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Highlights

- Immunological recognition has been traditionally restricted to three-dimensional molecular structures.
- I argue that the immune system can recognize microbial functions in addition to structures.
- This claim is based on a conceptual analysis and recent scientific findings.
- The analysis builds on and contributes to philosophical debates on functions.
- I introduce the concept of function-associated molecular patterns.
- Additionally, I argue that some immune sensors can directly recognize microbial activities.
- Sometimes, "what is going on" is more important than "who is there".

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Abstract

A central question for immunology is: what does the immune system recognize and according to which principles does this kind of recognition work? Immunology has been dominated by the idea of recognizing molecular structures and triggering an appropriate immune response when facing non-self or danger. Recently, characterizations in terms of function have turned out to be more conserved and explanatory in microbiota research than taxonomic composition for understanding microbiota-host interactions. Starting from a conceptual analysis of the notions of structure and function, I raise the title question whether it is possible for the immune system to recognize microbial functions. I argue that this is indeed the case, making the claim that some function-associated molecular patterns are not indicative of the presence of certain taxa ("who is there") but of biochemical activities and effects ("what is going on"). In addition, I discuss case studies which show that there are immunological sensors that can directly detect microbial activities, irrespective of their specific structural manifestation. At the same time, the discussed account puts the causal role notions of function on a more realist and objective basis.

keywords: immunology; recognition; function; structure; microbiota

1. Introduction

According to a widespread view in immunology, a limited set of so-called "pattern recognition receptors" (PRRs)[1] can recognize specific molecular patterns of pathogens and will trigger a corresponding immune response to fight them off (Medzhitov and Janeway, 2002). This picture has been challenged by several observations over the last years. On the one hand, it is increasingly realized that the immune system is not only there to attack pathogens but also plays an important role in repair and developmental processes (Pradeu, 2012; Tauber, 2017; Laurent et al., 2017; Rankin and Artis, 2018). On the other hand, the concept of molecular patterns that would be indicative of pathogenic strains in a "bar code"-like fashion (Aderem, 2003, p. S340) is challenged by the fact that some structural patterns are shared among pathogenic and non-pathogenic microbial strains (Rakoff-Nahoum et al., 2004). This remains a pressing explanatory gap: how can different microbes that share

[1] List of abbreviations: CRISPR (clustered regularly interspaced short palindromic repeats); DAMP (damage-associated molecular pattern); FAMP (function-associated molecular pattern); IgA (immunoglobulin A); ILC (innate lymphoid cell); MAMP (microbe-associated molecular pattern); MHC (major histocompatibility complex); PAMP (pathogen-associated molecular pattern); PRR (pattern recognition receptor); rRNA (ribosomal ribonucleic acid); SCFA (short-chain fatty acid).

structural molecular patterns be *recognized* differently – in addition to triggering different immune *responses* that depend on "context", i.e. with the aid of different additional signals?

The purpose of this paper is to argue that the immune system does not only recognize structural features as indicative of "who is there", i.e. which kinds of microbes (pathogens) or their parts are present, but that the immune system can also recognize microbial functions. This claim is built upon a philosophical and conceptual analysis of the notions of *structure* and *function*, and supported by reflections on how the immune system is able to perceive the microbiota (i.e. the totality of microorganisms living within and on a multicellular host organism). Microbiota and how their structure and function impact health and disease of human hosts have become a hot topic in many respects (The Human Microbiome Project Consortium, 2012). Besides recently gaining a lot of scientific and public attention concerning health and disease, microbiota and their interactions with their host have started to receive philosophical attention as well (O'Malley and Dupré, 2007; O'Malley, 2014), in particular with respect to the role of the immune system in these processes and their consequences for biological individuality (Pradeu and Carosella, 2006b; Dupré and O'Malley, 2009; Pradeu, 2010; Gilbert et al., 2012; Pradeu, 2016; Suárez, 2018; DiFrisco, 2019).

First, in section 2, I set the stage by outlining the philosophical starting point and implications of the paper: debates about the notion of function and philosophy of immunology. In section 3, I provide a very brief historical overview of the idea of structural recognition in immunology. In sections 4 and 5, I ask for different notions of structure and function, respectively, what the terms mean conceptually and in scientific practice – in particular with respect to being recognized by the immune system. Based on the notions of structure and function, I develop three claims about the recognition of microbial functions that differ in their strength – all of which diverge from views which have been dominant in immunology for decades. These claims are: that the immune system can recognize microbial functions (i) *indirectly* via function-associated molecular patterns (FAMPs), as well as *directly* in the form of (ii) biochemical activities and (iii) biological roles; summarized in section 6. Finally, section 7 provides a conclusion, open questions, and philosophical problems awaiting future research.

2. Functions and philosophy of immunology

Before going into the immunological details and the hypothesis that the immune system might be able to recognize microbial functions, let me address the notion of *function* and its

philosophical significance. Different accounts of function have continued to be debated in philosophy for several decades. Usually the two main accounts being discussed are Larry Wright's (1973) *selected effect* and Robert Cummins's (1975) *causal role* notion of function. In a nutshell, the former strives to explain "why" a biological entity operates in a certain way, whereas the latter addresses "how" a biological entity can operate in a certain way. In addition to these two families, there is a multitude of different accounts and variations, serving different epistemic and ontological purposes. This is not the place for an exhaustive review of that very rich literature (for an overview, see (Garson, 2016; Wouters, 2005; Godfrey-Smith, 1993)).

There is no "right" or "wrong" way to analyze function per se, only relative to particular goals. These goals and explananda do not differ just between disciplines such that one notion of function would be appropriate in one discipline, molecular biology let's say, whereas another notion was fitting another discipline, like evolutionary biology. Instead of this "between-discipline pluralism" there is rather a "within-discipline pluralism" (Garson, 2018) of notions of function. How their respective explanatory roles can complement each other to serve collaborative explanations (Fagan, 2015) remains an exciting open question for philosophers of science (Love, 2015). Confusing different notions of function and their respective explanatory scope with each other can lead to misunderstandings, like in the ENCODE debate about the percentage of DNA which has a function (Germain et al., 2014).

Also within the discipline of immunology, there are different epistemic goals for which different notions of function are required. I argue in this paper that two different notions of function can explain how the immune system is able to recognize microbial function – in addition to the well-established recognition of structures. Thus, we end up with a pluralism of notions of structure and function, each of which can play a role in explaining different aspects of the immune system. One could consider this to be a case of integrative pluralism (in the sense of (Mitchell, 2002, 2003; Brigandt, 2013)) insofar, as there is a relationship between some notions of structure and function, which need to be integrated in order to understand and explain immunological recognition. This relationship, however, does not allow a one-to-one mapping – and thus no theoretical, explanatory, or mechanical integration yet. The different notions of structure and function require more philosophical attention to be clarified. The present discussion in this paper sets the foundation for such philosophical questions as a direct consequence of the proposed notions of structure and function and their role in immunological recognition, thus contributing to a broader debate about integrating different notions of function in biology (Cusimano and Sterner, 2019).

Immunological recognition acts discriminatory and – by resulting in a certain immune

response – could also be viewed as being "normative" to some extent (what will or will not be tolerated by an organism). This comes together with ontological questions: to which entities can we ascribe functions? Do other agents than human researchers recognize and "ascribe" functions? If the immune system is indeed able to recognize microbial functions, this puts the causal role notions of functions defended here on more objective and realist feet, without ever alluding to selected effects or evolutionary advantages (which also allow only a weak notion of realism (Huneman, 2013)). These questions might very well be asked in addition, providing different explanatory projects that require different notions of function as explanans or explanandum. That being said, by focusing on the mechanisms and physiological processes of immunological recognition, I will not address any related evolutionary questions in detail. Once we have established *how* immunological recognition operates, future research will have to deal with *why* it provides evolutionary advantages for organisms (and perhaps also the microbes in question) to have such an immune system.

Given a satisfactory explanation of the phenomena of immunological recognition of functions, different explanatory projects can aim at explaining why these traits exist and what selective advantage they have for organisms. These will be difficult to disentangle in light of microbiota-host co-evolution (Morella and Koskella, 2017) and co-immunity (Chiu et al., 2017).

Yet another kind of pluralism emerges, as different notions of structure and function require different methods, tools, and techniques to be studied and represented. When it comes to representing and modeling immunological processes, mathematical tools for network structures (section 4.3), as an important neglected notion of structure in the discourse about immunological recognition, need to be explored in more philosophical detail, providing epistemic tools for *mechanistic* (Machamer et al., 2000) and *topological* (Huneman, 2010; Kostić, 2018) explanations in immunology. How these tools can be used to explain functions and behaviors of complex networks is not only important for immunology (Hart et al., 2009) and microbiology (Deulofeu et al., 2019), but also a burning question in philosophy of science in general.

The explanatory role of functions in immunology, the focus of this paper, is equally rich, as different notions of function play different explanatory roles for explaining different immunological phenomena. For explaining how immunological recognition works in particular, on which this paper is focused, I will propose two notions of function that fall into the broader family of causal role or systemic functions: biochemical activities and biological roles (along the lines of an earlier distinction made by Arno G. Wouters (2003); see also section 5). He distinguishes between functions as *activities*, i.e. what organisms or their parts

can do by themselves, and functions as *biological roles*: "the way in which an item or activity contributes to a complex activity or capacity of an organism" (Wouters, 2003, p. 635). Wouters' other two notions address questions related to *biological advantages* and *selected effects* – why certain entities or activities benefit an organism's fitness, and why they have been selected for, respectively. These are different explanatory questions that will rightly consider different notions of function. The latter two notions are close to the selected effects account of function, whereas the former two belong to the causal role account.

One major philosophical result of this paper is a defense of the causal role approach to function against the objection of being subjective and too liberal, e.g. (Garson, 2017a). This way, functions could be introduced as something that is not relative to an epistemic agent. The "recognition" or "selection" criteria of the immune system are still something that developed historically and with some selective advantages, as discussed in Justin Garson's (2017b) generalized selected effects notion of function, also applied in immunology in terms of clonal selection theory (Garson, 2012, p. 468)). However, as the immune system also operates as a physiological mechanism without any such means of selection, we do not want to explain why or how it happened to be the case that the immune system recognizes microbial functions, but simply *how it does so mechanistically*.

The microbial functions, understood as microbial activities and effects, that could be recognized by the immune system do not fall under Garson's generalized selected effects theory of function (Garson, 2017b), although the microbial activities and their roles might eventually lead to their tolerance by the immune system, and thus their differential persistence in a population. In the case of pathogens, however, the immune system would react by eliminating rather than retaining the microbes responsible for certain traits. Thus, the arbitrariness and subjectivity of the selected effects perspective, even if generalized, becomes apparent – which is ironic, since the systemic, causal role accounts used to be accused of being too liberal and subjective in the way they ascribe functions. Philosophical discussions used to consider functions as something "real" in nature if and only if they could be accounted for from an etiological perspective. Causal and systemic perspectives, on the other hand, remain notoriously open and vague about what counts as a "function" – and from which perspective; thus making it effectively an epistemic notion by proposing that it is the observers or researchers who delineate a system according to their epistemic interests and then identify functions as causal contributions within that system. The approach defended in the present paper, which argues for the possibility of an immunological recognition of functions, opens up the possibility that functions could not only be something recognized by human observers, but also by a biological system such as the immune system. In other

words, this perspective provides a more ontological and potentially realist approach to functions than the ones that have been traditionally developed within the causal role accounts of functions (Amundson, 2000; Allen, 2002).

Taken together, the case of immunological recognition of microbial functions discussed in this paper sheds new light on the plurality of notions of function that have been discussed in philosophy, as well as the pluralism of different explanatory projects related to them. Of immediate relevance is a follow-up question of whether and how this pluralism can be integrated. Thus, the philosophical questions addressed here do not only contribute to the small domain of philosophy of immunology, but also to more general debates in philosophy of science. Avoiding biases from a one-sided diet of examples, from which the function debate has suffered in the past, I believe that immunology deserves more philosophical attention regarding a wide range of other philosophical questions.

Taking a function-centered perspective also has consequences for prokaryotic evolution and pluralism when it comes to species (Bapteste et al., 2009), classification (Dupré, 2001), and what information can be gained from taxa (Reydon, 2019). Away from the self/non-self distinction and considering "who is there", drawing the boundaries of biological individuality and pathogenicity might be based on functional rather than structural criteria. By putting the emphasis on function, some microbial functions could then be characterized as "pathogenic functions" (Rath et al., 2018). This has consequences on how we classify microbes (according to those different notions of structure and function) and how to characterize any of them as "pathological". The relevant difference, I argue, is not "who is there" but "what is going on". Because the immunological recognition does not discriminate between accidents and functions or between functions and malfunctions (in terms of selected effects), it will, in fact, often utilize accidental traits that come together with pathogenic microbial activities and roles. The "decision" whether or not to treat microbes as pathogens or how to react more generally is a question of immune *response*, in addition to the question of immunological *recognition*. As a first step, however, the novel view of immunological recognition of microbial functions by the immune system has immediate consequences for the question of pathogenicity (Méthot and Alizon, 2014). Given the offered conceptual analysis, a more contextual conception of pathogenicity appears to be natural.

There is evidence that the immune system monitors – and influences – the structure and function of microbiota via IgA antibodies (Donaldson et al., 2018). More specifically, Nakajima et al. (2018) show that IgA can alter the microbial expression of so-called "mucus-associated functional factors" which promote colonization of two bacterial phyla. A general lesson from these studies is the fact that many functions are not the isolated product

of either microbiota or immune system, but oftentimes are the result of interactions between them. Enriching the scope of immunological *recognition* also allows to appreciate the fact immune *response* includes more than pathogen elimination. Rather, many immune responses, as the case of IgA shows, aim at maintaining and cultivating microbial functions.

While the conceptual clarification developed in this paper is also intended as a scientific contribution, the main goal of this paper is to provide a philosophical explication and conceptual analysis of the notions of structure and function that goes beyond reporting their use in scientific practice – although being informed by this very practice. This showcases how intimately the philosophical and scientific concerns are related. While the theoretical basis of immunology has only received little attention from philosophers of science so far, there is a clear opportunity for philosophers to contribute to the conceptual and theoretical foundations of a thriving and changing discipline. I believe that collaborative exchange will be to the advantage of both fields (Laplane et al., 2019).

Before we begin to explore the theoretical issues at stake concerning immunological recognition of microbial functions, let us begin by taking a look at the history of the predominant view in contemporary immunology: that recognition would be a matter of structures.

3. A brief history of the idea of immunological recognition of structures

The idea of the immune system recognizing particular structural motifs traces back to the early days of immunology. The side-chain theory, proposed by Paul Ehrlich, laid the foundation for the predominant view of stereochemical complementarity for understanding the interactions between immune receptors and their targets (Silverstein, 1999; Silverstein, 2009, pp. 47–49, pp. 102ff.). This view of receptors binding their targets, also influenced by Emil Fischer's "lock and key" metaphor (Prüll, 2003, p. 343), dominates the field of immunology up to this day. Driven by, or indeed driving, the success of molecular biology, the notions that sequence determines structure and structure determines function has given rise to very successful research programs in immunology, based on the synthesis of the chemical and biological aspects of immunology. The molecular details of the interactions between pattern-recognition receptors (receptors that bind to structurally similar and evolutionarily conserved molecular motifs) of the innate immune system, as well as the structural diversity and binding specificity of antibodies for the adaptive immune system

have provided explanatory strength for decades.

Several competing theories for the structural diversity and mechanisms of antibody formation have been discussed in immunology. The specific binding properties of antibodies for antigens used to be explained biochemically in a similar way to the innate pattern recognition receptors. The latter, however, do not show great diversity, but rather target evolutionarily conserved patterns which can be found commonly inside or on the cell surfaces of microbes, or are being secreted by them. These two lines of events for explaining antigen diversity and binding as well as innate pattern recognition receptors, respectively, have had their focus on structural patterns and interactions. These molecular interactions also provided the basis for the view of the immune system discriminating self and nonself (Burnet, 1969) or dangerous/infectious and harmless/benign (Matzinger, 1994). Both views share the focus on molecular patterns as being indicative for the immune system to recognize certain patterns as pathogenic or infectious/dangerous: the immune response depends entirely on the molecular patterns involved (so-called "pathogen-associated molecular patterns" (PAMPs)), or at least depending on the context of additional signals (that signal pathogenicity or danger in another way).

Together with the successful idea of structural recognition came the conviction that the immune system would trigger an according immune response once a particular molecular pattern has been bound. This could be called the 'one molecule–one receptor–one functional response idea' (van Eden et al., 2012, p. 283) or, in a more sophisticated form, 'Janeway paradigm' (Sansonetti, 2011, p. 9). Charles Janeway, Jr., a key figure in immunology, played a major role in putting forward a theory of pattern recognition, developed these ideas and was responsible for their wide-spread success to become textbook canon. Even though the 2011 Nobel Prize was awarded to Bruce A. Beutler and Jules A. Hoffmann "for their discoveries concerning the activation of innate immunity" (Nobel Assembly, 2011) and to Ralph M. Steinman "for his discovery of the dendritic cell and its role in adaptive immunity" (Nobel Assembly, 2011), respectively, it can be argued that the emerging views on the innate and adaptive immune system are to a large degree the legacy of Janeway – who, unfortunately, died in 2003. The idea of molecular pattern recognition, together with the clonal selection theory, constitute the "two major paradigms" of modern immunology (Medzhitov, 2013). In a seminal paper of his, entitled 'Approaching the asymptote? Evolution and revolution in immunology' (Janeway, 1989), Janeway suggested that immunological knowledge was reaching a state of saturation:

> I believe it is safe to state that our understanding of immunological recognition is approaching some sort of asymptote, where future experiments are obvious,

> technically difficult to perform, and aim to achieve ever higher degrees of precision rather than revolutionary changes in our understanding. (Janeway, 1989, p. 2)

Twenty years later, Ruslan Medzhitov provided a perspective on the developments of the field of immunology in which he pointed to some of the remaining open questions that Janeway's pattern recognition paradigm failed to explain (Medzhitov, 2009). In particular, he stressed that "[i]n addition to pattern recognition, there are other forms of innate immune sensing" (Medzhitov, 2009, p. 766). Now, thirty years later, it is time to challenge pattern recognition as the only way for the immune system to recognize its microbial interaction partners. In particular, the ability of the immune system not only to respond differently, but also to recognize microbes differently despite common structural patterns, needs to be explained. As Philippe J. Sansonetti put it: "the 'Janeway paradigm' of PAMPs being recognized by PRRs needs updating to explain this discrimination process" (Sansonetti, 2011, p. 12).

One of the things that Janeway himself contributed was pointing out that just the presence of an antigen was not sufficient to trigger an adaptive immune response. Janeway called this the "Landsteinerian fallacy": "The Landsteinerian fallacy is that all antigens are not only equally recognizable, but also equally immunogenic, that is, equally able to stimulate an immune response" (Janeway, 1989, p. 7). For triggering an adaptive immune response the presence of so-called adjuvants was required, which challenged the idea that an antigen by itself would be sufficient. Janeway referred to this as "the immunologists' dirty little secret" (Janeway, 1989, p. 4), see also (Gayed, 2011). Besides the molecular structural features of the microbial components, the ability to trigger a lymphocyte immune response turned out to require something more. A "second" or "co-stimulatory signal" was needed. He proposed that this second signal would result from pattern recognition receptors recognizing conserved structural patterns as "infectious non-self" (Liu and Janeway, 1991, p. 323; Janeway, 1992):

> I contend that the immune system has evolved specifically to recognize and respond to infectious microorganisms, and that this involves recognition not only of specific antigenic determinants, but also of certain characteristics or patterns common on infectious agents but absent from the host [. . .]. By ignoring the importance of this microbial component of immunological recognition, I contend that we have collectively ignored a critical feature of self/nonself discrimination, the requirement for a microbially induced second signal [. . .]. Indeed, I believe that if we fail to incorporate such ideas into our thinking, we

> shall fail to understand immune recognition at its most fundamental level, that is, the discrimination of self from nonself, and in the defense of the host against infection. (Janeway, 1989, p. 7)

The idea of specific molecular patterns to tell "friend from foe" or "non-infectious self from infectious non-self" was appealing for simplifying the interactions with the immune system and how a distinction is being made between dangerous or pathogenic substances and microbes, and non-dangerous or non-pathogenic ones. What complicates the picture, however, is the fact that many structural features are shared among pathogenic and non-pathogenic microbial strains and substances. The same pattern recognition receptors recognize those features on the microbial surfaces, like, e.g. lipopolysaccharide (Rumbo et al., 2006). However, the outcome of recognition can often be different. The key question is: why? As it became apparent that the idea of molecular patterns as indicative for pathogens was suffering from the problem that also non-pathogenic microbes display some of these patterns without inducing an immune response, a change in nomenclature was proposed: instead of 'pathogen-associated molecular patterns' (PAMPs) the term 'microbe-associated molecular patterns' (MAMPs) was suggested, e.g. by (Koropatnick et al., 2004; Ausubel, 2005).

If it is not a difference in the molecular patterns presented and produced by the microbes that allow the immune system to recognize harmful and infectious microbial agents, what kind of signal would be needed to recognize them instead? Polly Matzinger's danger hypothesis introduced the concept of 'damage-associated molecular patterns' (DAMPs) (Matzinger, 1994). The main idea is that rather than distinguishing self from non-self, the immune system would be able to recognize certain signals that indicate "danger" or "damage". Pradeu and Cooper (2012) provide a "twenty years later" view on the danger theory, for a critical discussion see also (Pradeu, 2012, pp. 205–218). Among other things, the notion of "danger" has been criticized as problematic and in need for clarification in order to be useful:

> The problem with this model, in our opinion, is its inherent tautology. According to this hypothesis, the immune response is induced by a danger signal, but the danger signal is defined as just about anything that can induce an immune response. We believe that the major physiological role of necrosis-induced inflammation is to induce a tissue repair response, as tissue repair seems to be the most logical response to tissue damage. The induction of an immune response, on the other hand, is controlled by the innate immune system, which

> detects the signs of infection by decoding the patterns of self and nonself. (Medzhitov and Janeway, 2002, p. 300)

Besides the problem of a clarificatory definition of 'danger', one of the danger theory's problems is that it still remains within the view of the immune system's purpose being to fight pathogens, whereas tissue repair is certainly also an immune response in today's perspective.

Whether pathogenic, dangerous, or not, this structural perspective used to be center-stage in how the immune system would recognize and interact with its microbiota. However, that the immune system recognizes the resident microbiota at all has not been commonly believed until a few decades ago. For quite a while, the gut and other organs had been considered to be "immune privileged" areas where immune cells would have no access or only very restricted particular kinds of interactions could take place (Streilein, 1995; Iweala and Nagler, 2006). Microbes in the gut were considered to belong to the "outside" of the body, like microbes on the skin, where pathogenic, commensal, and beneficial bacteria keep each other in balance – maybe directed to some degree by the host's regulation of temperature and acidity, but not via immune interaction. This view of the microbiota-host interactions has proven to be wrong. There is indeed immunological recognition and interaction with the resident microbiota. The question is now *how* does the immune system recognize the microbiota: only via the involved structures, presented on cell surfaces? Or through their metabolic products that the microbes secernate to the surrounding host tissue? Or is there another way in which the immune system can detect microbial function directly? Before addressing these questions of structure and function systematically in the following sections, let us briefly take a look at early ideas of how functions could be the object of immunological recognition. Far from attempting a complete history of immunology here, let me offer an "alternative history" (Anderson et al., 1994) that focuses on the notion that the immune system mainly recognizes structures.

Structure and function have played different roles in the history of immunology as guiding principles, partly reflected in its early chemical and biological branches: "These new theories no longer focused on the *function* of antibodies, but rather on their chemical *structure*, and more specifically on the question of how such a large group of specific molecules able to interact with an ever-growing universe of potential antigens could possibly be produced within the vertebrate host" (Silverstein, 1991, p. 523, original emphasis). After studying molecular structures and cell types, their respective functions have become the main target of research: "Now the major cells of the acquired immune response had been identified and immunologists increasingly focused on their biological functions" (Kaufmann,

2019, p. 8). Similar distinctions between states and substances can be found in (Fleck, 1979), also fueled by the debate between colloidal versus structural chemistry schools in immunology (Mazumdar, 2002).

Putting function back to the center of attention for understanding not only immunological response but also recognition is the main hypothesis of this paper. This hypothesis will be spelled out and defended below. The following paragraph is intended to show that the rigid view of pathogen-specific structural patterns has been questioned by scientific findings in the past. For example, in a textbook which has been named after Janeway, *Janeway's Immunobiology*, the possibility that the immune system's recognition repertoire is wider than anticipated is explicitly acknowledged:

> Initially, innate recognition was considered to be restricted to relatively few pathogen-associated molecular patterns, or PAMPs [. . .]. In the last several years, with the discovery of an increasing number of innate receptors that are capable of discriminating among a number of closely related molecules, we have come to realize that a much greater flexibility in innate recognition exists than had been previously thought. (Murphy and Weaver, 2017, p. 77, bold face removed)

What does it mean for the immune system to recognize structure or function respectively? In the following sections, I will analyze different notions of structure and function, and how the immune system can recognize instances of these respective notions in turn.

4. The immune system can recognize different kinds of structures

The term 'structure' can be used to denote many different things. Accordingly, these different notions can play different roles in immunological recognition. Different meanings may also imply different techniques and methods that need to be applied, respectively. Five of the most frequently encountered notions of structure in scientific practice will be investigated in the following paragraphs – together with the question of how the immune system can or might be able to recognize instances of these notions of structure, respectively.

4.1. Three-dimensional structures

When talking about immunological recognition, the notion of the three-dimensional shape of molecules will immediately come to mind. As discussed in Section 3, the success of explaining molecular binding interactions between pattern recognition receptors and microbial structural motifs, as well as the antibody-antigen interactions have received much attention, as justified by their explanatory success. However, by the exclusive focus on the recognition of three-dimensional structures, other – both structural and functional – perspectives have been neglected. While undoubtedly successful for understanding immunological recognition in the last decades, some instances of immunological recognition do not fit the model of a unique structural motif binding to a complementary receptor. There is a case to be made that in some instances, another kind of structure – or function – is being recognized.

Pattern recognition receptors include most prominently Toll-like receptors and NOD-like receptors, which bind quite specifically to some pathogen- or microbe-associated molecular patterns. Antibody-antigen binding and T-cell receptor interactions with peptide-MHC complexes are similarly specific, although their diversity is being produced by sophisticated mechanisms of adaptive immunity, which allow the creation of antibodies for virtually any three-dimensional structural target.

Three-dimensional structure is not only an important aspect of individual molecules and their interactions, it is also relevant for cellular and tissue levels. Medzhitov and Janeway (2002) explicitly mentioned cellular structure and stressed the importance of the *location* of a particular molecular pattern: "It is important that PRRs do not distinguish between microorganisms that colonize the host (pathogenic or commensal) and microorganisms that evolved to occupy habitats other than the host, because all of them produce PAMPs [. . .]. However, only pathogens evolved the means to gain access to the compartments within the host where the host's PRRs can detect them and can induce immune responses." (Medzhitov and Janeway, 2002, p. 298). Similarly, the location of molecules belonging to the host can be recognized and trigger an immune response when found outside of their "normal" cellular environment. This idea has been labeled the "hidden self model" (Kono and Rock, 2008).

4.2. Sequences

It is customary in the chemistry of polymers to speak of the sequence of nucleotides or amino acids as 'primary structure'. At the same time, these molecules fold locally and globally into three-dimensional structures, which are being referred to as 'secondary' and

'tertiary structures', respectively. Primary structure or sequence is of particular interest for precursor immune systems and how recognition takes place there. Most prominently, CRISPR/Cas systems are able to recognize "foreign" nucleic acids by their their sequence, or rather by "genetic anomalies" (Pradeu and Moreau, 2019). Similar questions are also relevant for the idea of an "immune system" of the genome, where RNA silencing and other mechanisms are at work (Plasterk, 2002). To what extent immunological recognition and response depend on genetic sequence, or if these are ultimately the result of three-dimensional shapes of the nucleic acid strings in interacting with their recognition sites, or even their binding kinetics as functional features, is an open conceptual question that might be answered empirically in the future.

Considering the sequence rather than the three-dimensional shape here might seem to be just abstracting away from the structural manifestations of the sequence. Although nucleotide and amino acid sequences also differ in their three-dimensional conformation (hydrogen-bonds and secondary structures), the difference-making component is mainly their sequence. For example, in MHC presentation, short peptides are exposed to recognition receptors in a form in which their folding might differ from their conformation in a natural state. The sequence of amino acids, however, provides a rough three-dimensional profile that is enough to allow the selection of binding receptors, that will in fact not recognize the three-dimensional peptide portion in isolation, but as it is being presented together with other proteins in the three-dimensional structure of the MHC presenting complex together with the peptide fragment of the sequence in question. The paper by Rudensky et al. (1991) was seminal in examining the sequence of these peptides in addition to the three-dimensional details of MHC molecules (Bjorkman et al., 1987).

4.3. Network structures

Earlier, we discussed the danger theory and other hypotheses according to which it is not the three-dimensional structures in isolation that, after being recognized, will trigger a specific immune response. A recent idea is that "context", i.e. additional molecular and cellular signals will be integrated in order to "decide" the corresponding response to different structural recognitions. These network structures include spatial and temporal patterns that can be represented and explained with mathematical tools, as is prominently being done in systems biology. Network structures provide the framework and tools for studying complex patterns of interactions and their dynamics, e.g. (Bransburg-Zabary et al., 2013; Subramanian et al., 2015; Muller et al., 2018). Network-thinking traces back to Niels Jerne's immune network theory (Jerne, 1974; Hoffmann, 1975).

If we apply this to the microbiota, as argued by Swiatczak et al., "the distinction between pathogenic and non-pathogenic microbes is made by an integrated system rather than by single types of cells or single types of receptors" (2011, p. 983). This way, also the recognizing agent can be seen not only as a three-dimensional structure, but as an interaction network structure as well (for some conceptual and methodological considerations on networks and explanations, see section 2).

Pathogenicity, or the ability to trigger an immune response, depends not only on the presence or absence of a particular three-dimensional structural pattern, but is determined by an interaction network structure that provides context and "meaning" to a particular signal. Moving away from war/peace and self/non-self to a less black-and-white picture, not making pathogenicity a question of structural patterns or microbial taxa, resolves some puzzles concerning the response that certain entities can trigger when placed in a different network structure of interaction partners. For example, the immune response to the same molecular motifs (e.g. flagellin) is different, depending on the physiological state of the surrounding tissue where the recognition takes place (Park et al., 2019). The simplistic idea that recognition of a particular three-dimensional structural pattern would immediately lead to a corresponding response, independently from context and network interactions, is a remnant from the past – in particular for recognition of unique molecular patterns typical for certain pathogenic microbial strains.

4.4. Taxonomic compositions

Another meaning of 'structure' that also has consequences for immunological recognition comes from microbiota studies. The majority of microbiota studies focus on community structures and try to link taxonomic compositions, obtained from 16S rRNA sequencing, to phenotypes of the host in health and disease. Although simple and cost-effective, there are many problems with this approach. This is not the place, however, to discuss these problems in detail. Instead, I want to put emphasis on the fact that *community structure* or taxonomic composition is usually what is being referred to by 'structure' in microbiome studies, e.g. most prominently by The Human Microbiome Project Consortium (2012).

When it is claimed that the immune system can recognize and interact with the microbiota through their structure, this could either mean the totality of three-dimensional structural features by the collection of microbial taxa, or the relative percentage of taxa itself. Even though the latter option could be reconstructed as a version of 'network structure', it is difficult to imagine how immunological recognition should operate in such a way as to recognize the microbiome's taxonomic composition. It is much more plausible that the

immune response will depend on the community structure profile via integrated signals from individual microbial recognition receptors and cells (Thaiss et al., 2016).

This holds true not only for microbial communities residing in a multicellular host, but also in biogeographic studies, the "high taxonomic variability despite stable functional structure across microbial communities" (Louca et al., 2016a) has given rise to the conceptual need to rethink the structure-function relationship and for "decoupling function and taxonomy" (Louca et al., 2016b). Taxonomic composition or community structure is not a reliable proxy for function (understood as biochemical activity or biological role). Other methodological strategies are required to study functions directly – and for the immune system to recognize functions directly. There is no good mapping between taxonomic composition and function (Inkpen et al., 2017), let alone to host phenotype: "One of its [the Human Microbiome Project's] biggest initial revelations was that the taxonomic composition of the microbiota in the human body was not a reliable predictor of host phenotype, such as disease susceptibility" (Nature Editorial, 2019, p. 599).

This shift in focus has methodological consequences: in addition to 16S rRNA sequencing and consequent taxonomic profiling, other structural and functional aspects of microbial communities can be studied by multi-omics approaches, e.g. (Integrative Human Microbiome Project Research Network Consortium, 2019) or meta-omics approaches, e.g. (Mondot and Lepage, 2016), longitudinal studies, and the study of other notions of structure and function. Taken together, taxonomic composition is a less informative target for understanding microbial interactions with their host's immune system:

> This observation of similarity in habitat (niche) use with respect to functional genes, but not species, together with the relative ease with which bacteria share genetic material, suggests that the key level at which to address the assembly and structure of bacterial communities may not be "species" (by means of rRNA taxonomy), but rather the more functional level of genes. (Burke et al., 2011, p. 14288)

Moving away from the picture that the immune system's primary task is to fight off infections and pathogens, there is increasing evidence that the microbiota do play an important role not only in disease but also in health. For this to be the case, there ought to be ways in which the immune system is monitoring and controlling how the microbiota contribute functionally to the host's physiology (Belkaid and Hand, 2014). This might be via the proxy of taxa that have specialized for certain functions which can be recognized by signature three-dimensional structures. However, the boundaries between beneficial, commensal, and pathogenic bacterial taxa are not clear enough, and appear to depend much

more on their activities and functions. There is also a problem of multiple realizability: different taxa can fulfill the same functions. This is why a greater similarity can be observed in functional capacity than in taxonomic composition across individuals, also geographically.

4.5. Microbial products

Among the most important functional capacity of microbes is the production of certain metabolites and other products that the host can recognize, react to, or use – sometimes without being able to produce certain microbial products by itself. These microbial products include, for example, short-chain fatty acids and vitamin precursors (Tan et al., 2014; Spencer and Belkaid, 2012). In particular, short-chain fatty acid production has been investigated as one of the most important functions of the microbiota for the host metabolism, also involved in diseases and aging: "Mechanistically, the communication between the microbiota and the innate immune system seems to particularly rely on metabolites, such as tryptophan metabolites in the case of ILCs [(innate lymphoid cells)] [...] and short-chain fatty acids (SCFAs) in the case of myeloid cells" (Levy et al., 2017, p. 225). These and other microbial metabolites have been shown to play an important role in the physiology and health of its host (Sharon et al., 2014).

Since these microbial products can be produced by many different taxa, from the same "functional guild", it makes sense for the microbes to not be recognized directly but through their products. These products, of course, are still being recognized structurally (as discussed in Section 4.1), but they are not indicative of "who is there", rather of "what is going on". Both aspects are important for microbiota-host interactions (Ottman et al., 2012), the latter, however, still remains a neglected perspective. This might have to do with methodological constraints, because it is much easier to characterize the microbiome by sequencing the genomic material and assigning corresponding microbial taxa. In any event, by structurally recognizing microbial products, the immune system is able to monitor biochemical activities without screening for non-self or danger.

With taxonomic compositions or community structures (discussed in Section 4.4) being the dominant way in which microbiota are being currently characterized, functional considerations have become central – independent from the specific question of immunological recognition. Several claims, clad in clever wording, have been put forward which all make the case that functional aspects of the microbiota are more important than their taxonomic composition. Taxis et al. state that "the players may change but the game remains" (2015); Doolittle and Booth argue that "[i]t's the song, not the singer" (2017);

Heintz-Buschart and Wilmes stress "function first, taxa second" (2018, p. 571); and Suárez develops a "stability of traits" account (2020). While they provide a mainly evolutionary perspective across individuals, my aim is to explore the hypothesis that the immune system is able to recognize microbial functions physiologically. If true, this could help explain some of the evolutionary conservation findings reported in these studies. But for the task at hand, a conceptual clarification of the notion of function and possible mechanisms for it to be recognized by the immune system is required.

5. Can the immune system recognize different kinds of functions?

As we have seen from the discussion of the different notions of structures, there remains an explanatory gap that the hypothesis of recognition of microbial functions might be able to fill. A pressing issue remains: how does the immune system recognize the microbiota? Until recently, the answer to that question used to be: pattern recognition receptors recognize pathogen-associated molecular patterns which more or less directly leads to an immune response. However, recognition is not the same process as response; triggering an immune response, or immunogenicity, is an entirely different issue (Pradeu and Carosella, 2006a). Besides the question of how the immune system "decides" what a corresponding response to a particular stimulus is, the question of what is being recognized comes first. With the hypothesis that the immune system can also recognize functions, and is less concerned with "who is there" (i.e. which structures or microbial taxa are present), this shifts the perspective on the microbiota-host interactions through the immune system. However, these matters turn out to be less of a black-and-white categorization of taxa and their repertoire of structural patterns. The importance of function might be immediately evident for how the immune system *responds* to stimuli. The nature of these stimuli for *recognition*, however, might not always be merely structural in the first place.

At first sight, the idea that the immune system could recognize functions might appear absurd, contradicting fundamental common knowledge in immunology. Here, I want to argue that it is indeed possible for the immune system to recognize functions: (i) indirectly via the products typical for microbial functions, and that there exist immunological sensors that can directly recognize functions in the form of (ii) biochemical activities (section 5.1) and (iii) biological roles (section 5.2). Especially in the latter case, it would be difficult to argue that these phenomena could still be considered instances of recognition of structures.

While some of these functions that are being recognized still have a structural basis in some way, they no longer can be argued to be representing "who is there", both in terms of pathogens and symbionts, but rather representing "what is going on" biochemically and physiologically. Microbial metabolic products are a prime example (Nicholson et al., 2012). These, however, can be still recognized based on their molecular three-dimensional structure. The (modest) shift in perspective here would be that these are neither pathogen-, nor microbe-, nor damage-associated molecular patterns, but *function-associated molecular patterns* (FAMPs). The emphasis is directly on microbial functions, not whether the molecular patterns are associated with pathogens (PAMPs) or symbionts (SAMPs) (Round et al., 2011, p. 977). I propose FAMPs as an addition to the zoo of PAMPs, DAMPs, MAMPs, etc.

But, in addition to this modest modification, I think it is worth considering the even bolder hypothesis that the immune system can *directly* recognize some functions irrespective of their manifestation in a particular structural form. Eventually, structures will be involved in the underlying molecular processes, of course, but there are no shared structural patterns involved (unlike in the case of FAMPs); what they do have in common, and what the immune system is able to recognize, is something functional. Biochemical activities and biological roles can be recognized independently of their particular structural basis, as the examples discussed below will show. In some cases, these activities and effects can be multiply realized by different structures, i.e. there are many structures performing the same function, and only the latter is being recognized. By looking at the structural and functional space as objects of immunological recognition, recognition of microbes can be explained with respect to structural patterns associated to specific microbial functions (FAMPs), while at the same time opening up the previously neglected space of functions as potential targets for immunological recognition (Figure 1).

But what is function in the first place? Much ink has been spilled in philosophy on debating various notions of function, leading to different notions that ought to be kept apart (section 2). It is remarkable, however, that a recent *Nature Microbiology* paper (Klassen, 2018) brought the importance of "defining microbiome function" to the fore and suggested the importance of considering philosophical debates over function in order to do so. Traditionally, two main accounts of function are distinguished: the *selected effect* account and the *causal role* account. The philosophical discourse has become much more diverse and sophisticated over the last five decades. For the question at hand, however, it is clear that the selected effect account is not the target of immunological recognition. The claim is certainly not that the immune system recognizes selected effects. A different story could be told about

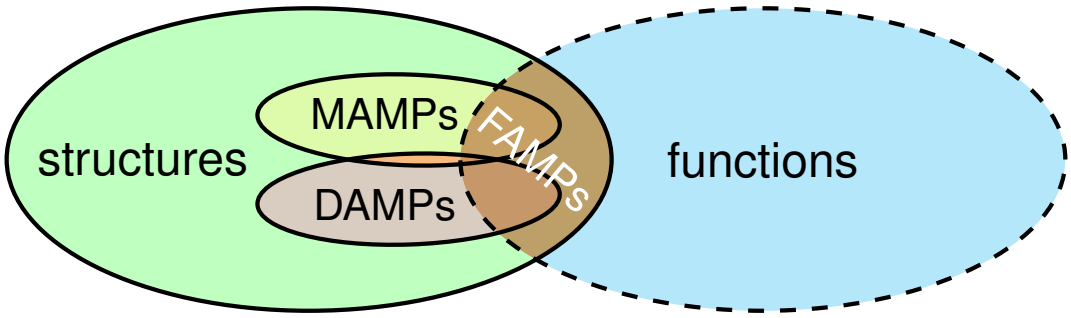

Figure 1: Structures and functions as objects of immunological recognition. The structural space (green) contains MAMPs (yellow) and DAMPs (red). The functional space (blue), on the other hand, provides different potential targets for immunological recognition, some of which are based on specific structures (FAMPs, overlap region shown in brown), whereas other functions can directly be the target of immunological recognition as biochemical activities or biological roles, irrespective of their structural manifestation. A particular functional aspect might be realized by a multitude of different structures that do not share any similar structural patterns and thus cannot be mapped to particular structures. The dashed line acknowledges the fact that functions are not material entities. The relative sizes of areas and their overlaps is not supposed to convey any meaning. Compare to (Matzinger, 2002, p. 303, Fig. 2).

the immune system's capacity to select for certain effects, i.e. shaping the host's habitat and immune system effector mechanisms in such a way that only microbes having certain effects can survive in those habitats or niches, thus putting constraints on the co-evolutionary trajectories that are permissive (maximize fitness). However, that is not the question either. We are interested in *whether and how the immune system might be able to recognize microbial functions on the physiological level*, sensing and monitoring its microbiota in organismic processes, not their selection dynamics.

The causal role account, on the other hand, suffers from other problems, as a causal role is hardly something that can be recognized or detected directly. Arno G. Wouters's distinction of four notions of function (2003) is very useful in this context. Recall form section 2 that he distinguishes between: "(1) function as (mere) activity, (2) function as biological role, (3) function as biological advantage, and (4) function as selected effect" (Wouters, 2003, p. 633). The latter two notions are of particular interest for evolutionary issues, like addressing the "function" of immunological recognition and the immune system for the organism, i.e. what the biological advantage and selected effect of such a capacity would be. But for the question itself of whether and how the immune system can recognize function, only the former two notions are relevant. While it is already a difficult case to be

made for the immune system to recognize activities and roles, it would be much harder to argue that the immune system can recognize biological advantages or selected effects. Neither of these options will be the claim of this paper.

This leaves us with two options to consider: (i) can the immune system recognize biochemical (or other kinds of) activities? And (ii) can the immune system recognize biological roles? I will argue that both questions can be answered positively, using the distinctions developed in the earlier sections, and discussing case studies which support the conceptual claims.

5.1. Biochemical activities

Besides receptors for structural features that are indicative of certain microbial functions – what I have called 'FAMPs' – there are several examples of immunological sensor systems which are able to recognize functional features directly, not merely the structural products of these functions. Perhaps the best example to illustrate this point is the study by Issa et al. (2018).[2] The authors describe the *Drosophila* serine protease Persephone which can recognize any kind of protease activity, irrespective of their particular microbial or structural manifestation. Whenever the bait region of this protein sensor is cleaved, by whatever biochemical means, Persephone is activated. Thus, it serves as an immunological sensor for protease activity, being able to recognize this microbial biochemical activity, not any particular structural pattern (see also (Chamy et al., 2008)). The general lesson that can be drawn from this example is that immune sensors exist which can recognize biochemical activities, i.e. something functional that is not related to any particular structural pattern.

Iwasaki and Medzhitov (2015) argue that both structural and functional features can be recognized by the immune system. That other recognizing immune sensors, similar to the Persephone case, exist is suggested by detectors like the inflammasome which can be activated by a diversity of different structural patterns. The NLRP3 inflammasome, for example, can be activated by ion fluxes (Gong et al., 2018), which might be the functional result of a diversity of biochemical activities. It is reasonable to expect that similar biochemical activities rather than just structures could be involved in immunological recognition.

For the immune system to monitor and maintain homeostasis, a constant surveillance not only of "who is there" but rather of "what is going on" is essential. Such functional parameters that the immune system needs to recognize include, e.g. pressure and mechanic

[2] Thanks to Bruno Lemaitre for pointing out this example.

forces (Solis et al., 2019), ion concentrations (Feske et al., 2015), and different stress conditions (Chovatiya and Medzhitov, 2014). Effects of virulence factors, enzymatic effects of allergens, and multicellular parasites are other candidates mentioned by Iwasaki and Medzhitov (2015). Boyer et al. showed that "the host indirectly sensed the pathogen by monitoring for the effector that modified RhoGTPases" (2011, p. 536). Effector-triggered immunity in plants can be considered to be another instance where an immune system does not recognize microbes or their structures, but rather their functional effects on the host (Jones and Dangl, 2006). Such effector-triggered immune mechanisms appear to be not restricted to plants, but employed in animals as well (Stuart et al., 2013). Similar ideas have been defended earlier with the "guard theory": "The idea of the guard theory is that rather than detecting pathogens directly, the products of at least some individual resistance genes monitor, or "guard," certain cellular processes that are often targeted by the virulence factors of pathogens" (Medzhitov, 2009, p. 770).

Functional effects could still manifest themselves structurally, but the effect of their activities is what is being recognized by the immune system, not their presence or any of their structural features themselves. Vance et al. (2009) discuss such "patterns of pathogenesis" which can also be understood as indicative of "what is going on" rather than "who is there".

Taken together, there is rich evidence that the immune system can recognize different kinds of structures as well as different kinds of functions – as the previous discussion of different notions of structure and biochemical activities, as one notion of function, has shown. While the emphasis in immunology has almost exclusively been dedicated to three-dimensional structures, the current shift in viewing the immune system not only as a means to fight off pathogens, a functional perspective should be useful for understanding and explaining the broader scope of immunological processes. In order for the immune system to be able to respond to microbial functions, it needs to be able to recognize functions in the first place. The case studies mentioned above clearly show that the immune system can recognize microbial functions in the form of biochemical activities which can be detected by immunological sensors.

5.2. Biological roles

The hypothesis that the immune system can recognize not only biochemical activities but also functions as biological roles is even more at odds with predominant immunological convictions. However, I think there is a way to frame this as a meaningful, reasonable, and testable hypothesis. First, let us recall how Wouters characterized biological roles: "how a

certain item or activity contributes to the emergence of a complex capacity of an organism" (Wouters, 2003, p. 638). There is a number of ways in which microbes play biological roles, e.g. in dietary fiber digestion. The immune system is monitoring these through short-chain fatty acids (SCFAs), which can be recognized as FAMPs by SCFA-receptors. Their role in higher-level processes like the microbiota–gut–brain axis is currently being investigated (Dalile et al., 2019). However, there are other higher-level effects to which microbes contribute, that can be neither attributed to single molecules nor their biochemical activities. One example is the exertion of pressure on a tissue or local microenvironment. Solis et al. (2019) have shown that PIEZO1 is an innate immune sensor capable of mechanosensation. Detection of pressure and force, a more complex and higher-level microbial activity than mere biochemical activities, via PIEZO1 allows myeloid cells to "also functionally integrate this signal to drive a potent and selective proinflammatory response even in the absence of classical pathogen-associated molecular patterns" (Solis et al., 2019, p. 70).

Immunologists increasingly acknowledge that "cells of the innate and adaptive immune system also sense complex tissue- and environment-derived signals, including those from the nervous system and the diet" (Rankin and Artis, 2018, p. 554). For recognizing such biological roles, the recognizing agent cannot always be a simple sensor in the form of a three-dimensional structure, but rather an organizational network structure which integrates a diversity of different signals (recall the notion (iii) of structure) and uses those signals to trigger a corresponding immune response. Here, we move into the domain of systems biology and its recent sub-discipline in the form of systems immunology (Davis et al., 2017; Villani et al., 2018). In this currently developing domain, immunological recognition and response need to be explained at the level of network structures and the biological roles that cannot be explained by the individual components and their activities. In a recent study, Rumpret et al. (2020) show that in order to maintain tolerance and homeostasis, two categories of inhibitory immune receptors (threshold receptors and negative feedback receptors) allow the fine-tuning of the immune response to microbial and other disturbances. The integration of different immunological signals in network structures facilitates the monitoring of quality, quantity, and temporal patterns of immune signals, thus allowing the immune system to recognize how microbial entities and activities contribute to complex capacities of microbes or the immune system itself, i.e. biological roles à la Wouters (2003). Studying these entities and activities in isolation will fail to explain certain immunological features that go beyond the structural receptor-target, epitope-paratope kinds of interactions for immunological recognition.

All of this is a step beyond the anthropomorphic view of the immune system's main role

being to fight off pathogens which wear *field signs* or *badges*, i.e. structural motifs, to be recognized on the "battlefield" of "war and peace" (Sansonetti, 2004); viewed in terms of the theory – or metaphor – of self/non-self (Tauber, 1997); or in its modification of being dangerous/benign (Matzinger, 2002). All these views have in common that there is a clear-cut boundary between two antagonistic parties, which are either "good" or "bad". The fact of the matter is less black-and white. Monitoring and maintaining the functional integrity of the host together with its microbes could rather be the immune system's main role. For this kind of functional integration, it suggests itself to consider a functional perspective for immunological recognition. Neither are these functions restricted to being pathogenic and dangerous, nor is it the immune system's only responsibility to recognize and respond to these harmful microbial aspects. In fact, many of the interactions of a host with its microbiota through the immune system are not about fighting off pathogens, inducing inflammation and the like, but rather aiming at keeping a homeostatic physiological balance, where useful interactions are promoted (Eberl, 2010).

It remains questionable, however, whether immunologists would still like to consider these phenomena under the term 'immunological recognition'. For understanding the working mechanism of the immune system, this network perspective of interacting immune components and their interaction dynamics requires us to consider network structures with theoretical models that allow for dealing with biological roles of the immune system and its interacting components (sections 2 and 4.3). Such a perspective in immunology can be found, for example, in the equilibrium account of immunology (Eberl, 2016).

5.3. Biological advantages and selected effects

While not claiming that the immune system would be able to recognize any of these notions of function, they nonetheless raise some important questions about the evolution of immune systems, especially their co-evolution with microbes. What are the biological advantages for host organisms and their microbiota? What have they been selected for? The answers might be found in what the microbes are doing, rather than their mere presence. Beyond fighting off pathogens, establishing symbiontic relationships is a process in which the immune system is of crucial importance. Both microbes and the immune system play a central role in the development and evolution of these communities of organisms. To mention just one example: Chiu and Gilbert argue that this kind of niche co-construction was essential for the evolution of herbivory in ruminants (2020). With the immune system being a key player in these processes, they also stress that the immune system itself is continuously co-constructed by the host and its microbes (Chiu and Gilbert, 2020, p. 460).

For the co-adaptation and co-selection of certain microbial traits, the immune system needs to be able to recognize such microbial functions, i.e. biochemical activities and biological roles, in the first place. I have argued in the previous sections that there is good evidence for this to be the case. Recall from section 2 that the evolutionary and adaptionist questions concern different explanatory aims than the one addressed in this paper. However, by using the framework of different notions of structure and function, and putting more emphasis on function, these interesting questions can be addressed with more clarity in the future – when "rethinking the role of immunity" (Bosch, 2014).

6. The immune system can recognize different kinds of microbial structures and functions

After going through the philosophical, historical, systematic analysis and evidence for what it could mean for the immune system to recognize microbial functions and how that is possible, we can answer the title question affirmatively:[3] in addition to microbial structures, the immune system can in fact recognize microbial functions in terms of biochemical activities and biological roles. The philosophical analysis of different notions of structure and function results in some conceptual clarification and scientific hypotheses for how the immune system is able to recognize different kinds of microbial structures and functions.

The point is not to pit one against the other. But since the focus has almost exclusively been restricted to recognition of structures, putting more emphasis on functional aspects will be important for future research, following the hypotheses put forward. Several immunological phenomena can be explained by recognition of functions, others by recognition of structures. There is a kind of explanatory pluralism where the right explanatory tool might differ in individual scenarios. The resulting pluralism of explanantia and explananda is not necessarily an undesirable feature, as the immune system itself consists of a plurality of entities, processes, mechanisms, and sub-systems. Restricting the view exclusively to three-dimensional structures means missing out on the other kinds of structures and functions that also play an important role in immunological recognition. In the words of Ruslan Medzhitov:

[3] That is, unless one insists on reserving the term 'function' only for the selected effects notions of function and would label the other causal role notions just as 'effects' (Doolittle et al., 2014). However, this would mean a divergence from the language that immunologists and other scientists use; I believe that the framework developed in the present paper, based on the distinction of "four notions of biological function" by Wouters (2003) is a viable approach, to which immunology provides a novel perspective. I thank the reviewers for making me stress this point more explicitly.

> Pattern recognition also does not explain immune responses to transplants and to most allergens. However, there is no other theory (and there may never be) that can explain all immune responses, simply because they do not all follow the same rules. [...] different theories need not be competing, so long as they explain distinct phenomena. (Medzhitov, 2009, p. 769)

With the perspective of including functions in the picture for immunological recognition, the "pattern recognition concept will continue to evolve and eventually integrate with other concepts into a more general theory" (Medzhitov, 2009, p. 772). Biochemical activities, like protease activity, have been shown to be a characteristic of many allergens (Sokol et al., 2008; Reithofer and Jahn-Schmid, 2017). Structural recognition by IgE antibodies has proven insufficient for explaining allergies, whereas their functions remain a more promising – yet under-investigated – place to look. Thus, focusing on functions rather than structures might also be a useful change of perspective for understanding allergies (Bufe, 1998; Palm et al., 2012), vaccinations (Van Regenmortel, 2016), and autoimmune diseases (Theofilopoulos et al., 2017; Gianchecchi and Fierabracci, 2019). Although much remains hypothetical and speculative at this point, the suggested distinction between different notions of structure and function, together with the hypothesis that the immune system is able to recognize them, could serve as a step in the direction in which more evidence has to be collected. But it also leaves some open questions which need to be addressed in the future, both conceptually and experimentally.

Immunology should not only take structural models into account, but also consider functions for experiments and theories concerning immunological recognition, which include mechanistic and mathematical models (Baetu, 2014). Even if function remains a "loose concept" (Löwy, 1992), it provides a promising perspective for addressing some pressing issues within and beyond the disciplinary boundaries of immunology. Putting functional features into the center of attention for immunological recognition also has consequences for accounts and immunological theories like the "discontinuity theory" (Pradeu et al., 2013; Pradeu and Vivier, 2016). In addition to recognizing sudden changes in the repertoire of structures that are present, microbial functions and their sudden changes might be recognized by the immune system.

7. Conclusion

The main purpose of this paper was to address the title question: can the immune system recognize microbial functions? I argued that it can, based on a conceptual analysis of the

notions of structure and function. I defended the claim that there are microbial products and other – still structural – effects that are recognized by the immune system as indicative of "what is going on" rather than "who is there". I introduced the term 'function-associated molecular patterns' (FAMPs) for this kind of recognition of structures that shifts the narrative of how the immune system deals with the recognition of (and response to) such structures. Rather than monitoring certain taxa as pathogenic, or restricting the focus to damage and other harmful effects of microbes, this perspective has conceptual consequences that are in line with how the host-microbiome interactions are generally viewed recently. This picture has begun to shift away from the idea that the immune system's main purpose is to fight off pathogens as a well-defined class of taxa, structural patterns, or sequences. By opening up the perspective to functions, including neutral and even useful functions from the host's perspective, the recognition of FAMPs can be considered in line with most recent immunological theories, while providing a needed update in the context of microbiota and MAMPs.

Besides this modest shift in perspective, for which a broad scientific consensus is to be expected, I put forward a more controversial hypothesis: that there exist sensors that can directly recognize microbial functions irrespective of their structural manifestation, i.e. in the form of biochemical activities and biological roles. There are some well-documented recent examples in the scientific literature supporting this idea for functions understood as biochemical activities; for functions as biological roles to be recognized by the immune system, network structures might need to be taken into account as recognizing agents, rather than simple pattern recognition receptors. How these interactions and dynamics operate to recognize and respond to microbial functions promises to be a fruitful line of research. Whether this hypothesis turns out to be true and can be supported by more observations is up to empirical testing, for which I hope the suggested conceptual distinction between different notions of structures and functions will be useful.

Philosophical debates about notions of biological function can be fruitfully applied to exploring these immunological hypotheses, while at the same time fueling novel perspectives on different notions of function, their explanatory goals, their epistemic and ontological status, and integrative pluralism. In particular, immunological recognition allows to defend systemic causal role accounts of function against the accusation of not being sufficiently objective and realist. Future research will permit to explore and assess this hypothesis and its philosophical implications in more detail.

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