CHAPTER 11

The Role of the Immune System from an Evolutionary Perspective

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11.1 Introduction

Evolutionary medicine emphasizes that to better understand modern human health and disease, the underlying evolutionary history and evolutionary consequences must also be understood. Thus, evolutionary medicine will contribute significantly to our understanding of the fitness consequences and the phylogeny (evolutionary history) of diseases and disease related traits, explaining why disease exist even though it reduces fitness (Gluckman et al., 2009; Perlman, 2013; Stearns et al., 2016).

For example, when trying to understand why chronic inflammatory diseases occur, evolutionary biologists pointed out that it is crucial to consider the effect of chronic inflammatory diseases on lifetime reproductive success. This success depends on the species-specific life history traits such as age at first reproduction, reproductive lifespan, and life expectancy (Straub et al., 2016). However, evolutionary medicine faces the challenge and difficulty to integrate physiological mechanisms with evolutionary function (Gluckman et al., 2009; Lozano, 2010; Nesse et al., 2012). This challenge is not unique to evolutionary medicine, but is one of the main topics in organismal research in biology (Mayr, 1961), and has been especially addressed in the research on animal behavior (Tinbergen, 1963).

Biological research has traditionally been divided into the study of proximate (physiological or pathophysiological) mechanisms on the one hand and ultimate (evolutionary) causes on the other hand (Mayr, 1961). Most researchers take only one of these two approaches into account (Drickamer, 1998). For example, immunological research is mainly proximate, focusing on the pathophysiological mechanisms underlying the most prevalent infectious diseases (malaria as an example), allergic diseases, and chronic inflammatory diseases. Studies in behavioral ecology, on the other hand, are primarily ultimate, focusing on the fitness consequences of behavior, which means whether individuals showing a specific behavior have more offspring than other individuals (Krebs et al., 1993; Wilson, 1975). Behavioral ecologists have realized that studying physiological mechanisms as evolved traits that increase fitness provides an integrative understanding of animal behavior (Wikelski et al., 2001; Wingfield, 2008).

For example, the major histocompatibility complex (MHC), a set of proteins that plays a significant role in the immune response (a proximate factor), is known to affect behavior, enabling females to choose mates with complementary MHC proteins (the set of genes is called human leukocyte antigen (HLA) gene complex), which increases fitness of common offspring (Kamiya et al., 2014; Lerner et al., 1991). Thus, behavioral ecologists came to a more comprehensive understanding of behavior by

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taking into account the fitness consequences of its underlying physiological mechanisms.

At the beginning of this chapter, we will highlight why inflammation and the immune response is a key category for evolutionary medicine (in section 11.2.2). Then, based on the four questions of Tinbergen that he applied to animal behavior (Tinbergen, 1963), we want to tackle the role of the immune system from an evolutionary perspective (section 11.3—11.4). With this knowledge, the special situation of chronic inflammatory diseases will be addressed using the Tinbergen approach (section 11.5). Finally, medical applications are presented, which can be relevant for medical education and medical decision making (section 11.6).

11.2 Inflammation and immune response—Why is it a key category of evolutionary medicine?

When we think of the major challenges during our evolutionary history, the following threats, the immediate responses, and the response systems come into mind (see bullet point list). Concerning response systems, the sympathetic nervous system (SNS), the hypothalamic-pituitary-adrenal axis (HPA axis), and the renin-angiotensin-aldosterone system (RAA system) belong to the hormonal stress axes that are controlled by the brain.

- *Predators* (response: fight-or-flight; response system: brain with SNS and HPA axis)
- *Intra-specific competition for resources, including mates* (fight-or-flight; brain with SNS and HPA axis)
- *Wounding and hemorrhage* (blood pressure stabilization and blood coagulation; brain with SNS, HPA axis, and SNS-dependent RAA system, and standby system of blood coagulation)
- *Food shortage* (foraging; brain with SNS and HPA axis)
- *Thirst* (water seeking; brain with SNS, HPA axis, and SNS-dependent RAA system)
- *Cold* (warming-up and warm seeking; brain with SNS and HPA axis)
- *Heat* (sweating/cooling and cold seeking; brain with SNS and HPA axis)
- *Infection* (inflammation and immune response; immune system)
- *Wounding and infection* (inflammation and immune response; immune system)

From this list, it is evident that only two major response systems are liable to protect the body from harmful threats: the brain and the immune system. The brain stimulates hormonal and neuronal stress axes and the locomotor system so that the brain controls activity of muscles. Brain and muscles are tightly coupled to build the psychomotor system.

Since the psychomotor system and the immune system require enormous amounts of energy (Box 11.1), they possess separate selfish rules to demand energy-rich fuels from energy stores by inducing insulin resistance (Straub, 2014; Straub, 2017). These energy stores are the fat tissue (fatty acids, glycerol) and muscles (mainly amino acids; e.g., for glucose generation). If a psychomotor or immune process takes very long, e.g., during chronic illness (psychiatric diseases and chronic inflammatory diseases as examples), selfishness of the two systems becomes more and more obvious. The separate rules of either the brain or the immune system inhibit the respective other system (Straub, 2017). This can lead to brain-induced immunosuppression or immune-mediated fatigue or depression.

Box 11.1 Energy expenditure of the major organs in the body.

An individual with a sedentary lifestyle who is 1.80 m tall and weighs 85 kg requires 10000 kJ/d (7500 kJ/d of which represents the resting metabolic rate) (Blaxter, 1989; Speakman et al., 2010). The total amount of energy required by the immune system in an inactivated state is 1600 kJ/d, and this level can increase by 25% during mild activation to 2,000 kJ/d (Straub et al., 2010). During sepsis, the immune system needs 30–60% more energy (Blaxter, 1989;, Torine et al., 2007). In contrast, the brain needs approximately 2200 kJ/day and it does not need much more when activated. The increased amount of energy expenditure through psychomotor activity depends on active muscles that need 2500 up to 30000 kJ/d (the latter number is relevant for a Tour de France bicyclist) (Straub et al., 2010).

It is important to understand selfishness of brain and immune systems as a fundamental principle because this explains why inflammation and immune response can be key categories of evolutionary medicine. Concerning the immune system and chronic inflammatory diseases, we discussed the evolutionary aspects in several publications (Straub et al., 2003; Straub et al., 2010; Straub, 2014; Straub, 2015; Straub et al., 2016; Straub 2017). Similarly, the brain and the psychomotor system have a central role in evolutionary medicine. In the late 1970s and early 1980s, several authors started to discuss evolutionary principles in the context of psychiatric diseases. They focused on maladaptive behaviors that can lead to chronic illness (Chagnon et al., 1979; McGuire et al., 1981; Nesse, 1984). By inclusion of evolutionary medicine, energy regulation, and neuroendocrine–immune crosstalk, we understand many maladaptive responses in chronic inflammatory diseases, in psychiatric diseases, and during ageing (Straub, 2017).

Long-term demand of energy-rich fuels by the brain or the immune system also blocks voluntary physical and mental activity (Straub, 2017). The long-term consequences of reduced physical and mental activity include cardiovascular diseases (Alves et al., 2016), metabolic diseases and obesity, cognitive dysfunction and pain (Chang et al., 2017; Paley et al., 2016), neurodegenerative disease (Phillips et al., 2014; Phillips et al., 2015), psychiatric diseases (Hallgren et al., 2016), frailty (McPhee et al., 2016), and other chronic diseases such as cancer (Kyu et al., 2016). These conditions all constitute risk factors for early death. An overactive immune system has a central role for these risk factors, and, thus, it is a key category of evolutionary medicine.

11.2.1 The four questions of Tinbergen

Tinbergen formulated four questions in 1963 (Tinbergen, 1963), which are the basis for an integrative approach to understand biological traits (Krebs et al., 1993). Each question is of equal importance. The four questions are (see also Bateson et al., 2013; Nesse, 2013):

- What is the *Function*, which means the fitness value of the trait?
- What is the *Phylogeny*, which means the evolutionary history of the trait?
- How did the trait develop in individuals over their lifetime (*Ontogeny*)?
- What physiological machinery causes the observable trait (*Causation*)?

The questions concerning the function and phylogeny address ultimate factors, whereas questions concerning ontogeny and causation address proximate factors. Evolutionary medicine focuses on the two ultimate factors. The question about the function concerns the fitness consequences of a trait, i.e., why did they evolve? In order to evolve through the process of natural selection, a specific trait must have fitness benefits for the individual, which means increase the number of off-spring produced during the individual's lifetime. The question regarding the phylogeny of a trait concerns the evolutionary history. Tinbergen regarded the responding central nervous system as the machinery causing animal behavior. He defined ontogeny of behavior as the "change of behavioral machinery during development." Thus, the question addressing causation is the question about the behavioral machinery leading to the observed behavioral pattern, and the question about ontogeny asks how this machinery develops until the behavior is shown (Tinbergen, 1963). In the context of an immune response, this machinery is called the "immune machinery."

11.2.2 The four questions of Tinbergen and the immune response

11.2.2.1 Function—fitness value of the trait

Reactions to acute inflammation serve the body to overcome short-lived infectious diseases and other threats such as exposure to allergic antigens. In both situations, the body tries to get rid of the stimulus. The mechanisms are thus adaptive, increasing individual fitness. Typically, inflammatory responses are highly adaptive, enabling individuals to overcome infections, to combat allergic threats, and to heal wounds. Thus, alleles of genes enabling this adaptive response got fixed within the gene pool.

Thanks to the last two decades of genome-wide association studies, we now recognize that hun-

dreds of genetic loci associated with chronic inflammatory diseases overlap with genes relevant in infectious and allergic diseases (Brinkworth et al., 2014). While in earlier time (before 2000), chronic inflammatory diseases were thought to have one unique immune disease pathways, it is now very clear that this is incorrect. In chronic inflammatory diseases inflammation is typically regulated by a network of genes that are implicated in multiple diseases (Cotsapas et al., 2011). The unique disease pathway is known in monogenic autoinflammatory diseases, which also employ immune pathways relevant to infections and allergies.

11.2.2.2 Phylogeny—evolutionary history of the trait

The evolutionary history of human immunological pathways is shared with sharks, birds, and rodents, spanning more than 420 million years (Boehm, 2011). The best known association between infections and genes has been established for the HLA allele system, which is an important element of antigen presentation in the MHC molecules. Polymorphic HLA alleles have been retained because they helped to overcome various infections (Mangalam et al., 2013), leading to positive selection. For example, the genetic factor HLA-DR4 (DRB1*04) protects from dengue hemorrhagic fever (LaFleur et al., 2002). Furthermore, clearance of virus infections is much better for hepatitis B virus in the presence of HLA-DR13 (Wang et al., 2016) and for human immunodeficiency virus in the presence of HLA-B27 (Chakrabarti et al., 2010). There are many more examples also outside the HLA allele system, presentation of which would go beyond the scope of this chapter. The reader is referred to important reviews (Brinkworth et al., 2014).

11.2.2.3 Ontogeny—development of the trait in individuals over a lifetime

The environment of an individual during development and adult life together with the genotype determine how the inflammatory response system develops and will later respond. The immune system is equipped with a system to memorize antigens, and this influences its later responsiveness to the same antigens. We call it immunological memory (Murphy et al., 2011), which is very personal depending on the exposure of the individual to infectious agents during the lifetime. For example, most people in Europe have been exposed to smallpox virus and are thus immune to it. This was completely different for native Americans at a time point of arrival of European seafarers in the sixteenth century, leading to mass extinction of local inhabitants (Patterson et al., 2002).

Another example in the neuroendocrine immune field further demonstrates the impact of ontogeny. Neonatal exposure of a new-born rat to lipopolysaccharide changes the hypothalamic-pituitary adrenal axis markedly (Shanks et al., 1995). As adults, neonatally endotoxin-treated animals exhibited significantly greater adrenocorticotrophic hormone and corticosterone responses to restraint stress than controls. Neonatal endotoxin treatment reduced glucocorticoid receptor density across a wide range of brain regions (Shanks et al., 1995). Exposure to gram-negative lipopolysaccharide in early life can alter the development of neural systems, which govern endocrine responses to stress and may thereby predispose individuals to stress-related pathology. Indeed, it has been demonstrated that neonatal endotoxin treatment of rats protects animals from experimental arthritis later in life (Shanks et al., 2000). This long-term imprinting of central nervous changes in the early phase of ontogeny can also change the behavior of the immune system throughout life.

11.2.2.4 Causation—the "immune machinery"

Inflammation is caused by specific antigens, including pathogens or cell material of damaged tissue (wounds), to which the immune system responds (Murphy et al., 2011). There are several supportive reactions of the neuronal and endocrine systems that foster the immune response in acute infectious diseases (Straub, 2015), altogether representing the causation of inflammation and immune response. In line with Tinbergen's terminology (i.e., behavioral machinery), this might be called the immune machinery. The immune machinery consists of immune cells (neutrophils, lymphocytes, macrophages, dendritic cells, natural killer cells, and many others) with specific surface receptors to activate these cells, causing the release of inflammatory mediators (Murphy et al., 2011).

The immune machinery is highly dependent on the availability of energy-rich substrates in the body because immune cells demand enormous amounts of energy (Gaber et al., 2017, Straub et al., 2010). We may call the immune system selfish, because during infection it is the major dominating factor operating at the highest hierarchical level to acquire energy-rich substrates (Straub, 2014). This selfishness has been positively selected for infectious diseases, and it is an important determining aspect of the immune machinery (causation).

11.2.2.5 Integrative approach—the immune system in evolutionary medicine

The immune machinery has been positively selected for short-lived infectious diseases (causation), which leads to measurable immune responses and inflammation (diagnostic, red box in Figure 11.1), protecting the individual from infections/helping during wound healing. This increases the chance of survival and reproduction at a later stage, increasing evolutionary fitness (Schmid-Hempel, 2011). Genes improving the immune response increased in frequency in the gene pool (phylogeny). The individual genotypes together with the individual specific environment lead to an individual specific development of the immune system (ontogeny). A classical ontogenetic factor of the immune response is immunological memory of the adaptive immune system towards pathogen-specific antigens (Murphy et al., 2011). If a microbial antigen is known to the immune machinery (causation), then it is rapidly activated, i.e., an immediate response towards an infectious agent is generated. The immune machinery with memory consists of educated specific T or B cells (physiological response)

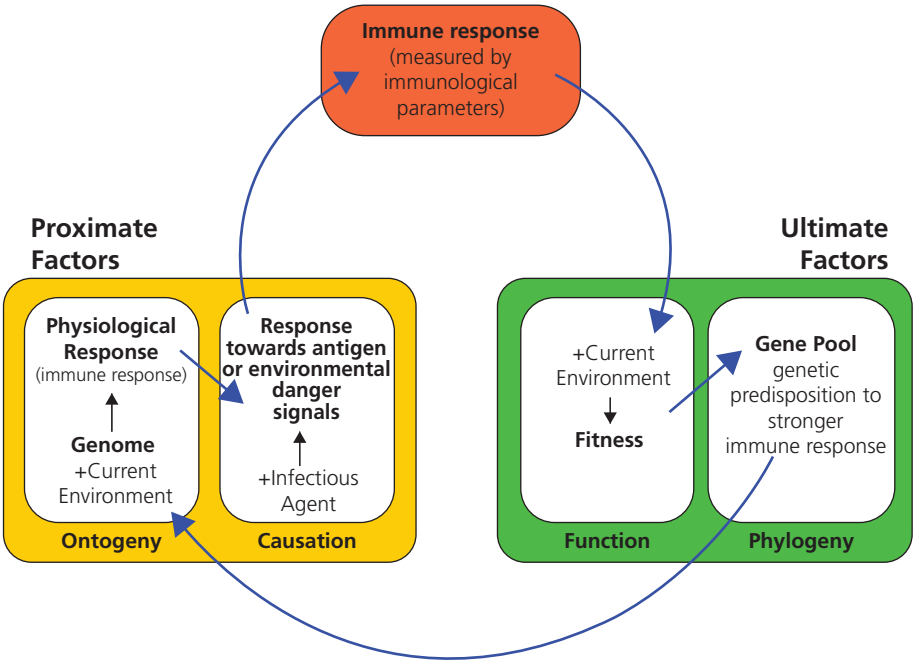

Figure 11.1 Integration of the four questions of Tinbergen to come to a comprehensive understanding of the immune system. The individual's immune system is stimulated by an infectious episode induced by an infectious agent (Causation). Inflammation starts, which can be measured as a change in immunological parameters (e.g., increase of antibodies, secretion of cytokines in circulation, proliferation of antigen-specific T cells etc.). This influences the evolutionary fitness (Function) of the individual, influencing the gene-pool (Phylogeny) of future generations. This can lead to a stronger and faster immune response. Offspring with the inherited genetic predisposition install a stronger immune response during their development (Ontogeny) leading to a better recognition and presentation of antigens in an encounter between antigen-presenting cells and T/B lymphocytes, secretion of the correct cocktail of cytokines and efficient phagocytosis (Causation). In adaptive short-term inflammation with the correct response towards a microbial antigen, the immune machinery enables the individual to survive critical infections and, thus, to reproduce later and increase individual fitness

that can be observed as a phenotypic trait, causing a stronger and faster immune reaction towards the antigen (causation).

11.3 The four questions of Tinbergen and chronic inflammatory systemic diseases

Chronic inflammatory diseases are characterized by a continuous immune response towards harmless autoantigens (reaction against innocuous self) or harmless microbes on the surface of the body (reaction against innocuous foreign) (Firestein et al., 2013). Examples for chronic inflammatory diseases are rheumatoid arthritis, multiple sclerosis, ankylosing spondylitis, systemic lupus erythematosus, Sjögren syndrome, pemphigus vulgaris, and many others. While an immune response is usually confined to a small space, it becomes chronic and widespread in chronic inflammatory diseases (Hochberg et al., 2015; Straub, 2015). A chronic inflammatory disease leads to new energy requirements in an affected person, which supports many unwanted disease-related signs and symptoms recently demonstrated (Straub et al., 2016).

11.3.1 Ultimate factors—function and phylogeny

While reactions to acute inflammation serve the body to overcome short-lived infectious diseases, a long-term chronic inflammatory disease is detrimental. In chronic inflammatory diseases, the positively selected immune mechanisms, which usually support fitness and function (Figure 11.1), are continuously activated by harmless antigens, and the response becomes maladaptive (Straub et al., 2016). Importantly, a chronic inflammatory disease—while costly—will not have a significant influence on fitness (function), because it typically happens after the reproductive phase (Figure 11.2).

Chronic inflammatory diseases have a multifactorial genetic background. The HLA allele system

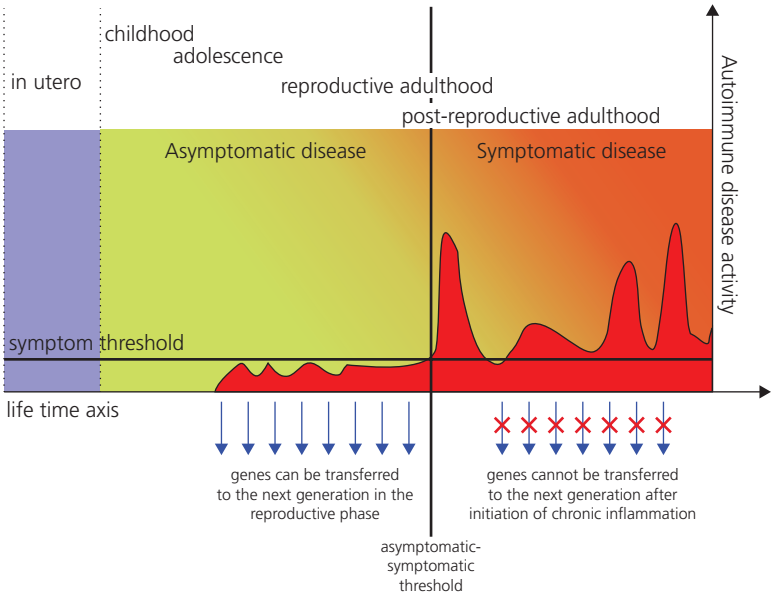

Figure 11.2 The influence of chronic inflammatory diseases on fitness. There is a critical difference between typical inflammation and chronic inflammatory systemic diseases, which separates the asymptomatic phase from the symptomatic phase of a chronic inflammatory systemic disease, the asymptomatic-symptomatic-threshold (a-s-threshold). Importantly from an evolutionary point of view, reproduction is only impeded during the symptomatic, but not during the asymptomatic phase. Genes enabling an adaptive inflammatory response, allowing the organism to overcome an infection, will thus increase survival probability and the potential for future reproduction and as such evolutionary fitness in young age. After initiation of chronic systemic inflammation, however, reproduction is inhibited, and this for prolonged periods, often for years and until death, causing fitness costs. However, as these costs typically occur only at the end of the reproductive life-history stage or in post-reproductive age, these fitness costs are lower than the fitness benefits in early life leading to an overall increase in Darwinian fitness.

plays an important role in chronic inflammatory diseases. For some HLA alleles, the risk to develop a chronic inflammatory disease is ninety times increased (Brewerton et al., 1973; Schlosstein et al., 1973). However, negative selection against specific HLA alleles was most probably weak, because in most individuals carrying these alleles the disease did not develop due to the lack of additional risk factors (Straub et al., 2016) that are important during ontogeny. HLA alleles were positively selected due to their role in infection (see section 11.3.2). We described the link between HLA-DR4 (DRB1*04) and dengue hemorrhagic fever, but the same HLA allele is known to be positively associated with rheumatoid arthritis, type I diabetes mellitus, and other chronic inflammatory diseases.

We described HLA-B27 as an important factor to overcome human immunodeficiency virus infection (see section 11.3.2), but the same allele is linked to ankylosing spondylitis (Brewerton et al., 1973; Schlosstein et al., 1973). Thus, many traits have an evolutionary history (phylogeny) developed in the context of infectious disease, but these traits are used again in another somatic environment in later life (Williams, 1957). This phenomenon is called antagonistic pleiotropy (Williams, 1957), which means fitness benefits at one life history stage being higher than fitness costs at another life history stage. Here, they can support the development of a chronic inflammatory disease.

11.3.2 Ontogeny—development of the trait in individuals over a lifetime

We learned that the immune system has a memory for antigens. However, cross-reactivity towards harmless autoantigens (reaction against innocuous self) or harmless microbes on the surface of the body (reaction against innocuous foreign) as in chronic inflammatory diseases can also occur. Now, the immune memory is directed against the harmless antigens, which leads to a chronic immune attack in chronic inflammatory diseases. The new memory is an autoimmune memory.

Sometimes autoantigens are post-translationally processed, which can be supported by factors that appear during individual development. For example, smoking may change self-peptides leading to an exchange of arginine with citrulline (Quirke et al., 2011). This post-translational modification with the new citrulline is foreign to the immune system and may be attacked as an antigen. Thus, smoking is one environmental factor during development known to increase the risk that the immune system later attacks harmless autoantigens fostering chronic inflammatory diseases (Klareskog et al., 2011; Mathews et al., 1973). Another environmental risk factor for some chronic inflammatory diseases is silica exposure, for example during construction work, which might overstimulate the immune system and trigger the autoimmune process leading to chronic inflammation (Pollard, 2016).

Another environmental risk factor is psychological stress. We already saw that neonatal endotoxin exposure can change the adult immune system response, and it seems that the childhood immune system is more vulnerable to stressors as compared to the adult immune system (see 11.3.3). In several studies, it was demonstrated that childhood trauma (death of a parent, sexual abuse, violence in the family etc.) was positively linked to later appearance of chronic inflammatory diseases (Dube et al., 2009, Neufeld et al., 2013, Spitzer et al., 2013). These examples are indicative of how the individual development influences the immune system and the appearance of overt chronic inflammatory diseases in the future.

11.3.3 Causation—the immune machinery

In chronic inflammatory diseases, the role of the immune machinery was described for more than 100 years, reaching enormous detail since the start of molecular biology and functional genomics in the 1980s and 1990s. Today, we realize that many important pathways have been discovered that cause and support chronic inflammatory diseases (Firestein et al., 2013; Hochberg et al., 2015). These novel factors led to the development of biological therapy such as anti-TNF strategies (Feldmann et al., 2010). Nevertheless, much detail needs to be learned, particularly, with respect to human chronic inflammatory diseases. Importantly, the immune machinery for chronic inflammatory diseases is the

same as the immune machinery for infectious diseases and allergy.

On top of the specific immune machinery, which was called selfish (see 11.3.4), a general bodily reaction supports the immune system (Straub et al., 2013). The immune system is selfish because it makes use of other systems (nervous and endocrine) to redistribute energy-rich fuels (Straub, 2014). While this has been positively selected for short-lived infectious diseases, the long-term application of these adaptive programs leads to many unfavorable signs and symptoms in chronic inflammatory diseases (Straub et al., 2016). These are daytime fatigue, low mood, sleeping alterations, anorexia, inflammation type of anemia, muscle loss (sarcopenia), bone loss, insulin resistance, decreased fertility and libido, high blood pressure and volume overload, and increased blood coagulation (Straub et al., 2016). These phenomena were positively selected as a machinery outside the immune system that supports the immune machinery. However, if these pathways are used too long, many problems appear that need specific extra treatment besides immunosuppression. Long-term use of these programs is maladaptive (Straub et al., 2016; Straub, 2017).

11.3.4 Integrative approach to understand CIDS in evolutionary medicine

Ultimate factors have been positively selected for short-lived infectious diseases and not for chronic inflammatory diseases (Straub et al., 2016). Net fitness is increased because the fitness benefits in early life are much higher than fitness costs in post-reproductive life, so that favorable genes stay in the gene pool (function and phylogeny). The individual genotypes together with the individual specific environment lead to an individual specific development of the immune system (ontogeny). Here, environmental factors such as smoking, silica exposure, and childhood stress can prepare the immune machinery for the unfortunate development of a chronic inflammatory disease. When several factors come together (genetic and environmental), the individual can develop an immune response towards harmless self and harmless foreign antigens. Then, the response is imprinted in the immune memory, which leads to measurable immune responses such as autoantibodies towards citrullinated peptides (diagnostic, red box in Figure 11.3).

11.4 Medical applications and conclusions

Many chronic diseases might be studied and understood using the same framework as outlined in Figure 11.3. The evolutionary approach here considers three points:

1. One must take into account the fitness consequences of the trait leading to disease.
2. To be done at the different life history stages (pre-reproduction, reproductive age, and post-reproductive; Figure 11.2).
3. To determine life-time reproductive success.

This will enable us to understand the evolutionary history of the disease, especially why alleles favoring the disease have been established in the gene pool and have not been out-selected. On the basis of the "antagonistic pleiotropy theory" of Williams (Williams, 1957), we start to understand that disease alleles found related to chronic diseases often play a beneficial role in pre-reproductive and reproductive life history stage. In later life, the same alleles and related mechanisms can play a harmful role by stimulating a chronic disease in a different life history stage. Clinicians do not know this phenomenon and often think that disease-associated alleles are specific for a certain chronic disease without understanding their overall adaptive function. In other words, the idea is completely wrong that specific alleles have been positively selected to support a chronic disease. The example of HLA-DR4 was given previously.

Our approach might thus also benefit clinicians: it is often less relevant to know which genes and alleles favor the expression of a specific disease (there are often many little influences with small effects), but it is more important to know the interplay with environmental factors, which trigger the disease. This is because we cannot easily change the genotype of individuals, but we can interfere with environmental threats in an individual life. The example of smoking was given.

Another example is described as the "Barker phenomenon" according to David Barker (Barker et al., 1989; Hales et al., 1992). The hypothesis says that

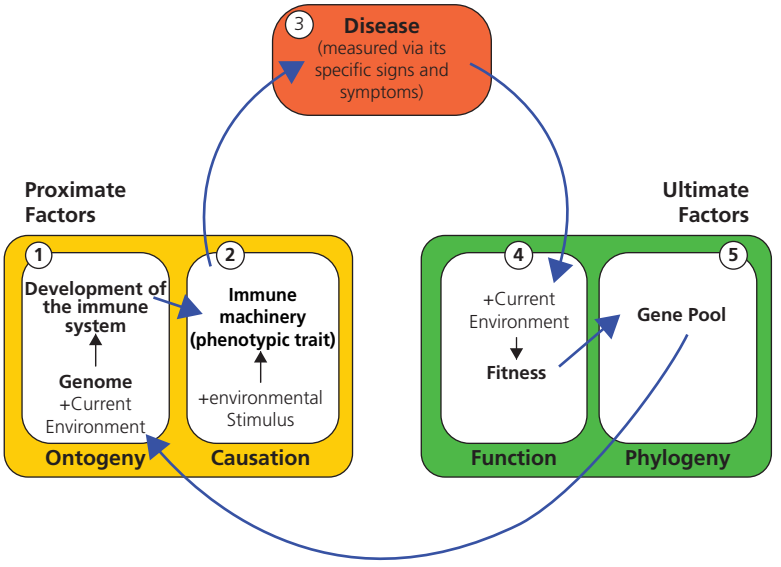

Figure 11.3 Integration of the four questions of Tinbergen to come to a comprehensive understanding of the development of chronic inflammatory systemic diseases

1. The immune machinery depends on the development of the immune system in an individual that can be influenced by different stimuli in the vulnerable phase of fetal, perinatal, and postnatal life or childhood (ontogeny), for example smoking or the exposure to silica dust.
2. In CIDs, the immune machinery is switched on by an immune response towards an autoantigen to induce autoimmunity or by monogenic defects in immune pathways to induce autoinflammation (causation).
3. The disease can be measured through specific signs and symptoms, one of which are autoantibodies.
4. Usually, the disease influences evolutionary fitness (function), but the influence is often very low, because CIDs appear late in or after the reproductive phase (Figure 11.2).
5. Thus, we do not expect a marked change in the gene pool that would support or prevent an autoimmune disease. The gene pool was positively selected for infectious diseases but not for CIDs (Figure 11.1).

reduced fetal growth by fetal constraints like undernutrition of the pregnant mother is strongly associated with a number of chronic conditions later in life in humans but also in experimental animals like rats. These chronic problems include coronary heart disease, stroke, diabetes, and hypertension. Since the phenomenon is stimulated during fetal life, it must have a strong environmental component. Typically, poor nutritional conditions were mentioned as the major trigger but other forms of fetal constraint play similar roles.

A third major element that is relevant to clinicians is the understanding that there is major crosstalk between different systems in the body. The most important systems are the psychomotor (brain and muscles) and immune systems due to their selfish role in combating threats. Since both systems use independent measures to achieve their goals, understanding of these interrelated pathways helps to explain many problems in chronic diseases and aging (Straub, 2017). These disease sequelae frequently seen in patients with chronic inflammatory diseases are fatigue, depressed mood, sleep alterations, loss of appetite, muscle wasting, cachectic obesity, bone loss, hypertension, and many others. The new understanding is based on the principles of evolutionary medicine, energy regulation, and neuroendocrine-immune crosstalk (Straub, 2017).

Fourth, understanding the evolutionary function of the immune machinery leading to CIDS could be of important psychological consequence. When clinicians can explain to patients how overall function of this system in earlier life is beneficial, this could reduce psychological and emotional suffering. The clinician can explain to the patient that nothing is genetically wrong and that the disease is rather a combination of unfortunate circumstances.

It helps the patient to understand that there is no personal weakness that causes the disease.

Finally, the absence of physiological mechanism acting against a chronic disease is no indicator that such a mechanism does not exist or is impossible; it only indicates that such a mechanism would not necessarily increase fitness. However, our human aim is to reduce suffering and costs of public health, not to increase evolutionary fitness. This leads to the conclusion that biomedical research might be most successful in diseases that have no or low lifetime fitness cost, but high costs for public health and a high load of individual suffering.

Last but not least, current research topics in evolutionary medicine where our graphical model might fail could nevertheless benefit by taking the four questions of Tinbergen into account. Examples could be maladaptation, environmental mismatch, and evolved traits that are not adaptive in the current modern environment. By applying the model and then identifying where it fails, the reason as well as the consequences why the trait is not adaptive or why environmental mismatch occurs could be identified. Thus, not all disease can be explained and described by Tinbergen`s four question, but identifying why and when this concept fails will nevertheless improve our understanding of why our body is constructed in a way that sometimes leads to disease.

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