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Workshop summary

Current concepts in chronic inflammatory diseases: Interactions between microbes, cellular metabolism, and inflammation

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Marburg, Munich, Dresden, Munster, Giessen, Erlangen, and Mainz, Germany; Cambridge and London, United Kingdom; Adelaide, Australia; Copenhagen, Denmark; Boston, Mass; Zurich, Switzerland; Madison, Wis; Helsinki, Finland; Vancouver, British Columbia, Canada; St Louis, Mo; and Maastricht, The Netherlands

Recent research indicates that chronic inflammatory diseases, including allergies and autoimmune and neuropsychiatric diseases, share common pathways of cellular and molecular dysregulation. It was the aim of the International von-Behring-Röntgen Symposium (October 16-18, 2014, in Marburg, Germany) to discuss recent developments in this field. These include a concept of biodiversity; the contribution of urbanization, lifestyle factors, and nutrition (eg, vitamin D); and

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new mechanisms of metabolic and immune dysregulation, such as extracellular and intracellular RNAs and cellular and mitochondrial stress. Epigenetic mechanisms contribute further to altered gene expression and therefore to the development of chronic inflammation. These novel findings provide the foundation for further development of preventive and therapeutic strategies. (J Allergy Clin Immunol 2016;138:47-56.)

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Chronic inflammatory diseases, including allergies and autoimmune and neuropsychiatric diseases, have common pathogenic features of dysregulation of the host immune response. There is increasing experimental evidence that chronic inflammatory diseases are induced and maintained by combinations of host factors and changing environmental influences. In this regard it is well accepted that a variety of anthropogenic factors related to urbanization and adherence to a modern lifestyle, including air pollution, smoking, nutrition, and obesity, represent essential aspects of an altered environment related to the development of chronic inflammatory disease conditions. The effect of these factors has been thoroughly discussed recently.[1-6] Special focus of this review, which summarizes the proceedings of the International von-Behring-Röntgen-Symposium (October 16-18, 2014, in Marburg, Germany) is given to the role of microbes combining both environmental and body surface–associated microbes. New findings in this field were discussed in the symposium, with an emphasis on new aspects of cell metabolism, cellular and mitochondrial stress, and the role of intracellular RNAs and extracellular RNAs (eRNAs) as mediators of inflammatory signals, and future research directions for chronic inflammatory diseases were defined.

Abbreviations used
Del-1: Developmental endothelial locus 1
eRNA: Extracellular RNA
GR: Glucocorticoid receptor
IBD: Inflammatory bowel disease
miRNA: MicroRNA

MICROBES AND DEVELOPMENT OF IMMUNITY

Both internal and external microbiota play a role in the development and regulation of our immune system and, subsequently, the development of chronic inflammatory diseases (Fig 1). The hygiene hypothesis, which was first proposed in 1989 after the observation that having older siblings provided some protection from allergic disorders,[7] states that a lack of exposure to microbes in early life increases susceptibility to allergic diseases, indicating that altered immune regulation is linked to chronic inflammatory diseases (Graham Rook, London, United Kingdom). Human subjects, like all vertebrates, coevolved with a symbiotic microbiota, particularly in the gut, which plays a pivotal role in the development and function of all organ systems, including the brain.[8] The microbiota also has an essential effect on immune system regulation,[9] and many aspects of modern life, such as cesarean delivery, lack of breast-feeding, use of antibiotics, and untargeted hygiene, tend to disrupt transmission of the microbiota to the infant. There are probably specific windows of opportunity for this transmission during infancy, and animal data suggest that if these are missed, immunoregulatory, metabolic,[10] and central nervous system[11] dysfunctions can result.

Additionally, human subjects evolved as small hunter-gatherer groups and coevolved with the "old infections," which did not kill the host and persisted for life. These organisms limited immunopathology and evolved to drive immunoregulatory responses. This resulted in selection of mutations within the human immune system that partially compensated for these immunoregulatory activities. However, in the absence of these infections, in the era of modern medicine, these proinflammatory mutations lead to "inflammatory overshoot" and have become risk factors for chronic inflammatory diseases. Some studies suggest that the exchange of organisms and genes (by means of horizontal gene transfer) from the microbiota of the natural environment is also important.[12] Together, these observations highlight immunoregulatory links between commensal and environmental microbiota and their connections to health and disease.

Studies are required to merge these different lines of research and characterize the balance among these factors that maintains health.

The biodiversity hypothesis states that reduced biodiversity leads to alterations in human microbiomes, which contribute to inflammatory diseases (Tari Haahtela, Helsinki, Finland). Biodiversity is defined as the variety of life on Earth. It includes the genes found in living things of all species and the ecosystems these species comprise. In 1850, the world population was somewhere between 630 and 930 million, and 160 years later, it is more than 7 billion. The exponential population growth and rapidly escalating urbanization has led to biodiversity loss. This loss and climate change secondary to human activity are now being associated with various adverse health effects. Immune tolerance is an active process throughout life; however, early events are the most important for building connections to beneficial commensals that are prerequisite to health. Naturally biodiverse environments include ancient microorganisms, which modulate the human microbiota and keep immune processes alert. The interplay between the environmental metagenome, human microbial genome, and human cell genome determines health and disease.[13] The modern epidemics of chronic inflammatory diseases, including allergy and asthma, are largely a result of reduced exposure to natural environments, changed diet, and sedentary lifestyle. Biodiversity loss (poor macrobiota/microbiota) leads to poor human microbiota (dysbiosis), immune dysfunction (poor tolerance), inappropriate inflammatory responses, and finally symptoms and diseases.[13-17]

Research is needed to characterize connections between the environmental microbiota and the human microbiota, to characterize how interactions between these and the immune system create and maintain immunologic competence and tolerance, and to guide the development of novel therapeutics that are useful and safe interventions for maintaining the balance between environmental and human microbiota.

In addition to external and internal microbiomes, host cell structures are factors that contribute to immune regulation. Epithelial surfaces play a regulatory role in innate immune responses (Thaddeus Stappenbeck, St Louis, Mo). The innate immune system is responsible for initial recognition of infection

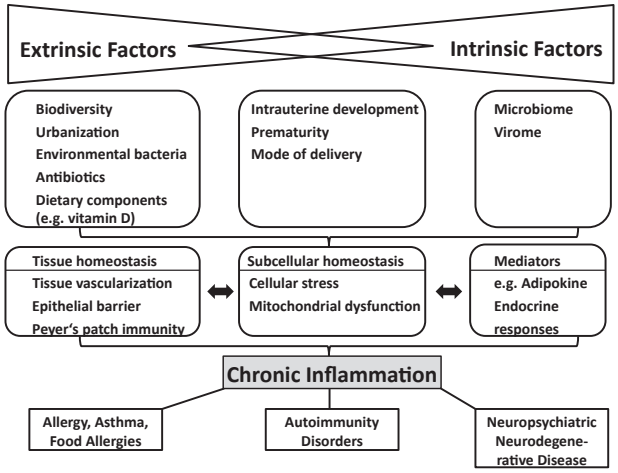

FIG 1. A broad variety of extrinsic and intrinsic factors control the development of chronic inflammation, which manifests in different clinical phenotypes and entities.

and damage and quickly triggers a range of host responses. Epithelial surfaces rapidly react to environmental insults to maintain barrier function and prevent further injury. However, some interactions between epithelial barriers and innate immune responses are still unknown. Chronic viral infection can stimulate epithelial turnover and repair in part through type I interferons that signal through myeloid cells. These events link together the responses of the innate immune and epithelial systems to damage and infection.[18] The human virome is a relatively unexplored component of the microbiome and is the complex collection of chronic viruses within a given host.[19] Most human subjects are chronically infected with multiple viruses, and the long-term consequences of repeated cycles of epithelial inflammation, damage, and repair are not yet fully characterized.

Other environmental factors that guide host immune responses are food antigens. The mechanisms by which dietary antigens stimulate intestinal T cells and the fate of these lymphocytes are unknown.[20] Ulrich Steinhoff et al (Marburg, Germany) demonstrated that the oral uptake of food antigens resulted in the expansion and accumulation of food antigen–specific $CD4^+$ T-cell populations and subsequent anergy and apoptosis in Peyer patches. The activation and death of food-reactive CD4 T cells is a default program required for normal development of the small intestine. Furthermore, removal of apoptotic cells by macrophages leads to increased production of anti-inflammatory IL-10, which suppresses inflammatory lesions in the small intestine.

The mechanisms of immune stimulation by food antigens under physiologic conditions are still unknown and might be important in understanding chronic intestinal inflammation. Characterizing the immunologic and structural effects of food antigen recognition might reveal patterns in food tolerance, inflammation, and intestinal structure/barrier function that are disturbed in disease states.

Immuno-ontogeny, or the developmental stage and conditions during antigen exposure, is another host factor that plays a role in influencing the outcomes of immune responses. Differences are observed in preterm versus term neonates with or without exposure to extrauterine microbiota (Michael Zemlin, Marburg, Germany). Current thinking is that the origin of allergies and autoimmunity occurs within the fetal and neonatal periods of development. Thus changes in the immune system can be influenced by exogenous factors or those that occur because of endogenous triggers in an age-dependent manner. Preterm birth prematurely elicits humoral immune responses.[21] However, the expressed secondary antibody repertoires are unique in neonates. This could contribute to the increased risk of infection observed in neonates but might also influence the ability to induce immune responses against self-antigens or allergens.[22]

Future research is needed to determine why preterm compared with full-term neonates have a reduced risk of atopic dermatitis and an increased risk of bronchial asthma.

NOVEL MECHANISMS IN INFLAMMATION

Ongoing research into the pathogenesis of chronic inflammatory diseases continues to reveal host cell functions that can trigger or exacerbate disease states (Table I). Leukocyte recruitment is a central process in inflammation and immunity (Triantafyllos Chavakis, Dresden, Germany). Although several adhesion receptors and chemokines/chemokine receptors have been identified that promote leukocyte infiltration into an inflamed tissue, little is known about endogenous inhibitors of the leukocyte adhesion cascade. Developmental endothelial locus 1 (Del-1) is a secreted molecule that interferes with β_2-integrin–dependent neutrophil adhesion to the endothelium and subsequent recruitment of inflammatory cells.[23,24] In addition, these authors observed that downregulation of Del-1 expression predisposes experimental animals to IL-17–dependent inflammation and inflammatory bone loss.[25] Thus Del-1 is an endogenous tissue homeostatic factor that modulates the inflammatory response.[26] It remains to be investigated whether Del-1 expression modulates the outcome of chronic inflammatory diseases as well.

A novel role for endogenous eRNA functioning as a proinflammatory signal has been described (Klaus T. Preissner, Giessen, Germany). Previous studies from this group have shown that eRNA is released under conditions of tissue stress or injury or during pathological conditions, such as ischemia or tumor growth, and acts as a prothrombotic, permeability-increasing, and proinflammatory factor.[27-29] eRNA released from activated mast cells provides a newly recognized alarm signal that triggers an endogenous inflammatory cascade, which appears to be essential for the release of cytokines in health and disease.

Additional research is needed to determine whether the eRNA-triggered inflammatory cascade also plays a role in allergic diseases. Such experiments can be done in established mouse models and by using biomarker analysis in patients.

Exosomal cell-to-cell transfer has been described as another way to transmit extracellular signaling and communication with a potential role in regulating inflammatory responses (Bernd T. Schmeck, Marburg, Germany). It has been shown that microbes can interfere with host immune regulation (ie, by injecting specific histone modifying enzymes).[30] These changes can then be propagated to other cell types by cytokines or their antagonists.[31] Recent findings show that cell-to-cell communication can also take place through exosomal transfer of noncoding RNAs that act specifically on the gene expression of a recipient cell.[32] Schmeck et al found that microbial exposure of human macrophages impaired the pro-inflammatory reactivity of neighboring epithelial cells. Interactions took place partly by

TABLE I. Novel subcellular and intercellular mechanisms

- eRNA
- Noncoding RNA
- Long noncoding RNA
- miRNA
- Exosomal cell-cell communication
- Cellular stress
- Mitochondrial dysfunction
- Epigenetic regulation

cytokines but also by exosomes that were able to transfer microRNAs (miRNA) to the "target cells." Bacteria-exposed macrophages change the inflammatory phenotype of bystander cells by soluble mediators and exosomes.

Research is needed to determine the function of RNA, protein, and lipid components of exosomes in immune regulation; whether microbes participate or interfere in this vesicle transfer; and which differences exist between the effect of a beneficial microbiome and the detrimental effects of pathogens.

The microbiome also plays a role in host structural components that can be involved in disease (Christoph Reinhardt, Mainz, Germany). Indigenous microbiota affects tissue remodeling and formation of intricate capillary networks in small intestinal villus structures through mechanisms involving Paneth cell function and coagulation factor signaling.[33,34] The gut microbiota and its metabolic functions have been identified as risk factors for the development of cardiovascular disease.[35] Moreover, symptomatic atherosclerosis is associated with an altered gut metagenome.[36] Data are still lacking that provide a causal link between colonization of the gut by microbial communities and the pathomechanisms that trigger atherosclerotic plaque rupture and thrombotic disease states. Experiments in germ-free mice showed that microbiota colonization of the gut affected its epithelial Toll-like receptor expression and downstream signaling to induce experimental thrombus formation through Toll-like receptors.[37,38]

Future work with germ-free mouse models combined with bacterial mutant strains will show how constituents of the microbiota might affect host metabolism, will provide a mechanistic link to coagulation factor signaling, and could influence the development of cardiovascular disease and the sequelae of thrombotic events.

ALLERGY AND ASTHMA

Interactions between the external environment (eg, allergens and environmental microbes) and internal host factors (eg, commensal microbiomes, diet, genetics, and developmental stages) affect the health but also the disease states of host organisms (Fig 1). Allergy and asthma are 2 medically important chronic inflammatory diseases in which these interactions are out of balance. Here the human microbiome plays an important role in allergic asthma (Hans Bisgaard, Copenhagen, Denmark) because a link between the type of human microbiomes and the risk for asthma was proposed in several studies.[39] For example, maternal use of antibiotics is associated with increased risk of childhood asthma in a dose-related fashion independently of pregnancy periods and antibiotic type.[40] Also, delivery by means of cesarean section is associated with changes in the neonatal gut flora and an increased risk of asthma in the child.[41] The lung microbiome might also play a role in asthma development because pathogen-affected airways are associated with the risk of asthma in neonates.[42]

Future work is needed to further characterize the associations that might guide the use of therapeutics to alter the gut and lung microbiomes for the prevention or treatment of asthma, respectively.

Like host microbiomes, environmental microbiomes also affect the development of allergic diseases. Some environmental bacteria exert protective effects for allergic disease (Holger Garn, Marburg, Germany), and recent observations from epidemiologic studies suggest that a higher environmental microbial diversity is associated with increased protection form allergies and asthma.[43] Certain bacterial strains are specifically associated with protective effects of farming environments.[44] Here insights from studies using ovalbumin- and house dust mite–based murine models of allergic airway inflammation proposed that nonpathogenic environmental bacteria can exert protective effects on allergy involving different effector pathways.[45,46] However, the underlying mechanisms by which higher microbial diversity is associated with increased protection from allergic disorders remain unresolved.

Future work can reveal involvement of the following mechanisms: (1) higher microbial diversity increases the probability to provide signals for a single or a few decisive signaling pathway(s); (2) various signals from different microbes recognized by a variety of receptors converge on a common decisive effector pathway; and (3) various signals from different microbes involve multiple distinct effector pathways that synergize to result in optimal allergy protection.

The developmental stage during which exposure to environmental allergens occurs can also influence asthma and allergic diseases (James E. Gern, Madison, Wis), whereby early-life environmental exposures modify the risk for allergic diseases and asthma.[44] A prospective birth cohort study was conducted (Urban Environment and Childhood Asthma [URECA]) involving 560 babies of families residing in urban neighborhoods with high rates of poverty in Baltimore, Boston, New York City, and St Louis.[47] Results from this study provide evidence that in urban environments exposure to allergenic proteins in the first few months of life might be associated with a reduced risk of recurrent wheeze,[48] whereas exposure to microbes might reduce the risk of atopy and atopy plus wheeze. Furthermore, the findings imply that prolonged exposure to microbes rather than limited exposure to allergens might be the best strategy to reduce the incidence of recurrent wheezing and atopy in urban populations.

Future work is needed to identify the mechanisms by which environmental bacteria affect the reduced rates of atopic diseases in children and how exposure to allergens during early life leads to reduced rates of recurrent wheeze. It is possible that this is an effect of exposure to proteins themselves, allergen-associated microbes, or other yet undefined factors.

The prevalence of food allergy has increased dramatically over the past decades for reasons that likely reflect environmental influences related to modern lifestyle, including changes in the composition of resident gut commensal species. The microbiome also plays a role in food allergy (Talal A. Chatila, Boston, Mass), which is a major public health problem in all industrialized countries. Recent studies have shown that food allergy is

associated with a gut microbiota signature that can be reset by enforced tolerance with allergen-specific regulatory T cells.[49,50] Furthermore, susceptibility to and protection from food allergy are phenotypes that are transmitted by the intestinal microbiota of mice with food allergy and food-tolerant mice, respectively.[51]

Future studies are needed to confirm that intestinal microbiota communities can influence the development of food allergy and that reprogramming the intestinal microbiota in favor of tolerogenic communities can promote tolerance induction in patients with food allergy.

Disease severity is another factor in allergic pathologies that is apparently influenced by changes in the gut microbiota (Shannon Russell, British Columbia, Canada), whereby rates of aberrant immunologic disorders, such as allergies and asthma, are steadily increasing in developed countries, arguing for an environmental cause. The increasing indiscriminant use of antibiotics is one risk factor identified in the development of allergic diseases, such as asthma.[52,53] It is known that the infant gut microbiota has a critical role to play in shaping proper immune system development in the host and that altered exposures to these beneficial microbes (ie, antibiotics, birth mode, and exposure to green space) in early life could affect allergic disease susceptibility.[54] Studies by Russell et al[55,56] in murine models of asthma and hypersensitivity pneumonitis indicate that the effect of shifts in gut flora on disease severity depend on the immunologic nature of the disease. The mechanistic details of how 2 different antibiotics that promote opposing shifts in the gut microbiota have differential effects on 2 immunologically distinct lung inflammatory diseases have not yet been completely elucidated.

These data are currently under analysis with data from a cohort of healthy or atopic children enrolled in a Canadian study called Canadian Healthy Infant Longitudinal Development (CHILD). Comparing and contrasting the intestinal microbiome and metabolomics data from murine and human studies might reveal correlations between healthy and atopic scenarios that can be translated into human studies.

AUTOIMMUNITY

Pathogenesis in autoimmunity is caused by dysregulation of the immune system and is associated with several chronic inflammatory diseases within multiple medical fields, including endocrinology, gastroenterology, and rheumatology. Novel proinflammatory signaling pathways, such as epigenetic regulation,[57] have been described that can play a role in rheumatic diseases (Table I; Steffen Gay, Zurich, Switzerland). Epigenetics predominantly contributes to the regulation of gene expression; is mediated by acetylation, methylation, phosphorylation, and sumoylation; and involves miRNA and long noncoding RNA as well. Karouzakis et al[58] have shown that synovial cells in patients with rheumatoid arthritis are endogenously activated through global hypomethylation and the bromodomains BRD2, BRD3, and BRD4. Moreover, this activated cellular phenotype is maintained and protected from apoptosis through expression of Sumo proteins and characterized by distinct sets of miRNAs and long noncoding RNAs. Targeting specific miRNAs might lead to inhibition of proinflammatory signaling and identification of new therapeutic targets.

Further research is needed to optimize the organ-specific delivery of the antago-miRNAs and to evaluate the side effects of the therapeutic modulation of acetylation, methylation, or both.

Adipokines, cytokines secreted by adipose tissue, represent another proinflammatory signaling network important for the pathophysiology of rheumatic diseases (Ulf Müller-Ladner, Giessen, Germany) and are potent molecules associated with chronic inflammatory diseases (Fig 1).[59-61] Adipokines, such as adiponectin, isoforms regulate expression of the proinflammatory effector molecules TNF-α and IL-6, as well as factors of the complement system, growth factors, and adhesion molecules. Release of these factors is followed by an influx of inflammatory cells. Adipokines contribute to substantial tissue remodeling and destruction caused by the secondary dysregulation of matrix metalloproteinases and their inhibitors. Given the strong immunomodulatory potential of adipokines, therapeutic intervention by altering the synthesis or function of adipokines is of interest for treating chronic inflammatory diseases.[62]

Further research is needed to characterize the individual temporal and spatial distribution of the adipokines within a given stage of a disease or an affected organ and to regulate or modulate the negative effects of the adipokines. Also, adipokines are central factors of metabolism, whereby their systemic inhibition or overexpression can lead to unknown or unwanted side effects. A potential solution to this problem might be the modulation of specific isoforms or isoform-specific adipokine receptors to change cell-specific responses to these isoforms.

Cytokines also play a role in inducing and maintaining chronic inflammatory bowel disease (IBD; Markus F. Neurath, Nürnberg, Germany). Both Crohn disease and ulcerative colitis are chronic relapsing disorders of the gastrointestinal tract characterized pathologically by intestinal inflammation and epithelial injury[63,64] and caused by cytokine-mediated activation of the mucosal immune system.[64,65] Mucosal immune cells, including macrophages, T cells, and the recently discovered subsets of innate lymphoid cells, respond to microbial products or antigens from the commensal microbiota by producing cytokines that can promote chronic inflammation of the gastrointestinal tract, leading to an imbalance between proinflammatory and anti-inflammatory cytokines that perpetuate gut inflammation.[65] New anticytokine agents are potential therapies for patients with IBD.

Yet research is needed to identify the key drivers within the microbiome that cause IBD, determine how microbiome components induce T-cell activation in patients with IBD, determine whether specific anticytokine therapies can be designed and are effective in patients with IBD, determine what causes spontaneous flares and remission phases in patients with IBD, and determine whether intestinal barrier function can be strengthened as a therapy against IBD.

Complex genetic and environmental interactions contribute to the development of chronic inflammatory diseases. Immune programming by environmental exposures is time dependent (Harald Renz, Marburg, Germany). In particular, the “window of opportunity” for the operation of environmental exposures on the programming of immune responses seems to be opened during prenatal and early postnatal periods. Many external factors have recently been identified that affect early immune programming. Epigenetic events determine innate immune responses in fetal and early postnatal life and are an important link between environmental exposures and disease development.[45,54,66,67]

Future studies are needed to determine the most susceptible timeframe during which environmental exposures alter immune programming. It is still unknown how environmental factors, such as stress, nutrients, infections, and microbes, alter immune programming. Studies on epigenetic mechanisms can reveal important contributions to immune programming, including the regulation of different epigenetic mechanisms involved in modifying gene expression, such as methylation, histone acetylation, ubiquitination, and miRNA actions. Furthermore, deciphering such gene-specific epigenetic regulations and their stability (ie, transgenerational effects), allowing us to apply therapeutic interventions in epigenetic regulation, might be possible.

The quantity and composition of diet is another environmental factor that plays a role in autoimmunity, and one example is the connection between vitamin D and autoimmune disease development (Scott Weiss, Boston, Mass). Vitamin D is an important factor in the initiation and development of autoimmune disease because it is a critical control element of dendritic cell signaling and regulatory T-cell function.[68,69] The proper level of vitamin D in the body needed for adequate immune function is unknown, which complicates the observational research. In addition to its direct effects on immunity by altering gene expression, vitamin D influences the development of autoimmune diseases by affecting the gut microbiome as a result of (1) sensing the antigenic burden; (2) influencing the gut metabolome, including critical controller species of bacteria; and (3) disturbing the integrity of the gut epithelial barrier.[70]

Clinical trials with known dosages and concentrations of vitamin D are necessary to define the role of vitamin D in patients with autoimmune disease. Here the vitamin D antenatal asthma reduction trial is a randomized controlled trial in pregnant women to prevent asthma in their offspring, and analysis of the results from the first 3 years of follow-up might allow us to provide important information on the aforementioned topics.[71]

NEUROINFLAMMATION AND NEUROPSYCHIATRIC DISEASES

Another group of medically and socially important diseases with links to chronic inflammation and possible involvement of the microbiome include neuropsychiatric and neurodegenerative pathologies. Work is in progress to identify disease biomarkers for schizophrenia and translate them from the laboratory to the clinic (Sabine Bahn, Cambridge, United Kingdom).

Schizophrenia is a multifaceted neuropsychiatric disorder. Its onset is the result of complex interactions between genetic, developmental, and environmental factors. Multi-omics profiling approaches can be used to investigate a better molecular understanding of disease onset and its progression and to identify the intrinsic molecular signatures and patient subgroups with potentially distinct biochemical pathways underpinning their symptoms. Circulating peptides and proteins have been identified that distinguish patients with first-onset paranoid schizophrenia from healthy control subjects, including alterations in glucoregulatory, inflammatory, and hormonal processes in drug-naive patients with first-onset schizophrenia.[72,73] Disease-relevant metabolic and inflammatory changes in affected and unaffected siblings of patients with schizophrenia were also identified. There is now preliminary evidence for the existence of schizophrenia subgroups based on the occurrence of serum proteins.[74,75] Validation of the schizophrenia biomarker panel in prospective clinical trials will determine its clinical utility regarding the accurate prediction of conversion to schizophrenia. The role of inflammatory changes in patients with schizophrenia requires further investigation, and the efficacy of different anti-inflammatory medications for the treatment of patient subgroups is unknown.

Although infections at early and later stages of neurodevelopment can contribute to neuroinflammation, other factors, such as stress and resulting hippocampal brain alterations, might play an important role as trigger mechanisms for neuropsychiatric diseases during the whole lifespan of an individual subject (Bernhard T. Baune, Adelaide, Australia).[76] Neuroimmunologic mechanisms affect neuroplastic changes, such as in long-term potentiation, neural stem cell survival, synaptic branching, neurotrophin regulation, neurodegeneration, and neurogenesis. Various cell types in the brain, such as microglia, oligodendrocytes, and astrocytes, contribute to these immune-related pathomechanisms, particularly in patients with depression and schizophrenia.

Our understanding of the influence of the innate and adaptive immune system on brain function and behavior has increased significantly in recent years. Peripheral proteins and immune biomarkers (eg, IL-1β, TNF-α, and IL-6) have been associated with decreased hippocampal volumes, depression, and antidepressant treatment response.

Further research is required to identify possible biomarkers for disease risk and onset of major psychiatric diseases, as well as to explore possible therapeutic targets within the immune system. Anti-inflammatory treatments for depression and schizophrenia have been proposed but are controversial because of extended modifying effects on the immune system and possible side effects.[77] Further comparative clinical studies are needed to improve the mechanistic understanding, treatment efficacy, and safety of anti-inflammatory drugs for psychiatric disorders.

The links between stress-related psychiatric disorders, genetic components, and stress resulting from adverse life events are still undefined. For example, genetic variants in the cortisol signaling pathway can be associated with increased risk of stress-related psychiatric disorders (Elisabeth Binder, Munich, Germany). Cortisol, which is released in response to stress, activates the glucocorticoid receptor (GR), which directly acts as a transcription factor. By using a stimulated expression quantitative trait locus analysis, common genetic variants in long-range enhancer elements were shown to modulate the immediate transcriptional response to GR activation in blood cells, and these are distinct from the genetic variants, altering baseline transcription.[78] Furthermore, imaging genetics links common risk variants with dysregulated amygdala reactivity, an important trigger of the stress hormone response and a risk factor for major depression. Finally, animal experiments, as well as network modeling approaches, indicate that the transcripts regulated by these long-range enhancer elements might mediate stress-related risk for depression by altering a functional gene network regulated in the brain and related to immune activation, proteasome degradation, and ubiquitination, as well as neurite outgrowth. Overall, these studies imply that genetic variants that alter the short-term transcriptional response to GR activation also moderate the long-term risk for stress-related psychiatric disorders, possibly by affecting stress-sensitive neural circuits.

Further research is needed to identify the links between molecular and genetic changes associated with disease risk to differences in cellular or neuronal function and also the genetic

TABLE II. Research gaps

Microbiome and noncommunicable disease
• Organizational and functional interrelationship between environmental microbiota and human microbiome
• Microbiome and immune function: cellular and molecular mechanisms
• Microbiome and host metabolism (energy harvest, protein, lipid, and carbohydrate metabolism)
• Environmental microbiota and disease development (eg, IBD) or disease protection: cellular and molecular mechanisms
• Interference of microbial/environmental diversity with disease development and protection
• Consequences of viral infections and the human virome for noncommunicable disease development or protection
Immunologic mechanisms
• Physiologic responses, including innate and adaptive immune mechanisms to food antigens
• Role of inflammation, intestinal structure and barrier function, hepatology in the development of food tolerance, and disturbed mechanisms in food intolerance development
• Role of exosomal components, including RNA, proteins, and lipid mediators, for immune function and immune regulation
• Role of eRNA as a trigger for inflammatory cascades, especially in the development of allergic immune reactions
• Effect of distinct epigenetic mechanisms (eg, methylation, histone acetylation, ubiquitination, sumoylation, and miRNAs) integrated into the regulation of gene expression with regard to gene-environment-interactions
• Importance of mitochondrial function impairments for peripheral and central nervous system dysregulation
Windows of opportunity
• Reasons for opposing prevalences of preterm in contrast to term neonates for atopic dermatitis (reduced risk) and bronchial asthma (increased risk)
• Major determinants for transgenerational effects
• Identification of the most receptive window of opportunity for effects of environmental exposure on immune programming
Therapeutic implications
• Development of new kinds of preventive and therapeutic interventions based on environmental and intestinal microbiome studies
• Development of new anti-inflammatory treatment approaches for a broader spectrum of noncommunicable diseases, including neurobiological disorders

and epigenetic interplay in combination with environmental interactions.

Metabolic changes are key hallmarks in neurodegeneration and neuroinflammation with promising potential for therapeutic interventions (Carsten Culmsee, Marburg, Germany; Table I and Fig 1). Accumulating cellular stress provides a pathological factor in acute and age-related degenerative neurological disorders, such as Alzheimer disease, Parkinson disease, or stroke. Inflammatory processes significantly contribute to mechanisms of neurodegeneration through microglial activation in the brain that might be further modulated by the immune system and microbiome. Cellular stress in neurons mediated damage to mitochondria and the release of proapoptotic factors that mediate impaired neuronal function and initiate the final steps of cellular death.[79] In microglia cellular stress leads to increased production and release of proinflammatory cytokines. These neuroinflammatory responses can be reversed by compounds that mediate mitochondrial protection and preserve metabolic homeostasis.[80,81] Functional and structural mitochondrial alterations are potential therapeutic targets and can serve as diagnostic markers of disease risk and development.

Future studies should address the question of whether reversing mitochondrial impairment in the brain and periphery is an effective therapeutic strategy for these brain diseases.

Host genetics contributes to development of depression and schizophrenia disease. Polymorphisms in cytokines are associated with neuropsychiatric disorders (Udo Dannlowski, Marburg, Germany). Cytokines, such as TNF-α and IL-6, have been implicated in dual functions in patients with neuropsychiatric disorders, and neuroimaging studies have revealed the neurodegenerative or neuroproliferative roles of genetic polymorphisms in the TNF-α and IL-6 genes, respectively, on brain morphology in healthy subjects.[82] Hippocampal formation is highly susceptible to neurodegenerative processes and is implicated in several neuropsychiatric disorders, including affective disorders, schizophrenia, or Alzheimer disease. Experimental results indicate that genetic variations in cytokines are associated with neurostructural aberrations related to neuropsychiatric disorders.[83]

Future imaging studies on the role of such single nucleotide polymorphisms in populations of psychiatric patients with neurodegenerative components might provide information on, for example, genetic susceptibility, especially in those patients with an affected hippocampus (because of maltreatment or stress). Furthermore, genetic and environmental interactions affecting brain structure remain to be studied in the context of cytokine involvement in patients with neuropsychiatric disorders.

Because chronic inflammation increases the susceptibility of patients to psychiatric disorders (Graham Rook, London, United Kingdom), it is estimated that depression will become the second major cause of human disability by 2030.[84] A link between depression and chronic low-level inflammation has already been described,[85] and an inability to switch off background inflammation might be associated with reduced stress resilience. The decreasing exposure to microbial biodiversity, such as by reducing the efficiency of immunoregulatory circuits, is likely to contribute to the disabled turn-off switch.[86] When exposed to a standardized laboratory stressor, depressed subjects tend to show increased and prolonged release of inflammatory mediators, which is an example of synergy between inflammation and a stressor.

Combinations of environmental and genetic factors are involved in susceptibility for psychopathology as well (Jim van Os, London, United Kingdom). Multidimensional psychotic syndromes can be understood as an imbalance in the cycle of adaptation to the social context. Onset of psychotic disorder is

robustly associated with early-life adversity, suggesting a mechanism involved in exposures affecting the developing "social" brain.[87]

Longitudinal research is needed to characterize interactions between genetics and the environment that would drive variations in human behavior in the general population, which subsequently might give rise to more severe expression of diverse psychopathology. Furthermore, new technologies are required to directly assess molecular genetics in relation to situated phenotypes of patients[88] and to increase the translational effect for studying social-reactive mechanisms.

The microbiome influences autoimmunity, gastrointestinal disorders, and major psychoses in patients (Tilo Kircher, Marburg, Germany), and genetic and environmental risk factors that affect the cause and potentially the longitudinal course of autoimmunity contribute to disease development. The emerging field of microbiome research lies at the center of these interactions by defining the abundance and diversity of resident gut microbiota that play a role in digestion, inflammation, gut permeability, and behavior.[89] Dietary modifications of core bacterial compositions might explain lifestyle or social status as risk factors for major psychoses.[78,79,90,91]

Future work is needed to establish causal links between epidemiologically validated genetic and environmental risk factors, such as exposure to microbiota, in the cause of depression and schizophrenia.

CONCLUSION

Major progress has been achieved to better understand the pathogenesis of chronic inflammatory disease. The concept of gene-environment interactions still provides the framework to explain the explosion in the incidence and prevalence of these diseases worldwide. The content of this framework is elucidating a multidimensional degree of complexity. This includes extrinsic environmental factors and exposures with strong and long-lasting effects on tissue homeostasis and cellular and subcellular metabolism. All of these factors (recent developments are summarized in Fig 1) contribute to development of the respective clinical phenotypes. Although clinical phenotypes are quite heterogeneous, ranging from autoimmunity and allergies to neuroinflammatory and neurodegenerative diseases, it is striking that despite certain differences, there is a common ground of pathogenic factors and pathways that lead to development of these conditions and trigger maintenance of inflammation. Although there are still numerous important unanswered questions in this regard (Table II), these common pathways might open the opportunity to develop effective and hopefully broadly applicable prevention strategies, and an important starting point in this regard is affecting underlying environmental conditions and lifestyle factors. This great challenge can only be tackled with a better medical and pathomechanistic understanding of the underlying disease.

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