as HIV suggests the involvement of pleiotropic factors that affect immune cell life span, proliferation, differentiation and maturation. One such factors is *FOXO3a* which was originally characterized by an integrated transcriptomic, proteomic and functional analysis as being the key transcription factor involved in survival of central memory CD4+ T cells (Tcm) [59]. Specifically, it was the phosphorylated and hence transcriptionally inactive form of FOXO3a which provided protection of Tcm from apoptosis. Roles of *FOXO3a* include transcriptional induction of pro-apoptotic [60], anti-proliferative genes [61], genes regulate carbohydrate metabolism [62] and reactive oxygen species (ROS)-related detoxification [63]. It was subsequently demonstrated that down-regulation of *FOXO3a* either by small interfering RNA (siRNA) or by a dominant-negative form of *FOXO3a* could extend the life span of Tcm cells [64] and increased *FOXO3a* transcriptional activity resulted in a loss of memory B cells via *TRAIL*-mediated apoptosis [65]. The immune dysfunction mediated by *FOXO3a* is reversible even after long-term infection so the pathway could be explored for the development of new therapeutics [66].

Host response to vaccination and infection

Significant progress in systems analysis of host response to vaccination and pathogen infection has been made in the past few years due to 1) the advancement in whole blood/leukocyte transcriptome analysis [67, 68, 69, 70, 71, 72]; and 2) the availability of high-through put technologies such as DNA microarray, single nucleotide polymorphism (SNP) profiling and next-generation sequencing (NGS)-based platforms [73, 74, 75]. Instead of using single genes, an algorithm was developed by grouping co-expressed blood or PBMC genes from large disease data sets into modules which could be easily quantitated and used as potential biomarkers for predicting clinical outcomes such as antibody response [76, 77]. Advantages of the module analysis approach include reduction of data dimensionality and facilitating data interpretation since each module usually is associated with a particular biological pathway or function. For example, with respect to Staphylococcus aureus infections, Banchereau et al. [77] were able to identify gene-network modules related to (i) neutrophil myeloid lineage inflammation, (ii) hematopoiesis cell cycle, and (ii) T-cell cytotoxicity lymphoid lineage that are correlated with clinical traits. The major transcriptional patterns identified included pro-inflammatory myeloid signature, linked to sampling early in the course of infection, high neutrophil and monocyte counts and elevated C-reactive protein. Inflammatory response, for example, is mediated by calmodulin B, interleukin and TLR signaling targeting NF-κB and TNFα-mediated pro-inflammatory pathways.

Similar progress has been made with respect to cell-based model systems. In particular advancements in high-thoughput RNAi screens are instrumental to decipher molecular host-pathogen interaction networks. Watanabe et al. compared published RNAi studies on host-factors required for influenza infections and identified 128 targets common between at least two of each screens[78]. Novel host processes, such as, V-type ATPases important for endocytosis, *COPI* vesicular transport or the pre-mRNA splicing machinery with *PTBP1* and splicing factors *SF3A1/SF3B1* have been identified. Host-response is certainly gene-context dependent, as Ward et al. demonstrated with respect to influenza H1N1 infection. By combining RNAi screening data from influenza replication assays with cell viability data, Ward et al. [79] identified a pharmacologically addressable network involving cell cycle/DNA damage checkpoint protein *CHEK1*. Employing SB218078, an investigational *CHEK1* inhibitor, severely limited viral protein production in nontransformed bronchial epithelial cell lines at single cell resolution. Remarkably, SB218078 had no consequence on H1N1 replication in A549 cells, a cancer cell line often employed to test for modulators of viral replication and host responses (Figure 1A).

Another example of a cancer related molecular network relevant for infectious disease has been identified by Mata et al. [80] By chemical screening a class of naphtalimides has been identified that activates a novel host-defense factor *REDD1* (or *DDIT4*). When activated, *REDD1* inactivates the mTORC1 pathway which is required for viral replication, thus essentially preventing viral protein production (Figure 1B).

A web-based interactive software tool has been designed for data analysis/visualization and was applied for comparative analysis of two vaccines, the trivalent influenza vaccine (TIV) and 23-valent pneumococcal vaccine covering polysaccharide components from 23 most widely encountered strains of *Pneumococcus pneumoniae*[81]. More recently, Li et al. [82] conducted a similar blood transcription module (BTM) analysis of five vaccines (yellow fever YF-17D, trivalent inactivated influenza virus [TIV], live attenuated influenza virus [LAIV], meningitis quadrivalent polysaccharide vaccine [MPSV4] and meningitis quadrivalent conjugate vaccine [MCV4-PS] which is conjugated to diphtheria toxoid [MCV4-DT]) in three different categories (naïve attenuated viral, recall peptide and anti-polysaccharide vaccines) by using an integrated large-scale network approach employing public human blood transcriptome data from 500 studies with more than 30,000 samples. The results indicated correlations between antibody titers and 1) type I interferon modules for YF-17D vaccine, 2) dendritic cell and complement activation modules for MCV4-PS and MPSV4, and 3) BCR signaling/plasma cells–immunoglobulins modules for peptide recall responses (i.e. TIV and MCV4-DT). These authors also identified previously unknown innate immune networks which should be further investigated to enhance our understanding of the vaccine response[83]. The identification of genes such as *TLR5, CASP1, PYCARD, NOD2* and *NAIP* suggested previously unknown mechanistic links between host innate immunity and humoral responses. The implication from these analyses is that each category of vaccine induces immunogenicity by a different mode of action (MOA) and there is probably no consensus gene expression predictor for antibody response.

The inflammasome

Inflammasome is the signaling platform of the innate immune system that activates proinflammatory cytokines after microbial pathogens are sensed or sterile danger is detected. The kinases Syk and Jnk control inflammasome activation by mediating phosphorylation of the inflammasome adaptor ASC. Inflammasomes are large intracellular multiprotein complexes that control activation of the protease caspase-1, which in turn mediates the proteolytic maturation of the highly inflammatory cytokines *IL-1β* and *IL-18*[84,85]. Several types of inflammasomes have been identified that can respond to distinct bacterial, viral or fungal infections, to sterile cell damage or to other stressors such as metabolic imbalances. Inflammasomes are composed of a sensor (such as *NLRP3, AIM2* or *NLRC4*), the adaptor ASC and caspase-1. Whereas *NLRP3* and *AIM2* depend critically on *ASC* for engagement of caspase-1, the inflammasome sensor *NLRC4* can directly interact with caspase-1. The regulated activation of inflammasomes after microbial infection or injury is critical for the maintenance of tissue homeostasis, but deregulated inflammasome activity has emerged as a major contributor to the pathogenesis of prevalent diseases, including inflammatory bowel disease, coronary heart disease and cancer. Therefore, it is importance to understand how the activities of inflammasomes are regulated[86].

The core inflammatome

Given the inflammatory nature of many common chronic diseases, a recent study of multiple disease models further demonstrates that chronic diseases share a common inflammatome gene signature and network structure[12]. Specifically, a representative gene signature was identified by an integrated analysis of 12 expression profiling data sets derived from 9 different tissues of 11 rodent inflammatory disease models. This “inflammatome” signature significantly overlaps with coexpressed gene modules linked to metabolic disorders, cancer, neuron-degenerative diseases. Moreover, the inflammatome signature is highly enriched for immune response-related genes tested causal for adiposity, adipokine, diabetes, aortic lesion, bone, muscle, and cholesterol traits, suggesting the causal nature of the inflammatome. Integration of this inflammatome signature and gene regulatory networks reconstructed based on multiple independent mouse and human cohorts uncovered a set of key regulators, which appeared to be more biologically important than the non-drivers in terms of the impact on mutant phenotypes. At the conceptual level, the inflammasome is distinct to the inflammatome as illustrated in **Fig. 2**. However, both substantially overlap with the innate immunity genes[87] (the statistical test result of the intersection of the three sets by SuperExactTest, P=2.74E-33). Further, whether such inflammation core gene sets are overlapped with infectious disease and complex disease signatures has been examined. For influenza virus related signatures, two gene sets were generated, one from a combined RNAi-screening data from six studies on host-factors required by the influenza virus for replication (I1)[78], and a consensus response of 487 (I2, 73 up- and 414 down-regulated) genes inferred by an in-house integration of gene-expression profiles (GSE19392, GSE28166, GSE31524, GSE33142, GSE36555, GSE37571, GSE37951, GSE40844). **Fig.3** illustrates interested intersections among the GWAS gene sets of the six common complex diseases (OB, T2DM, CHD, PD, AD, CA)[88], the inflammatory gene signatures (the innate immunity and the inflammatome gene sets), and the two influenza signatures. Of

particularly interest, the I2 signature is significantly over lapped with the Inflammtome and Innate Immunity sets (P=5.40E-05) involving eleven overlapped genes, ABCA1, CCL5, CTSB, CXCL10, GRN, IFITM2, IFITM3, MYH9, OAS1, OAS2, and *PRKCA*. Moreover, three genes, *AIG1, B2M, C21orf33* have been observed in the intersection of the inflammtome, I1 and I2 (P=4.10E-3). Intriguingly, the *CDKN2A* gene is the element of innate immunity, CA, T2DM, as well as CHD. Eight genes, *NR, BMP4, SLC41A1, HLA, CNNM2, C10orf32, CYP17A1*, and *SFXN2*, consist of the intersection of CA and PD GWAS sets (P=7.27E-05). Meanwhile, there are fourteen genes, including ADSS, BCAS3, SLC8A1, CNTNAP2, TTLL7, RFC3, CSMD1, GPC6, HECW1, LIPC, MYO16, PLEKHG1, DYNC1I1, and *SLCO3A1*, overlapped between AD and OB(P=1.51E-05). These data suggest the instrumental role of inflammation in the molecular and genetic pathogenesis of complex diseases connected by the inflammatome. Further, **Fig. 4** shows a core gene causal network conserved across tissues and species and its key drivers. Highly consistent driver genes such as *HCK, CD53* and *TYROBP* have been found being involved in many inflammation-related disorders. The discovery of the data-driven “inflammatome” gene signature and its corresponding regulatory networks provide a general framework to not only study the common mechanisms underlying complex chronic diseases but also identify key intervention points as therapeutic targets.

Molecular and genetic inflammation networks underlying complex metabolic diseases

In the context of metabolic disorders, inflammation is considered to be primarily induced by nutritional or metabolic perturbations and is of low-grade and chronic nature, in contrast to the strong and short-term classic inflammatory response associated with injury and infection. The metabolism-induced inflammation is attributable to the tight connection and coevolution between metabolism and immune systems, two fundamental and conserved mechanisms to ensure survival [36]. When the delicate balance between the two processes is disrupted by nutrient overAD, as in the typical case of long-term consumption of high fat high fructose diet in the modern society, inflammatory processes enter the stage via mechanisms that are shared between nutrient sensing and the immune system in central metabolic tissues like white adipose tissue (WAT) and liver. Although conventionally perceived as an energy and fat storage tissue, WAT is also tightly connected to the immune system due to its ability to secrete adipokines with pro- or anti-inflammatory properties [89], presence of resident T cells regulating metabolic and inflammatory response [90,91], and accumulation of macrophage upon adipocyte expansion[92].

In order to better understand the mechanisms of molecular processes involved in the onset of inflammation and the downstream events, major research efforts have been focused on investigating individual inflammatory mediators and their respective signaling pathways using classic molecular biology techniques. Such studies have provided strong evidence supporting the causal roles of cytokines, chemokines, and receptors such as tumor-necrosis factor alpha (TNF-α), interleukin 6 (IL6), interleukin 18 (IL18), and toll-like receptors (TLRs) in mediating metabolic cues such as lipid overAD in the WAT. The detailed inflammatory signaling cascades involved have been well illustrated and documented [36].

However, the complexity of metabolic disorders that involve multiple organ systems, tissue types, and multiple molecular pathways demand a systems view of how inflammation interplays with other processes throughout the organism to induce disease onset. In this section, we review the recent attempts to obtain such comprehensive views using integrative and systems biology approaches that involve objective screening of tissue-specific, genome-scale molecular information.

Obesity

Obesity reflects increased adiposity, primarily visceral WAT, in the body. A large number of animal and epidemiological studies have consistently revealed low-grade chronic and systemic inflammation as a major characteristic of obesity[93]. However, the extent of inflammatory signals in individual obesity-related tissues was poorly evaluated. In a genetic and genomic study of an extreme obese population comprising ~1000 individuals who underwent gastric bypass surgery, Greenawalt et al. systematically investigated the genetics of gene expression, gene-disease correlations, and the gene regulatory network structures in four individual tissues including liver, omental adipose tissue, subcutaneous adipose tissue, and stomach[94]. They found that genes correlated with multiple obesity traits such as BMI and leptin levels in liver, omental adipose tissue, and subcutaneous adipose tissue were significantly enriched for inflammatory signals including macrophage- and spleen-related inflammatory genes, immunoglobulins, and genes involved in B-cell and antibody mediated immunity. Based on a weighted gene coexpression network analysis, they also identified coexpression modules from liver and subcutaneous adipose tissues that were highly correlated with obesity traits. Similarly, these modules were primarily enriched for immune and inflammatory response genes. This systems genetic study objectively uncovered inflammation in liver and WAT (but not in stomach) as the central player in obesity through large-scale systems screening. However, the causal nature of inflammatory was not clear through these correlative analyses.

To tackle the causal versus reactive nature of inflammation, Kwon et al. conducted a time-course with 8 time points over 24 weeks to assess changes in adipocyte morphology, adipokines and transcriptome in visceral WAT from four depots (epidydimal, perirenal, retroperitoneum, mesentery) during the course of high fat diet-induced obesity[95]. Through gene expression microarray analysis, they identified early and sustained activation of the immune response and inflammatory genes including multiple TLRs, Irf5 and Cd14 that are involved in metabolism-induced inflammatory signaling and their downstream pro-inflammatory cytokines such as Tnf, Il1rn, Saa3, Emr1, Adam8, Itgam, and chemokine (C-C motif) ligand genes. These changes were mainly observed in epididymal and mesenteric depots and preceded morphological onset of obesity. The early activation of TLR-mediated inflammatory signaling cascades revealed from this time course study convincingly placed inflammation in visceral WAT into the causal position. Using a similar time course design, Oh et al. combined liver gene expression profiles with gene network analysis to identify gene networks and key regulators (hubs) of high-fat diet induced obesity and liver non-alcoholic steatohepatitis. A network associated with inflammatory response was among the five core networks uncovered; Tlr2, Cd14, and Ccnd1 were found to be the central regulators of this network and these genes appear to interact through the ErbB/insulin signaling

pathway. Taken together, these new systems-level genomic studies clearly and consistently confirm the central causal role of inflammation in WAT and liver in inducing obesity.

T2 Diabetes Mellitus

T2DM is often associated with obesity as a consequence of overnutrition with or without genetic susceptibility. Impaired insulin signaling, or insulin resistance, usually follows obesity onset and precedes T2DM. Evidence has been converging on inflammation as a primary cause for insulin resistance as well as for pancreatic islet β-cell deterioration and failure, two key events leading to T2DM. Considering the critical role of inflammatory in obesity as discussed above, it is intuitive to understand why obesity is a risk factor for T2DM. Through analysis of key tissues involved in insulin resistance and insulin secretion – adipose, liver, islet and muscle, Imai et al. recently discovered that hormone and cytokine production by adipose tissue and infiltration of immune cells such as macrophages in liver, adipose, and islet (but not in muscle) are partially responsible for impaired insulin signaling and bβ-cell failure in T2DM [96,97].

Recent systems studies have uncovered many inflammatory genes as playing causal roles in T2DM development and highlight the key role of adipose tissue inflammation in T2DM development. In a series of studies, Butte and colleagues conducted systematic analysis of gene expression datasets across 130 independent experiments that included a total of 1,175 T2DM case-control microarrays, they identified CD44, encoding a T cell-related cell adhesion molecule, as the top differentially expressed gene across studies and experimentally confirmed its role in modulating adipose tissue inflammation, insulin sensitivity, and glycemic control[98]. In an integrative analysis involving T2DM GWAS, genetic of gene expression in liver and adipose tissues, and biological pathways, Zhong et al identified complement and coagulation, and antigen processing and presentation as key pathways contributing to T2DM pathogenesis[99]. Recently, Mori et al. conducted an extensive comparison between two mouse strains with different susceptibility to T2DM. They integrated metabolic characterization, gene expression, protein-protein interaction networks, and other analyses of adipose, skeletal muscle, and liver tissue of the two mouse strains at two different time points, and identified an inflammation- and immune system-related adipose subnetwork that predicts and contributes to the differences in T2DM risk[100]. Particularly, increases in T-cell related molecules such as SDF1α, CCL5/RANTES, IFNγ and CD80 are accompanied by T-cell and macrophage infiltration in adipose tissue. In another study, Gao et al. screened six tissues of two strains of mice at two obesity status and two ages. Again inflammatory pathways especially the T cell receptor signaling pathway, autoimmune processes, and focal adhesion were predominant in adipose tissue in T2DM, whereas metabolic pathways are more prominent in other tissues (e.g., glycolysis/gluconeogenesis in liver and insulin signaling in muscle) [101].

Coronary Heart Disease

The role of inflammation in coronary heart disease (CHD) was first captured by C-reactive protein (CRP), an acute phase protein released from liver and adipose tissues and a strong indicator of coronary heart disease risk [102]. Through studies of coronary heart disease, a condition characterized by the hardening and narrowing of arteries that is the key feature to

coronary heart disease development, increasing evidence supports an important role for inflammation in all phases of coronary heart disease, from initiation of the fatty streak to final culmination in acute coronary syndromes [103]. Numerous inflammatory biomarkers including cell adhesion molecules, cytokines, chemokines, and acute-phase reactants such as fibrinogen, serum amyloid A, and CRP have been shown to predict coronary heart disease events. TLRs, pattern recognition receptors and members of the innate immune system, contribute to inflammation and appear to play key roles in coronary heart disease. Similar to obesity and T2DM discussed above, coronary heart disease and coronary heart disease are also highly complex and involve the interactions among diverse biological processes in various tissues and organs. In the past few years, systems biology and integrative genomics approaches that aim to provide a comprehensive view of molecular mechanisms underpinning coronary heart disease have again highlighted inflammation as a key causal mechanism that tightly interact with lipid metabolism [104,105].

In a study involving more than 300 F2 mice derived from a cross between the strains C3H/HeJ and C57BL/6J on a hyperlipidemic apolipoprotein E-null background, Wang et al. conducted a genetical genomic analysis of coronary heart disease, aiming to objectively identify genetic loci and tissue-specific biological processes contributing to coronary heart disease. By correlating DNA genotyping with coronary heart disease traits, they identified 10 quantitative trait loci for lesion size; by performing expression analysis for 23,574 transcripts of the livers and adipose tissues, they identified genetic loci regulating gene expression and genes correlated with atherosclerotic lesion development. Genes involved in cholesterol metabolism, mitochondrial oxidative phosphorylation, and inflammation was found to be highly over-represented among the lesion-correlated genes[106]. Taking one step further to go beyond correlation into causation, Yang et al. employed a likelihood-based causality test [107] to identify causal genes for atherosclerotic lesions[108]. A total of 292 causal genes were identified from liver and adipose tissues and these genes were highly enriched for inflammatory genes involved in lymphocyte activation and B cell receptor signaling[108]. Validation experiments in two plaque progression mouse models, in a knockout mouse model of C3ar1 (a gene involved in complementation), and via cross-checking with human genome-wide association studies (GWAS) confirmed the causal nature of these genes.

Similar systems analyses have been conducted in human populations and inflammation related processes were consistently pinpointed as the causal factors of coronary heart disease. For instance, Huan et al. carried out an integrative analysis using whole blood gene expression profiling data obtained from 188 pairs of coronary heart disease case-control individuals in the Framingham Heart Study[109]. Although few differentially expressed genes between cases and controls were identified, gene coexpression network analysis revealed a network module comprising genes involved in B cell activation to be highly coexpressed in controls but disrupted in coronary heart disease cases. This module was further demonstrated to be enriched for genes whose functional genetic variants exhibit association with coronary heart disease in the GWAS from the CARDIoGRAM consortium[110], thus supporting a causal role in coronary heart disease. In two parallel studies of a Finnish cohort with ~500 individuals[111], Inouye et al. integrated blood transcriptomic, metabolomics, and genetic data and constructed gene co-expression networks to capture the molecular interactions. They linked network modules to >80 blood metabolites that are relevant to

coronary heart disease, such as lipoprotein subclasses and lipids[111]. A lipid-leukocyte module comprising primarily inflammatory genes was highly associated with and largely reactive to blood metabolites, and was genetically linked to variants controlling serum immunoglobulin IgE levels. The authors postulate that this immune response module is a key mediator that senses metabolite variations and then translates metabolic signals into inflammatory signals, which in turn contribute to atherogenesis. In one recent comprehensive investigation of the genetically perturbed molecular mechanisms of coronary heart disease, we systematically integrated diverse types of genomic data including genetic associations from GWAS, tissue-specific genetic regulation of gene expression, biological pathways, and tissue-specific gene regulatory networks. As a result we identified tens of molecular pathways, both known and novel, to be involved in coronary heart disease development[112]. Multiple immune/inflammation related pathways such as immunoregulation, antigen processing and presentation, Th1/Th2 differentiation, and adhesion and diapesis of lymphocytes are among the top signals. Furthermore, this study identified tens of potential key regulators of the significant processes using data-driven approaches including *PTPRC, NCKAP1L, FCGR1A, FYB*, and*FCER1G* for the inflammation gene network and *VPS52, PPIL1, GLO1, GFER*, and *DECR2* for the antigen-related gene network. These systems studies in both human and mouse revealed tissue-specific causal genes and unanimously pointed to the central role of inflammation in coronary heart disease.

As discussed above, when analyzing individual metabolic disorders separately, inflammation emerges as a causal mechanism shared among these diseases. The conclusion remains true when these diseases are assessed together. In fact, in two seminal systems biology studies, one focusing on data generated from a mouse F2 cross and the other studying an Icelandic human population, Chen et al. and Emilsson et al. identified a co-expression network module that is conserved between liver and adipose tissues, conserved between human and mouse, highly enriched for macrophage- and spleen-related inflammatory genes, and linked to various metabolic phenotypes including adiposity, coronary heart disease, and plasma lipids, insulin and glucose levels, all essential traits of metabolic disorders [4,113]. In our recent study, we analyzed 12 tissue-specific gene expression profiling data of eleven different mouse and rat disease models of metabolic disorders and other common diseases and identified a consistent inflammatome signature that are not only shared among all diseases but also demonstrate causal properties[114]. Therefore, inflammation serves as an attractive targeting point for therapeutics. In fact, recent attempts to alleviate metabolic diseases by targeting the inflammatory pathways have proven to be successful[115,116]. Kiechl et al. targeted RANKL, the receptor activator of NF-κB signaling and observed the preventative potential of the treatment for T2DM. In parallel, Reilly et al. used amlexanox, a drug approved for asthma and aphthous ulcers and an inhibitor of IkB kinases TBK1 and IKK-ε to treat obese mice and found overall improvement of metabolic profiles.

Molecular and genetic inflammation networks underlying neurodegenerative diseases

Complex neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS) share common molecular pathological mechanistic networks involving misfolded proteins, especially those prion-like proteins. The aggregation, deposition and propagation of prion-like proteins is tightly connected to immune response pathways [117]. However, the types of aggregated proteins and affected neuron cells vary from disease to disease[5,118-121]. A line of Prion-like proteins such as α-synuclein, tau, TDP-43, FUS, and C9orf72, have been characterized, with the former two specific to PD and AD respectively while the latter three mainly involved in FTD and ALS[120].

Blood-brain barrier (BBB) is critical to the brain's normal function. Accordingly, a compromise of BBB accompanies many neurologic disorders, and is tightly associated with brain inflammatory processes initiated by both infiltrating leukocytes from the blood, and activation of glial cells. Those inflammatory processes contribute to determining the severity and prognosis of numerous neurologic disorders, and can both cause, and result from BBB dysfunction[122-127].

A pathological hallmark of AD, aggregation and deposition of amyloid-β peptides, has been recognized as a potent activator of microglia-mediated neuroinflammation and neuronal dysfunction. Autophagy is a major cellular pathway leading to the removal of aggregated proteins of amyloid-β (Aβ) peptides and tau protein. Autophagy not only reduces intracellular components to compensate for nutrient deprivation but also selectively eliminates organelles to regulate their number and maintain quality control[128-130]. Mitophagy, the specific autophagy elimination of mitochondria, has been identified in yeast, mediated by autophagy-related 32 (Atg32)and in mammals during red blood cell differentiation , mediated by NIP3-like protein X (NIX; also known as BNIP3L) [131-135]. Moreover, mitophagy is regulated in many metazoan cell types by PARKIN and PTEN-induced putative kinase protein (PINK1), and mutations in the gene encoding these proteins have been linked to forms of Parkinson's disease[132,133,136]. Neoechinulin A can significantly suppress the production of neurotoxic inflammatory mediator tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and prostagladin E2 (PGE2) in activated BV-2 cells. Activated microglia-mediated apoptosis of PC-12 pheochromocytoma cells was significantly repressed by neoechinulin A[137]. The molecular mechanism studies suggested that neoechinulin A may block the phosphorylation of mitogen-activated protein kinase (MAPK) molecule p38, apoptosis signal-regulating kinase 1 (ASK-1) and nuclear translocation of nuclear factor-κB (NF-κB) p65 and p50 subunits.

Microglial cells constitute the first line of defense of the central nervous system (CNS) against microbial invasion. Pathogens are detected thanks to an array of innate immune receptors termed pattern recognition receptors (PRRs). PRRs have been thoroughly characterized in bone marrow-derived macrophages, but the PRRs repertoire and functionality in microglial cells remain largely unknown. Microglial cells express various Toll-like Receptors and the Nod1/2 receptors. Recently, a novel innate immune signalling

pathway, the inflammasome pathway has been uncovered. Inflammasome activation leads to caspase-1 activation, release of the proinflammatory cytokines, IL-1β and IL-18 and cell death in a process termed pyroptosis. One inflammasome receptor, NLRP3, has been characterized in microglial cells and associated with response to infections and in the initiation of neuro-degeneration in an Alzheimer's disease model, illustrating that microglial cells detect L. pneumophila infection in a flagellin-dependent manner leading to caspase-1-mediated bacterial growth restriction, infected cell death and secretion of the proinflammatory cytokines IL-1β and IL18. Overall, these data demonstrate that microglial cells have a functional Naip5-NLRC4 inflammasome likely to be important to monitor and clear CNS infections by flagellated bacteria. A more complete inflammation response pathway has been proposed based on data-driven molecular networks[9].

Autophagy, a fundamental eukaryotic pathway with multiple effects on immunity, can be induced by pattern recognition receptors and, through autophagic adaptors. Detailed mechanisms for the elimination of intracellular microorganisms involve controlling inflammation through regulatory interactions with innate immune signaling pathways, by removing endogenous inflammasome agonists and through effects on the secretion of immune mediators[138].

Autophagy is an intracellular degradation process that clears long-lived proteins and organelles from the cytoplasm (28). It involves the formation of double-membraned structures called autophagosomes that can engulf portions of cytoplasm containing oligomeric protein complexes and organelles, such as mitochondria. Autophagosomes fuse with lysosomes and their contents then are degraded. Failure of autophagy in neurons can result in the accumulation of aggregate-prone proteins and neurodegeneration. Pharmacological induction of autophagy can enhance the clearance of intracytoplasmic aggregate-prone proteins, such as mutant forms of huntingtin, and ameliorate pathology in cell and animal models of neurodegenerative diseases. The ways in which dysfunctions at multiple stages in the autophagic pathways contribute to numerous neurological disorders are highlighted through the use of examples of Mendelian and complex conditions, including Alzheimer disease, Parkinson disease and forms of motor neuron disease. The different ways in which autophagic pathways might be manipulated for the therapeutic benefit of patients with neurodegenerative disorders are also considered. As mitochondrial dysfunction is a common observation in these and other neurodegenerative diseases, the available data on AD and PD can be incorporated into a single integrated paradigm based on mitochondrial genetics and pathophysiology. Rare chromosomal cases of AD and PD can be interpreted as affecting mitochondrial function, quality control, and mitochondrial DNA (mtDNA) integrity. mtDNA lineages, haplogroups, such haplogroup H5a which harbors the mtDNA tRNA(Gln) A8336G variant, are important risk factors for AD and PD. Somatic mtDNA mutations are elevated in AD, PD, and Down Syndrome and Dementia (DSAD) both in brains and also systemically. AD, DS, and DSAD brains also have reduced mtDNA ND6 mRNA levels, altered mtDNA copy number, and perturbed Abeta metabolism. Classical AD genetic changes incorporated into the 3XTg-AD (APP, Tau, PS1) mouse result in reduced forebrain size, life-long reduced mitochondrial respiration in 3XTg-AD males, and initially elevated respiration and complex I and IV activities in 3XTg-AD females which

markedly declines with age. Mitochondrial dysfunction provides a unifying genetic and pathophysiology explanation for AD, PD, and other neurodegenerative diseases.

Key molecular pathways and modules in neurodegenerative diseases are typically pro-inflammatory

Recent advent highlighted the key role of over-activated NALP3 inflammasome linking IL-1β and IL-18 pathways in the molecular pathophysiology of Alzheimer's disease[139]. Deposition of Aβ peptide drives cerebral neuroinflammation by activating microglia. Indeed, Aβ activation of the NLRP3 inflammasome in microglia is fundamental for interleukin-1β maturation and subsequent inflammatory events. They demonstrated strongly enhanced active caspase-1 expression in human mild cognitive impairment and brains with Alzheimer's disease, suggesting a role for the inflammasome in this neurodegenerative disease. *Nlrp3*$^{-/-}$ or *Casp1*$^{-/-}$ mice carrying mutations associated with familial Alzheimer's disease were largely protected from loss of spatial memory and other sequelae associated with Alzheimer's disease, and demonstrated reduced brain caspase-1 and interleukin-1β activation as well as enhanced amyloid-β clearance. Furthermore, NLRP3 inflammasome deficiency skewed microglial cells to an M2 phenotype and resulted in the decreased deposition of amyloid-β in the APP/PS1 model of Alzheimer's disease. These results show an important role for the NLRP3/caspase-1 axis in the pathogenesis of Alzheimer's disease, and suggest that NLRP3 inflammasome inhibition represents a new therapeutic intervention for the disease.

While dysregulated CD36/TLR4-6 innate immune pathway related to endoplasmic reticulum (ER) stress are crucial to common inflammatory disease, it has been underscored that CD36/TLR4-6 are tightly connected to AD disease pathology[92,140-147]. Particulate ligands, including cholesterol crystals and amyloid fibrils, induce production of interleukin 1β dependent on the cytoplasmic sensor NLRP3 in coronary heart disease, AD and diabetes. Soluble endogenous ligands, including oxidized low-density lipoprotein (LDL), amyloid-beta and amylin peptides, accumulate in such diseases. Here we identify an endocytic pathway mediated by the pattern-recognition receptor CD36 that coordinated the intracellular conversion of those soluble ligands into crystals or fibrils, which resulted in lysosomal disruption and activation of the NLRP3 inflammasome. Consequently, macrophages that lacked CD36 failed to elicit IL-1beta production in response to those ligands, and targeting CD36 in atherosclerotic mice resulted in lower serum concentrations of IL-1β and accumulation of cholesterol crystals in plaques. The importance of CD36 in the accrual and nucleation of NLRP3 ligands from within the macrophage and position CD36 as a central regulator of inflammasome activation in sterile inflammation has been underscored. Phagocytosis controls CNS homeostasis by facilitating the removal of unwanted cellular debris. Accordingly, impairments in different receptors or proteins involved in phagocytosis result in enhanced inflammation and neurodegeneration. They show that the autophagy protein beclin 1 is required for efficient phagocytosis in vitro and in mouse brains; beclin 1-mediated impairments in phagocytosis are associated with dysfunctional recruitment of retromer to phagosomal membranes, reduced retromer levels, and impaired recycling of phagocytic receptors CD36 and Trem2. Interestingly, in the study, microglia isolated from human AD brains show significantly reduced beclin 1 and retromer protein levels. These

findings position beclin 1 as a link between autophagy, retromer trafficking, and receptor-mediated phagocytosis and provide insight into mechanisms by which phagocytosis is regulated and how it may become impaired in AD. The mechanisms linking Aβ to NADPH oxidase-dependent vascular oxidative stress have not been identified, however. The scavenger receptor CD36, a membrane glycoprotein that binds Aβ, is essential for the vascular oxidative stress and neurovascular dysfunction induced by Aβ1-40. Thus, topical application of Aβ1-40 onto the somatosensory cortex attenuates the increase in cerebral blood flow elicited by neural activity or by endothelium-dependent vasodilators in WT mice but not in CD36-null mice (CD36(0/0)). The cerebrovascular effects of infusion of Aβ1-40 into cerebral arteries are not observed in mice pretreated with CD36 blocking antibodies or in CD36 (null/null) mice. Meanwhile, CD36 deficiency prevents the neurovascular dysfunction observed in transgenic mice overexpressing the Swedish mutation of the amyloid precursor protein Tg2576 despite elevated levels of brain Aβ1-40. Thus, CD36 is also required for the vascular oxidative stress induced by exogenous Aβ1-40 or observed in Tg2576 mice. These observations have established CD36 as a key link between Aβ1-40 and the NADPH oxidase-dependent vascular oxidative stress underlying the neurovascular dysfunction and suggest that CD36 is a potential therapeutic target to counteract the cerebrovascular dysfunction associated with Aβ.

The mixed results from anti-inflammatory drugs for ameliorating AD or amyotrophic lateral sclerosis may suggest both local cytotoxic inflammation and protective systemic immune response occurs in these disease conditions[148]. Very recently, a new study offered evidence that PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of AD[149]. It appears that both systemic and local inflammation plays double-sword roles. Taken together, these results highlight the importance of complex immune responses both locally and systemically during of the progression of neurodegenerative diseases. To dissect the complexity of local and systemic immune responses in the initiation and development of complex diseases, systems immunology approaches need be adopted by leveraging multiscale network biology schemata and technologies.

Molecular and genetic inflammation networks underlying cancer

There is an emerging consensus that inflammation and cancer are tightly coupled together and mutually causal throughout all carcinoma progression stages spanning from normal epithelium, carcinoma *in situ*, local invasion, to distant metastasis[150]. Due to the complexities of cancer and inflammation, more explicit mechanisms remain elusive. Albeit solid epidemiological data revealed on the efficacy of anti-inflammatory drug, such as salicylate including aspirin, to preventing cancer[151-157], the arising precision medicine requires nuanced rational upon pinpointing in-depth mechanistic connections between inflammation and cancer [158,159], rather than completely depending on clinical cohort studies. In this section, we seek to underscore key principles that govern the functional links between inflammation and cancer. This holistic view via molecular networks is intended to convey systems molecular pathophysiology insights by highlighting crucial interplays between key modules of inflammation and cancer networks [12,160].

Cancer as a complex disease has been gaining more attentions as a malignant system rather than a bag of evil tumor cells solely, leading to substantial emphasis on tumor evolution micro-environment[161,162]. Such a malignant system is essentially consisted of active innate and adaptive immune cells which can promote or suppress cancer cell growth, thereby coupling cancer and inflammation together tightly[37,150,159,163-167]. This cellular composition heterogeneity appears to be underpinned by genetically and biochemically sophisticated molecular networks. Naturally it has been reaching agreement that tumor is generally heterogeneous at all levels[168-172]. These types of complex and heterogeneous systems generally result from a multistep development involving newly acquired cellular phenotypes, such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis[173,174]. Moreover, two fundamental cancer hallmarks recently highlighted, reprogramming of energy metabolism and evading immune destructions, are thought to crucial to drive cancer[173,174]. All of these cellular phenotypes are connected to molecular inflammation. Indeed, at the molecular level, both the extrinsic inflammation and the intrinsic oncogene activation can lead to activation of pivotal transcription factors, such as NF-κ B, STAT3, and HIF1α in tumor cells as well, resulting in the secretion of chemokines, cytokines, and prostaglandins [37]. These secreted factors further enable recruiting a variety of inflammatory cells, including macrophages, mast cells, neutrophils, eosinophil, as well as myeloid-derived suppressor cells. Intriguingly, these recruited cells, especially macrophages[174], have their essential function producing growth factors, chemokines, adhesion molecules, as well proteases. Thus, intercellular positive feedback loops can be formed, supporting the mutual causality between inflammation and cancer. Furthermore, these secreted macromolecules have been shown actively participating in cancer progression via a set of complex mechanisms, including promoting cancerous cells transformation, carcinoma in situ formation, local invasion, cancer cell homing, as well as tumor angiogenesis [37]. Apparently, such knowledge underpins the rational for anti-inflammatory intervening. Canonical reductionism wisdoms that have been deployed in uncovering crucial molecular pathways, such as integrin based cell signaling, metabolic switching controlled by AMPK and mTOR pathways, yet have been facing formidable challenges to dissect such complexities in terms of reaching a systematic fine-resolution. Therefore, systems biology approaches have been holding a great promise to detangle those sophisticated interplays between cancer and inflammation. Thus, how to pinpoint rate-limiting network modules has been emerging crucial to hold more promises in underpinning nuanced molecular mechanisms underlying cancer progression. Recent network biology advances have been further illuminating the power of filtering and integrating of large data sets in pinpointing key modules and driver genes, as well as novel anti-cancer potentials of classical anti-inflammatory or anti-diabetes drugs.

There are many lines of compelling evidence indicating the connection between carcinogenesis and inflammation in mouse models[175]. Genetic architecture of mouse skin inflammation and tumor susceptibility has illuminated the crucial role of *Lgr5* and *Vdr* in coordinated control of epidermal barrier function, inflammation, and tumor susceptibility[176]. Further expression quantitative traits locus (eQTL) analysis from the same research group further highlighted the critical role of tumor microenvironment, mitogen-activated protein,

kinase signaling, inflammation, and cancer susceptibility[175]. In ovarian cancer, network of inflammatory cytokine interactions appeared crucial to tumor progression[162]. Furthermore, in the prostate carcinogenesis, a hypothesis referred as proliferative inflammatory atrophy (PIA) has been proposed, with a specific emphasis on molecular mechanisms of inflammation-induced cancers[165].

Recently, by exploiting twelve expression data sets profiled from nine distinct types of tissues in eleven rodent inflammatory disease models, an inflammatome gene signature has been found in which around 2,500 genes and 151 key drivers and the network architecture therein are crucial to progressions of eleven representative complex diseases including asthma, emphysema, pulmonary fibrosis, lipopolysaccharide (LPS) induced sepsis, neuropathic pain, coronary heart disease, stroke, obesity, diabetes, and age-related sarcopenia [12]. Intriguingly, two most consensus drug targets are *Ppara* and *Prkaa*, both of which are pivotal during cancer progression[12]. AMPK encoded by *Prkaa* in mouse, has been demonstrated as a key kinase regulating metabolism and information flux, especially on cancer and inflammatory cells metabolism switching (Warberg effect) [159], as well as linking epigenetic modification [164]. Such efforts offer an opportunity to infer and rank key driver modules and genes that underlie the awry cancer genetic architectures Nonetheless, both cancer and inflammatory are driven by highly dynamic signaling networks, shared by key network attractors [177]. This raises a grand challenge to disclose the in-depth fine-resolution mapping of the molecular pathophysiology links between inflammation and cancer. Diagnostic or prognostic biomarker and lead compounds discover, as well as novel druggable targets ranking, have been practically adapted to next generation technologies by utilizing large data sets. Epigenetic modification may play key roles in bridging a variety of inflammation and cancer mechanistic links. For the long run, it will be exceptionally interesting on how to integrate those emerging large data sets (for example, the one million cancer genome warehouse) guided by explicit biomedical hypothesis and how to uncover sophisticated mechanisms linking information metabolism and metabolite influx by borrowing conceptual innovations from those arising mathematical framework on network properties, including stability [178,179], resilience [180], as well as dynamics [181,182]. In light of network biology, more exciting molecular pathophysiology mechanisms that underlie the inflammation-cancer axis have been emerging, thereby favoring the arising of next generation precise medicine upon complex diseases.

Immune Repertoire Sequencing

Recent advancement in massively parallel or next-generation sequencing (NGS) technology has revolutionized the way to conduct biological and medical research[183184185]. Among the active inflammation-related research fields which benefit from these high-throughput sequencing platforms are metagenomic analysis of microbial flora and immune repertoire sequencing (Rep-seq)[186187188]. Many excellent reviews about impacts of microbiome on health and disease have been published the past few years[189-192]. This section will focus only on applying Rep-seq in addressing key inflammation-related issues.

The adaptive immune responses mediated by B and T lymphocytes are keys to host defense against microbial pathogens and transformed cells or cancers. B cell receptor

(immunoglobulin) and T cell receptor are encoded by multiple V (variable), D (diversity) and J (Joining) gene segments. The enormous diversity of the immune repertoire required for providing protection is generated via a somatic rearrangement of the germline V, D, J genes and addition or deletion of nucleotides at the junctional regions during lymphocyte development. Traditional Sanger sequencing can at most sequence hundreds of immune receptors at a time and it is only when NGS technology become available that a comprehensive analysis of the immune repertoire can be achieved[193]. In oncology area, due to the aberrant oligoclonal expansion of T/B lymphocytes in hematological malignancies, Rep-seq has been applied to monitor disease progression and response to therapy in lymphoma/leukemia[194195] and demonstrated better sensitivities in detecting minimal residual disease (MRD) than more traditional flow cytometry-based methods[196,195]. For a separate application, a strong correlation has been established between tumor-infiltrating T lymphocytes (TILs) and increased survival in multiple cancer types but the current anti-CD3 immunohistochemistry (IHC) assay to identify TILs is suboptimal in terms of interpretability and quantifiability. By using multiple PCR primer sets targeting all functional TCR V segments, Robins et al. [197] introduced a Rep-seq based digital DNA assay to count and assess TILs and their clonalities in tumor tissues and were able to confirm, in ovarian cancer, an positive association between TIL counts and survival. They also made an observation that TIL repertoire is diverse with no obvious oligoclonal expansions. When the same approach was employed to examine lesions in cervical intraepithelial neoplasias caused by human papillomavirus (HPV16), it was found that intensity of CD8+ TILs increased significantly in patients receiving a therapeutic vaccine targeting HPV antigens and unlike the situation in untreated TILs [197] in other tumors, these CD8+ TILs showed clonal expansions, presumably as a result of recognizing cognate antigens [198].

It has been suggested that during CMV infection, T cell diversity rather than abundance could be more important in conferring protection to pathogen infection. In fact, CD8+ T cell diversity but not the size of CD8+ T cell response, was negatively correlated to CMV-specific antibody titers in the infected human subjects[106]. In this case, high anti-CMV antibody levels (and therefore low T cell repertoire diversity) were found to be associated with increased viral ADs and mortality risks. Patients suffered from septic shock were also reported to have a lower T cell repertoire diversity which was predictive of higher mortality rate and the development of nosocomial infections[199]. Combining transcriptional profiling and Rep-seq on genital skin and mucosal tissues at the neuronal release sites acquired by laser capture micro-dissection (LCM), it was shown that CD8+ T cells play a key immune surveillance role in responding to herpes simplex virus 2 (HSV-2) infections and express diversified TCR-V region genes with dominant clonotypes overlapping multiple infection episodes over extended period of time[108].

B cell response to vaccination is critical in providing protective immunity but detailed analysis of molecular nature of antibodies present in serum after vaccination remains lacking. Lavinder et al. applied high resolution MS proteomic and Rep-seq analysis following tetanus toxoid booster vaccination and detected ~100 antibody clonotypes with 3 constitutes more than 40% of all antibodies. The results also suggested that a small proportion of peripheral blood plasmablasts at day 7 post-vaccination and an even smaller proportion of memory B cells encode antigen-specific antibodies 9 months later[200]. Recent

published reports indicated that people 65 years or older have significantly lower antibody titers and repertoire diversity than younger population in response to pneumococcal [201] and influenza vaccines[202]. Although IgG is the most prevalent antibody isotype in serum and is most often correlated to vaccine protection, it is IgA, and to a lesser extent IgM, that show the most significant age-dependent titer decrease in the elderly post-vaccination; the significance of this observation is yet to be further explored[195]. It is interesting to note that inclusion of a Toll-like receptor (TLR) agonist (as an adjuvant therapy) in a malaria vaccine formulation not only increased the antibody diversity but also improved antigen neutralization[203].

Another large scale analysis has been conducted within the ImmVar project, where the impact of genetic variation on the ability of the immune system to protect against pathogen has been studied[204]. Although not by complete genome sequencing but by genotyping, the population variation of a cohort of 600 healthy individuals have been assessed and mapped to transcriptional responses of peripheral blood mononuclear cells (PBMCs). Transcriptional baseline as well as response against IFNβ, influenza virus and lipopolysaccharide (LPS) have been analysed. A number of SNPs are cis-eQTLs that are associated with the expression of genes encoding regulators, i.e. transcription factors (TFs), in pathways that were stimulated. Of these, rs2805435 was the most significant, associating with the expression of the master antiviral TF *IRF7* in cis only after influenza, IFNβ, or LPS stimulation. Seven more genes were associated with this SNP in trans (*IFNA4, IFNA5, IFNA10, IFNA13, IFNA17, IFNA21, NM1*)[205].

Perhaps the most advanced and productive immune repertoire analysis was conducted in studying the HIV broad neutralizing antibodies[206]. Combining B cell cloning, antibody isolation, B cell Rep-seq, structural analysis and viral genome sequencing, broad neutralizing antibodies (BnAbs) defined as cross-reactive antibodies capable of neutralizing the majority of HIV-1 strains which are generated in ~20% of HIV patients 2-3 years post-infection) targeting HIV gp120 [207] and V1V2 region of the HIV-1 envelope[206] were identified and characterized in details. These antibodies contain long complementarity-determining region 3 (CDR3) and are hyper-mutated. Longitudinal sequencing of BnAbs (and their unmutated ancestors) and viral genomes suggested a co-evolutional relationship started with a diversified viral population followed by antibody affinity maturation. These findings would not have been made without the availability of NGS technology and could be integrated into future HIV vaccine development. However, immune repertoire analysis is still at its infancy and will require more collaboration among researchers to share best practice and to standardize experimental protocols so results obtained from different labs can be compared and analyzed together.

Computational Approaches for Modeling Inflammation and Immune Response

Computational approaches have been long developed to model inflammation and immunology so as to derive a holistic understanding of immune systems. Seminal studies of dynamic models of immune systems by Perelson *et al.*[208], DeBoer *et al.*[209] and Nowak and

May[210] were based on differential equations. Early network models of host-pathogen systems utilized pre-existing knowledge of metabolic pathways. For example, the tryptophan biosynthesis pathway was investigated in the case of Chlamydia infection [211]. Metabolic network databases such as KEGG[212], MetaCyc[213] or WIT[214], were used in tandem with the comparative analysis of metabolic networks[215] to identify the interdependence and connectivity between the pathogen and the host that helped to explain the development of the chronic disease caused by the pathogen.

Early predictive multi-scale models have been conducted by Stokes and coworkers at the same time. Using the Entelos PhysioLab framework for simulating disease physiology, Stokes *et al.* developed a computation model of asthma[216], by combining organ level physiological responses with biological pathways and molecular networks. Different steady states of this disease, such as chronic asthma including chronic eosinophilic inflammation, chronic airway obstruction, airway hyper-responsiveness and elevated IgE levels, can be induced in the model. These *in silico* asthmatic models respond as expected to various drugs, such as β2-agonists, glucocorticoids and leukotriene antagonists.

The Ingenuity Pathway Analyzer (IPA) is another commercial tool. It has been successfully applied to the network based analysis of systemic inflammation in humans. As discussed in the metabolic network based approach, such an approach requires pre-existing knowledge of pathways and interactions for network analysis. Identified targets where superimposed with network information from the Ingenuity knowledge base. Pathways of highly interconnected genes were identified by statistical likelihood calculation[217].

Complementary to these model based computational approaches that rely on a priori knowledge are *de novo* network construction methods. A well-established approach in this direction is weighted gene co-expression networks (WGCNA)[218]. The method is based on gene-gene correlation using soft-thresholding (weighted) similarity measures to define a co-expression similarity between genes. Coexpressed gene modules are identified by average linkage hierarchical clustering of a topological overlap matrix of the transformed coexpression similarity matrix. A recent application of WGCNA showed that inflammatory response triggered downregulation of a gene (ADAR2) leading to a decrease in mRNA editing of serotonin receptor after spinal cord injury (SCI), which further contributes to a post-SCI spasticity[219]. However, WGCNA enforces the connectivity to exhibit a power-law distribution and it doesn't explicitly define more intuitive unweighted coexpression networks. To address these issues, Multiscale embedded Gene co-Expression Network Analysis (MEGENA)[220], an advanced version of Planar Filtered Network Analysis (PFNA)[221,222], have been developed. MEGENA first employs network embedding technique on topological sphere to construct unweighted coexpresion network and then identifies multi-scale organizations of coherently co-expressed modules of genes[220]. MEGENA shows superior performance over many existing coexpression network analysis approaches. MEGENA revealed a group of multiscale immune response modules that are associated with breast cancer[220].

For experiments under multiple conditions such as studying gene expression response at multiple time points in infectious diseases, cMonkey, which performs biclustering of co-

regulated genes together with observed experimental conditions[223], would be a more suitable tool. In cMonkey, each bicluster is modeled via an iterative Markov chain Monte Carlo process. The method uses simulated annealing to add genes or conditions to the bicluster with high probability of membership and drops genes or conditions from the bicluster with low probability of membership. cMonkey has been discussed in an review on Systems Biology of Innate Immunity, by Zak and Aderem[224].

While the above coexpression network analysis approaches can reveal biologically meaningful clustering structures, they are not capable of determining causal relationships between genes, which is critical for identification of key causal regulators. Bayesian network inference is a natural framework for integrating high throughput multi-omics data as well as a priori information into probabilistic causal networks. Integration of large genetic and gene expression data has systematically revealed novel causal relationships among genes and key causal regulators in complex human diseases such as diabetes and obesity[4,107,113,225], Alzheimer's disease[226]. Given the high complexity of Bayesian network construction, an emerging trend is to integrate both coexpression and causal networks by performing causal network inference on coexpressed gene modules[227].

Summary

Tremendous progresses have been made in exploring the roles of inflammation response in complex human diseases in the past two hundred years but only in the last 40 years we are able to pinpoint particular specific mechanisms at the molecular level thanks to the emergence of genomics. We curated a table (supplement Table S1), in which gene symbol, name, function accession including OMIM and COSMIC gene name, as well as relevant drugs from a variety of data setting, were cataloged[228-230]. However, we are still at the early stage of depicting a complete inflammation response pathway map because molecular mechanisms and physiological functions of inflammation still remain most unknown[231]. Recent progresses in system biology built up upon large-scale genomic, genetic, epigenetic, proteomic and pathophysiological data have substantially accelerated the process by reconstructing molecular networks in an unbiased manner. For example, for the first time in AD research, we could put together genetic, gene expression and pathological data to construct and prioritize gene networks that are causally linked to AD[9]. These predictive data-driven networks provide a blueprint to reconstruct inflammation and other pathway maps for subsequent hypothesis development and biological validation.

On the other hand, we should keep in mind that inflammation response is only one of many pathways contributing to complex human diseases. So, exploration of molecular mechanisms and physiological functions of inflammation should be carried out in a more global context of pathway-pathway interactions. Again systems/network biology holds the key to the success given its unbiased and more disease-relevant nature.

A fundamental goal of understanding inflammation in complex human diseases is to identify novel therapeutic targets and effective treatments[232]. The inflammatome signature previously identified was highly enriched with current marketed drug targets[233] and could be a resource for identifying additional new drugs. Discovery of common features of

inflammation related regulation in major human diseases will facilitate the development of drugs targeting many inflammatory diseases rather than only in a limited spectrum of diseases. Core molecular networks in inflammation and their drivers can be used to identify existing drugs that could be used to reverse the states of the networks and drivers.

Recent advances in high-throughput technologies, data analysis algorithm development have made integrated Omics analysis an achievable goal, especially in the immunology/inflammation area[234]. A well-cited example by Chen et al. performed an integrated personal omics profile (iPOP) analysis combining longitudinal genomic, transcriptomic, proteomic, metabolomics and autoantibody data from a single individual during healthy and viral-infected states[235]. An NIH-sponsored Human Immunology Project Consortium (HIPC) generated a large repository of multiple data types including enzyme-linked immunosorbent assay (ELISA), enzyme-linked immunospot (ELISPOT), flow cytometry and gene expression. HIPC also created a software analysis tool for researchers to use this resource (https://immport.niaid.nih.gov/). The other example recently announced by Institute of Systems Biology (ISB) is even more ambitious - in additional to key genomics analysis, the 100 participants involved in the first phase will be asked to continuously record multiple physical/biochemical activities including blood glucose, ~100 protein levels (for monitoring organ health), immune cell activities, heart rate and sleep patterns. The stool samples will also be collected for sequencing major microbial species in the gut. ISB planned on expanding the study to 100,000 subjects for up to 25 years if the results from first phase look promising[236]. Although not without significant challenges, these efforts will no doubt bring us closer to the goal of achieving personalized medicine in a way envisioned as predictive, personalized, preventive and participatory (P4)[237].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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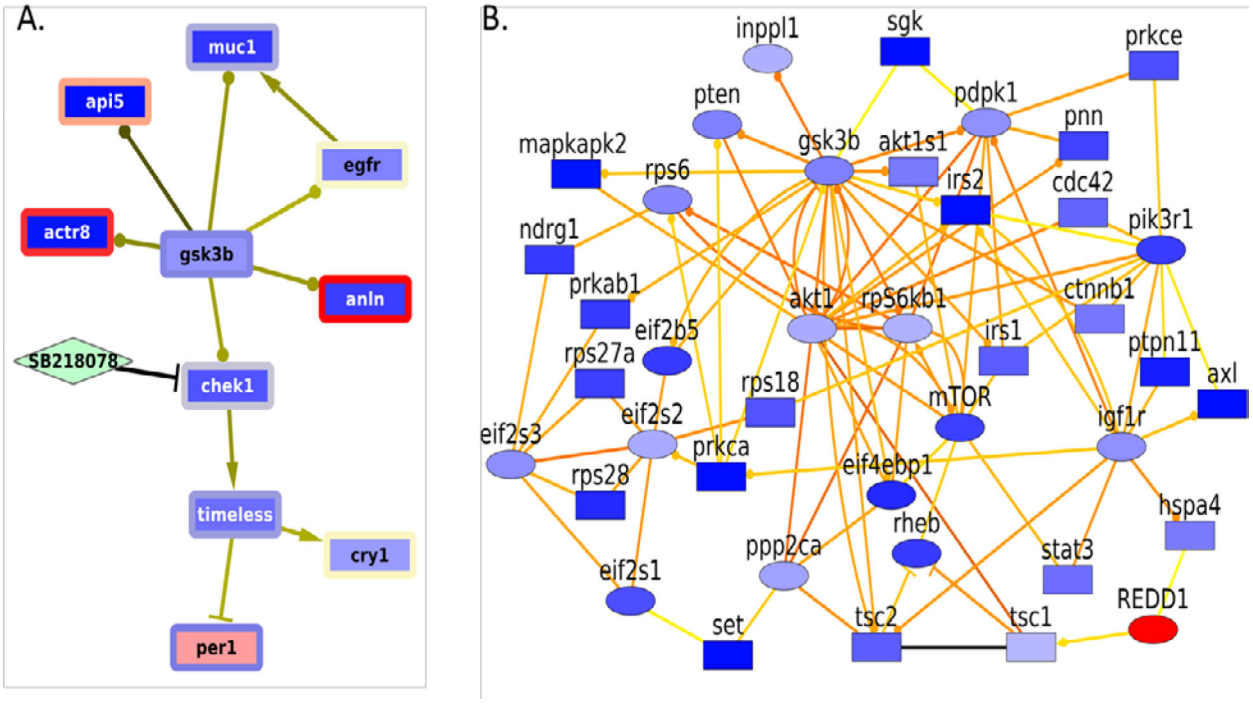

Figure 1. Example immune response networks

A) A pharmacologically addressable response network is shown. By inhibiting CHEK1, viral protein production is severely limited. Node colors (cell viability) and node border colors (viral replication) refer to negative (blue) and positive (red) Z-scores after RNAi analysis indicating low and high viral replication/cell viability, respectively[238]. **B)** Regulation of the mTOR pathway by a naphthalimide compound. REDD1 (DDIT4) is activated by the compound. Node colors indicate up- (red) and down- (blue) regulated genes between compound and DMSO (control) treated A549 cells. Edge colors denote edge scores (yellow edges have high score).

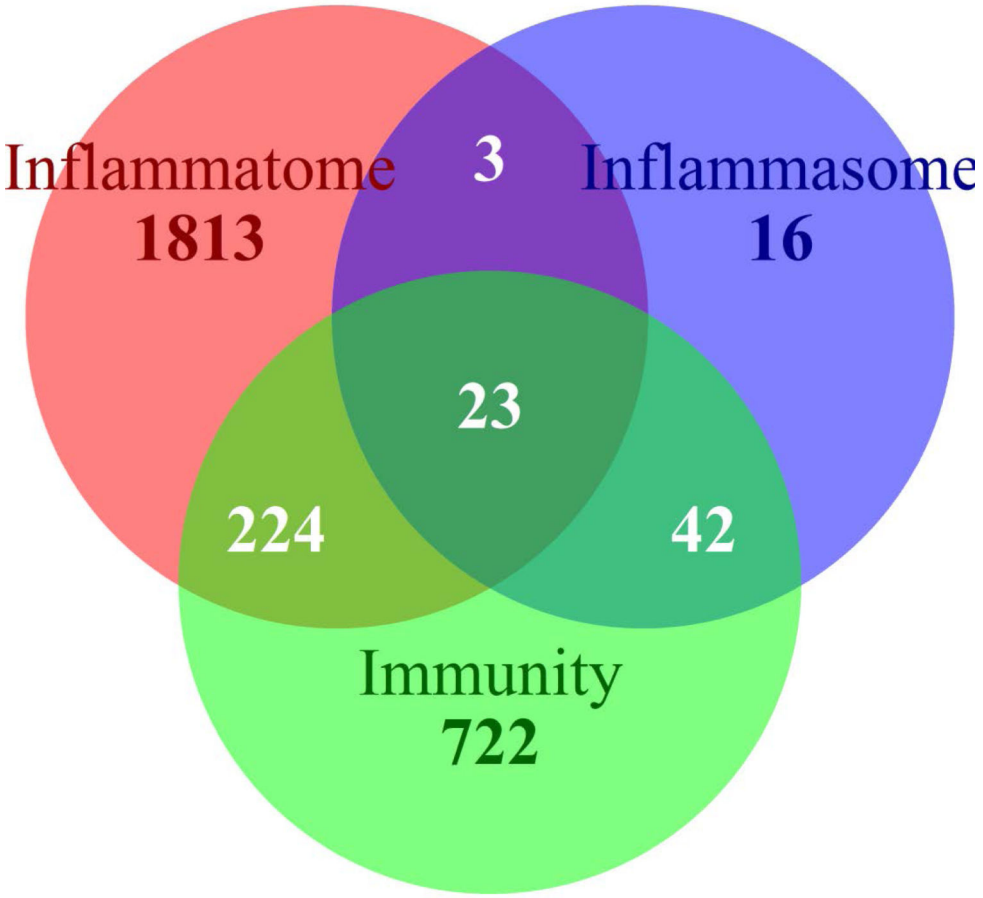

Figure 2.
The relationship between immune, inflammasome, and inflammatome gene signatures.

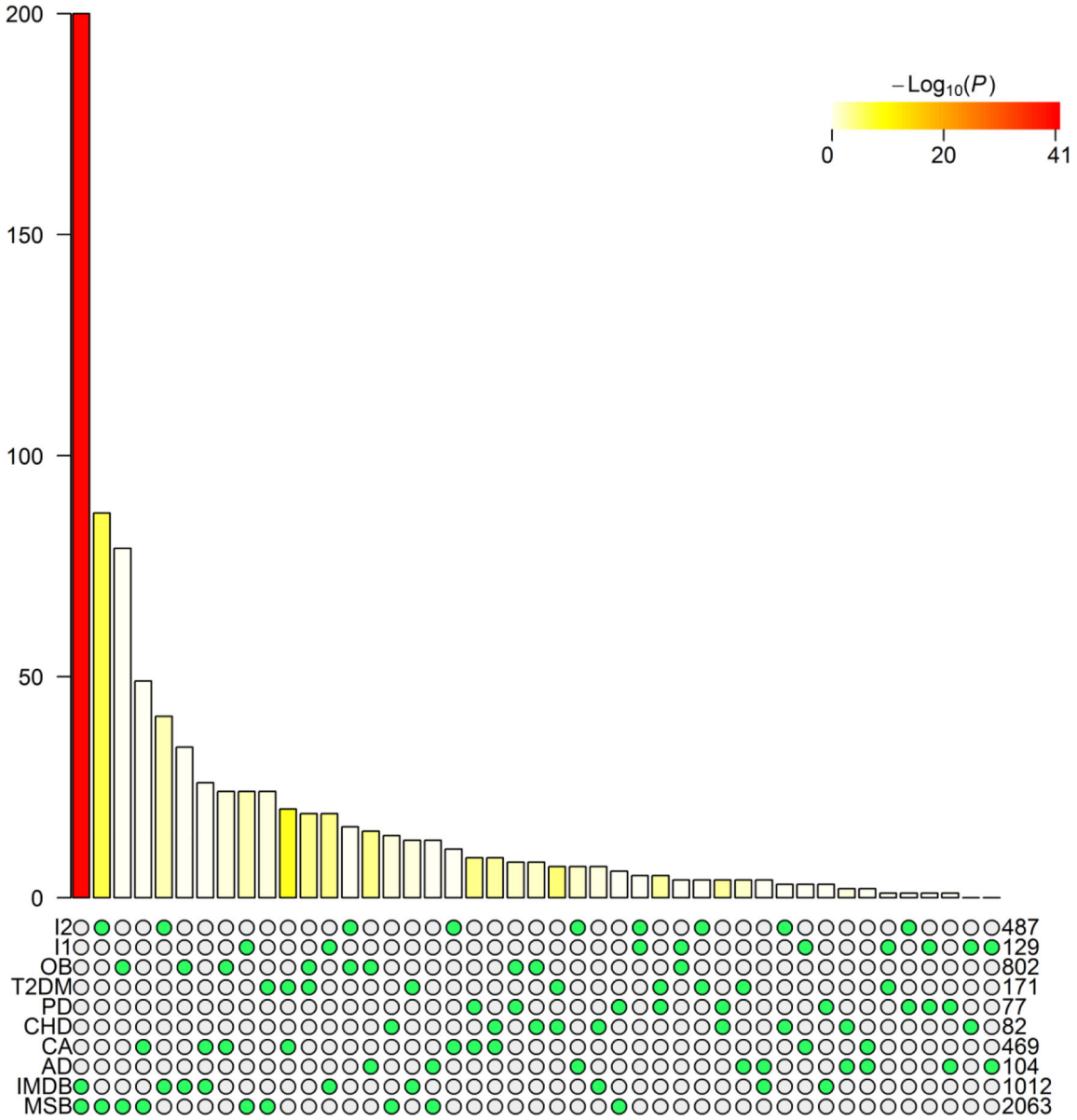

Figure 3.

A bar chart illustrating all possible intersections among the GWAS gene sets of the six common complex diseases and the inflammatory gene signatures. Complex diseases include obesity (OB), type II diabetes (T2DM), coronary heart disease (CHD), late onset Alzheimer Disease (AD), Parkinson disease (PD), and sporadic cancer (CA). Immune gene sets inflammatome (MSB) and innateDB curated immune genes (IMDB). Meanwhile, host factors (I1) and immune response signature (I2) are included. The matrix of solid and empty circles at the bottom illustrates the “presence” (solid green) or “absence” (empty) of the gene sets in each intersection. The numbers to the right of the matrix are set sizes. The colored bars on the top of the matrix represent the intersection sizes with the color intensity showing the P value significance.

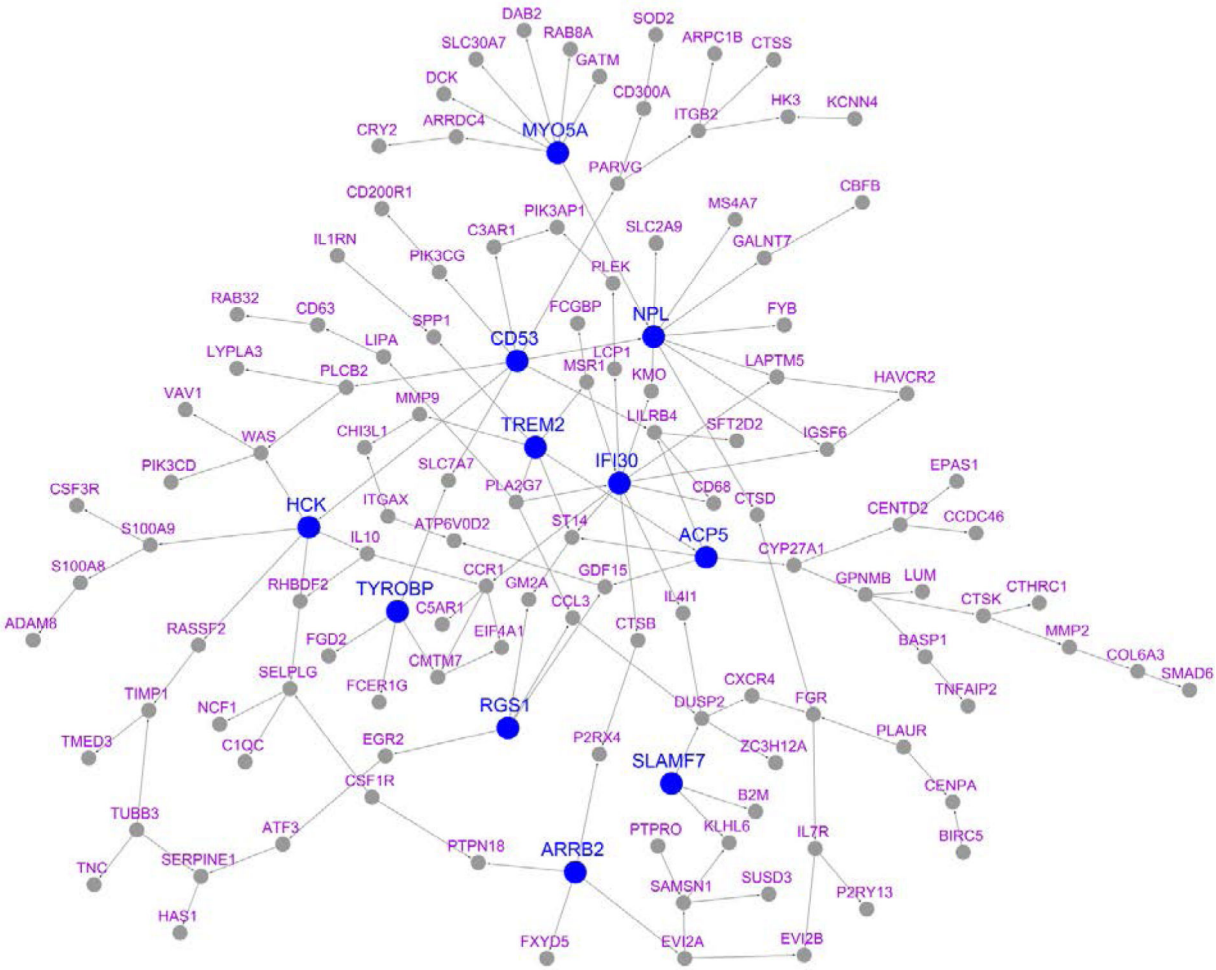

Figure 4.

A core causal network in inflammation. The predicted key drivers are highlighted in larger size and red color.