Biological Theory (2023) 18:210–224
https://doi.org/10.1007/s13752-023-00433-5

ORIGINAL ARTICLE

What Counts as an Immune Response? On the Role of Abiotic Stress in Immunology

Sophie Juliane Veigl[1]

Received: 11 July 2022 / Accepted: 21 February 2023 / Published online: 23 March 2023

Abstract

In the postgenomic era, interactions between organism and environment are central in disciplines such as epigenetics, medical physiology, and immunology. Particularly in the more "applied" medical fields, an emphasis lies on interactions of the organism with other organisms, that is, other living things. There is, however, a growing amount of research investigating the impact of abiotic triggers on the immune system. While the distinction between biota and abiota features heavily in other contexts, its status is not explicit within immunology. Do immunologists distinguish living from nonliving triggers? In this article, I will carve out whether and in which ways the biotic/abiotic distinction operates in immunology. I will look into responses to biotic and abiotic stressors in plant and invertebrate model species and ask how and why they are conceptually separated. I will trace the reasons by investigating the disciplinary situatedness of immune phenomena and the import of vertebrate immunology when conceptualizing immune responses in other model organisms. I will then investigate how the convergence of biotic and abiotic stress responses in plants and invertebrates adds to the recent philosophical programs advocating an ecological perspective on immune systems.

Keywords Biotic/abiotic distinction · Eco-immunology · Environment · Invertebrate immunology · Model organisms · Philosophy of immunology · Small RNAs · Taxonomic bias

Introduction

The distinction between biotic and abiotic stress is probably one of the least questioned dichotomies in physiological research. At the same time, it is one of the most ubiquitous, applicable to mammalian, invertebrate, plant, and prokaryote stress responses. The biotic–abiotic distinction divides things that exist into those that live and those that do not live. In doing so, it rests on an immediate intuition that a meaningful distinction can be made between, for example, my cat and my mat. For the study of stress responses, the biotic–abiotic distinction translates into the demarcation of the following groups of stressors: Viruses, bacteria, yeasts, fungi, or helminths are "biotic stressors." Heat shock, osmolarity, heavy metals, or radiation are "abiotic stressors."

The separation of biotic and abiotic stressors is sometimes not entirely straightforward or undisputed. For example, nutritional deficiency is classified as an "abiotic" stressor, even though food sources comprise living and dead matter (Shiriam et al. 2016). On the other hand, it is possible to question, or at least discuss whether viruses or, say, transposons are truly biotic, i.e., living (Godfrey-Smith 2009; Griesemer 2014; Koonin and Starokadomskyy 2016). Also, herbivory is often considered a biotic stressor, as it is caused by an organism, even though the result of herbivory is the physical damage of plant parts (Saleem 2017). The above-discussed issues concern the very definition of the criteria to count as "living" (Durand 2020).

It is not the goal of this article, however, to assess the categories of "biota" and "abiota" in terms of necessary and sufficient conditions. The question, instead, is whether and to what extent the differentiation is a guiding principle in immunology and what are the philosophical implications. One crucial philosophical consequence lies in the conceptualization of the environment. Recent developments in eco-immunology move away from viewing the immune system's primary task in providing "mechanisms of insularity" (Gilbert and Tauber 2016) but emphasize its role in "how the organism becomes an integrated constituent of a

✉ Sophie Juliane Veigl
sophie.juliane.veigl@univie.ac.at

[1] Department of Philosophy, Universität Wien, Vienna, Austria

large community" (2016). The question is, however, what is the place of abiota in this community? If immunology is extended to incorporate responses to abiotic triggers, how and where to draw the boundary of immune phenomena? How well do cognitive metaphors and agential thinking, omnipresent in immunological discourse, sit with responses to abiotic stimuli? Despite a general consensus that the immune system interacts with abiotic triggers, these questions still need to be addressed.

In this article, by investigating the small RNA-based stress responses of an invertebrate and a plant model organism (MO), I will first show how a particular version of the biotic/abiotic distinction is more or less tacitly assumed in these MOs. I will then question the validity of the distinction, arguing that responses to biotic and abiotic stressors mechanistically converge. I will proceed and inquire about the philosophical consequences of this convergence. First, I will ask how the disciplinary situatedness of certain sets of phenomena, such as immune phenomena, influences the conceptual resources at work. I will argue that the role abiotic triggers play in vertebrate immunology influences conceptualizing immune responses in invertebrates. Second, I will inquire how this situation bears on more prominent debates in immunology and its philosophy: How does the inclusion of responses to abiotic triggers influence our notions of immunity? How do cognitive metaphors square with interactions of the immune system with abiotic triggers? And, how does a denaturalization of the biotic/abiotic distinction contribute to eco-immunological perspectives? In short, I will consecutively argue that the mechanistic convergence between small RNA responses to biota and abiota (1) obtains; (2) is not acknowledged in current invertebrate and plant immunology; but (3) matters.

Small RNA Responses to Biotic and Abiotic Triggers in Invertebrates and Plants

In this section, I will first introduce some basics about small RNA biology and then move on to discuss small RNA responses to biotic and abiotic stimuli in a plant and an invertebrate MO. Quite generally, small RNAs are non-coding RNAs studied for their regulatory roles in almost all known species. Studies on small RNA-related effects in the 1980s and 1990s culminated in identifying the phenomenon of "RNA interference" (Fire et al. 1998), referring to the fact that small RNAs interfere with, that is, change, gene expression (Veigl 2021). Small RNAs' primary mode of action is the complementary binding of target RNAs, although mismatches are sometimes tolerated depending on the particular class of small RNAs (Saxena et al. 2003). To ensure this targeting, small RNAs often rely on other effector proteins. Small RNAs are best known for targeting and sometimes destroying complementary messenger RNAs, inhibiting the synthesis of a specific protein. Small RNAs are involved in several regulatory tasks, such as defense against selfish genetic elements (Malone and Hannon 2009), metabolic regulation (Cai et al. 2009), and defense against viruses (Hamilton and Baulcombe 1999). Several different small RNA species are defined based on different biochemical properties. Across MOs, however, tasks of particular species of small RNAs vary. Thus it is essential to point out before going into the details of small RNA responses in a particular MO that these are not general claims and cannot be extrapolated easily onto other model species or even transformed into general sentences.

In almost all organisms that display small RNA-based gene regulatory circuits, small RNAs have been implicated as important regulators of stress responses to biotic and abiotic triggers. In plant and invertebrate immune systems, small RNA responses to viral infections are believed to be critical effectors of what is generally perceived as the "innate" immune system. In these scenarios, small RNAs, together with other immune effectors, guarantee resistance to these triggers by implementing gene regulatory changes that guarantee specific resistance to the particular trigger. In the subsections to follow, I will focus on small RNA immune effector functions.

While small RNAs are generally handled as immune effectors in invertebrate and plant contexts, I will not presuppose this verdict but consider some properties of small RNAs that qualify them as immune effectors. First, small RNAs are responsive to a host of different stressors, amongst them pathogens. Second, small RNA responses to stressors are specific—a particular immune response is only launched against a particular pathogen. Third, small RNAs are immune effectors from a system perspective: they interact with other effector molecules of the immune system. Fourth, small RNAs persist and guarantee extended resistance against particular stimuli. They are, thus, also capable of ensuring immune memory. Philosophers of immunology tend to agree with this characterization. For instance, Pradeu characterizes small RNAs as immune effectors (Pradeu 2011; Pradeu 2020). Not only invertebrates and plants display small RNA-based immune functions. While there is a small RNA arm of the jawed vertebrate immune system, it is generally treated as neglectable, for it operates much slower than cell-based immune responses (Parameswaran et al. 2010; Cullen and Cherry 2013). In the remainder of this section, I will discuss small RNA-based responses to biotic and abiotic triggers in an invertebrate and a plant model system.

Arabidopsis thaliana

As is the case for most non-jawed vertebrate immune systems, plant immune systems are most of the time

characterized by a "lack of." In particular, plants are considered to lack cell-based and adaptive immunity. Plant immune responses are generally classified as those launched against biotic stimuli, such as viruses, bacteria, helminths, or fungi (Islam et al. 2018). Plant immunity has many different effectors, such as PAMP-triggered immunity, Avr effector-triggered immunity, cytokinins, volatiles, and small RNAs (Jones and Dangl 2006; Katagiri and Tsuda 2010). I will focus here on the small RNA-based arm of plant immunity; however, it is essential to note that on a systemic level, small RNA effects and other effector mechanisms are linked.

I will consider one particular MO, the thale cress *Arabidopsis thaliana*. Relatively uninteresting from an agricultural standpoint (compared to MOs such as tobacco and maize), *Arabidopsis* had become the prime MO for plant genetics in the 1990s (Leonelli 2007a). A handy MO because of its size, short generation time, large number of offspring, and relatively small genome size, the body of knowledge generated from *Arabidopsis* research has brought about trailblazing discoveries in several fields within plant biology (Leonelli 2007a). Projecting *Arabidopsis* results onto (agricultural) plants in general is often justified by the assumption that basic mechanisms ought to be applicable to other plants, particularly because of *Arabidopsis*'s close genetic relatedness with other flowering plants (Leonelli 2007a). *Arabidopsis* is both a model of all flowering plants as well as a model of the molecular processes individuated by flowering plants (Leonelli 2007b).

In *Arabidopsis thaliana*, small RNAs have been shown to respond to a host of different biotic and abiotic triggers, such as fungi, viruses, bacteria, heat, cold, and drought, amongst others (Liu et al. 2008; Nishimura and Dangl 2010; Seo et al. 2013; Zhang 2015). There are, basically, two possible mechanisms of action. Small RNAs can target a particular trigger directly, that is, complementarily target the sequence of the trigger, as is the case for viral RNAs. Or small RNAs cause specific changes in gene regulation by complementarily binding to mRNAs involved in different aspects of plant growth, development, or seed germination, amongst others. In these cases, small RNAs are triggered by the recognition of the pathogen through other mechanisms.

The case of viral infection in plants is somewhat special since it triggers the biogenesis of antiviral RNAs, small RNAs that are complementary to the virus and thus realize specificity to a trigger by their collinearity. Viral infections, along with bacterial, fungal, or helminthic infections, also trigger gene regulatory cascades through the up- or downregulation of many other small RNAs. The particular up- or downregulation profile is specific to the particular trigger, leading to physiological changes that ensure antimicrobial resistance. These small RNA-based gene regulatory cascades also occur when *Arabidopsis* is confronted with stimuli such as cold, heavy metals, hypoxia, or UV-B radiation. As with biotic triggers, small RNA-based cascades lead to changes in plant morphology, seed germination, or root development, amongst others. Thus, trigger-specific responses are ensured both in the complementary-based example of antiviral small RNAs, in small RNA-based responses to other pathogens as well as abiotic stimuli.

Caenorhabditis elegans

I shall next examine small RNA responses in the invertebrate MO *Caenorhabditis elegans* (*C. elegans*). The *C. elegans* MO was established starting in the 1960s in a genetics as well as neurobiology context and became in 1988 the first multicellular organism to be fully sequenced (Ankeny 2001). *C. elegans* was selected because of its rapid life cycle, a simple reproductive cycle and genome, as well as its small size. Furthermore, *C. elegans* has a predefined number of cells (around 1000, the specific number depending on whether the individual can self-fertilize or not) and is transparent. Most *C. elegans* research is situated in genetics and development and *C. elegans* is regarded as one of the most "basic" models for development in animals.

As in plant systems, small RNAs are usually considered effectors of the innate immune response in *C. elegans*. The *C. elegans* immune system is generally believed to cope without dedicated immune cells and rely besides its small RNA arm on several different signaling cascades, involving MAP-kinase, insulin, and TGF-beta signaling pathways and effector molecules such as antimicrobial peptides, lysozymes, and reactive oxygen species (Engelman and Pujol 2010; Ermolaeva and Schumacher 2014). In the context of the nematode's immune system, small RNAs are mainly studied for their role in antiviral immunity (Wilkins et al. 2005), but new results in *C. elegans* have also reported small RNA-based resistance to bacteria (Kaletsky et al. 2020).

Small RNA-based responses have, however, also been reported for several abiotic triggers, such as heat, starvation, and high osmolarity. Most recent studies on small RNAs in the *C. elegans* stress response have been conducted on a systemic level, that is, changes in small RNA concentrations are globally monitored. Current studies primarily describe quantitative effects. Let me thus explain the particularities of quantitative changes in small RNA pools after exposure to biotic and abiotic stressors.

There are millions of small RNA molecules in each cell. They compete for effector molecules. These effector molecules are involved in small RNA-based silencing. As effector molecules are limited resources, changes in small RNA concentration will change the gene-regulatory landscape. Because small RNAs are responsive to environmental triggers, the equilibrium of types of small RNAs changes if exposed to environmental triggers, i.e., more trigger-induced

small RNAs compete with other species of small RNAs for effector molecules (Sarkies et al. 2013; Veigl 2017). Thus with changes in effector molecule occupancy, changes in small RNA-based silencing are likely to ensue.

The "small RNA state" is the resulting equilibrium following exposure to a particular environmental trigger. Trigger-induced RNAs are heterogeneous and partially specific to the particular trigger. I will discuss two examples, one concerning a biotic, the other an abiotic trigger. As for plant-based small RNA responses, the encounter of viral RNAs leads to the synthesis of small RNAs complementary binding viral sequences (Rechavi et al. 2011). In addition, other infection-induced small RNAs target endogenous mRNAs in the course of infection and thus induce gene regulatory changes (Ren and Ambros 2015). This is also the case for abiotic triggers. For instance, it has been reported that after starvation, changes in pools of small RNAs can be monitored, amongst them, e.g., small RNA species that regulate yolk-protein coding mRNAs (Rechavi et al. 2014). These gene regulatory changes involve changes in food metabolism and how much yolk is packaged into the roundworm's eggs, suggesting a specific response to food deprivation. In the case of such quantitative studies investigating small RNA responses in *C. elegans*, it is important not to associate a particular small RNA species (that is, the group of small RNAs that display the same sequence) with the resistance. It is the RNA state that changes; thus, for example, decreasing concentrations of other RNAs that were not directly triggered by the environmental stimulus are necessarily part of the small RNA response to an environmental stimulus.

In Search of the Biotic/Abiotic Distinction

In the previous section, I have demonstrated that small RNAs are immune effectors that provide specific resistance to biotic and abiotic stressors. It is, however, interesting to note that small RNA-based responses to abiotic triggers are generally not discussed within the plant or invertebrate immunology literature.

Let me provide some examples: In attempts to define the plant immune system, accounts emphasize exclusively the immune system's interactions with the biotic world by focusing on plant–pathogen interactions (Nishimura and Dangl 2010) or describe the plant immune system as "a system that allows plants to resist attack from a wide variety of organisms ranging from viruses to insects" (Bentham et al. 2020). Most of the time, the immune system and the abiotic stress-signaling networks are treated as distinct matters (Dong et al. 2015; Bentham et al. 2020). Often, abiotic stress is not considered at all when discussing immune responses (Katagari and Tsuda 2010; Li et al. 2017). This also has methodological implications, using, for example, data from known abiotic gene regulatory networks as a control to study immune regulatory networks (Dong et al. 2015).

Recent scholarship in plant immunology has, however, emphasized the importance of studying immune and abiotic signaling networks together but nevertheless treats abiotic responses as distinct from immune responses (Jones and Dangl 2006). Instead, these strands of research inquire about which nodes both signaling networks converge (Nobori and Tsuda 2019). When biotic and abiotic stressors are considered together, research questions are raised in a way that asks for the effects of abiotic stressors on the immune system as in, for instance, increasing disease susceptibility, or how the plant fine-tunes immune responses in response to other environmental stimuli (Alcazar and Parker 2011; Nejat and Mantri 2017). Thus, plant immunologists consider the immune system "tunable" by abiotic stressors but only tunable with regards to pathogen (biotic) resistance (Nobori and Tsuda 2019). They observe "environmental modulation of plant immunity" and "roles for immune regulators in abiotic stress tolerance" (Saijo and Loo 2020). That the immune system might provide immunity to the abiotic is not part of these considerations, which is also mirrored in linguistic choices, describing responses to abiota as "resistance" or "tolerance," but not "immunity."

A somewhat striking finding is that frequently, small RNAs are not even mentioned as immune effectors or only casually mentioned for their involvement in virus response. Instead, researchers focus on pattern-triggered and receptor-triggered immunity (Nimchuk et al. 2003; Katagari and Tsuda 2010; Bentham et al. 2020), processes that are somewhat similar to vertebrate innate immunity. Most of the time, small RNA-based immunity is discussed in separate articles and reviews that exclusively consider the contributions of small RNAs to immunity. In these reviews, only small RNA responses to biota are considered (Padmanabhan et al. 2009; Seo et al. 2013).

Similar observations can be made for the case of *C. elegans*. When describing immune functions in general, only responses to biotic triggers are considered (Engelmann and Pujol 2010). Much like the case of plant model systems, if abiotic stressors are mentioned, it is by asking how two separate signaling systems—the immune response and the abiotic stress response—interact (Ermolaeva and Schumacher 2014). As for the plant example, the induction of general stress resistance through immune signaling is considered, but not whether small RNAs can provide specific resistance to particular abiotic stressors (Millet and Ewbank 2004; Nicholas and Hodgkin 2004; Ermolaeva and Schumacher 2014). Similar to the case of discussing small RNAs in plant immunity, small RNAs are seldomly specifically mentioned when discussing worm immunity in general, but there are separate papers that focus on the role of (biotic stress-induced) small RNAs in worm immunity.

Mechanistic Convergence and the Biotic/Abiotic Distinction

Even though there are several similarities of small RNA-based responses to biotic and abiotic stressors in invertebrates and plants, these similarities are not thematized in the immunological literature. Abiotic stress responses are not considered part of, but at most potential influences on the immune response. Given this status quo, let me thus formulate an argument why small RNA-based responses to biotic and abiotic stressors should be considered part of the immune response. Particularly in the plant immunology field, researchers have observed a certain convergence of abiotic and biotic stress responses, meaning that effectors have been reported to be involved in both types of pathways (Ramegowda et al. 2020; Tajima et al. 2020). With the small RNA example at hand, I shall, however, give the convergence argument more substance—not only are some effectors involved in both types of responses, but the small RNA-based system shows mechanistic convergence. This claim is more extensive since it does not only hold that certain entities might be part of (different) biotic and abiotic stress response mechanisms, but that certain entities engage in the same or similar activities (i.e., they realize the same mechanism) both in biotic and abiotic stress responses.

I will provide a detailed mechanistic argument in what follows. Small RNA responses to abiotic and biotic triggers converge at the mechanistic level. Response to a particular stimulus (be it biotic or abiotic) leads to small RNA-caused gene regulatory changes and changes in the small RNA state guaranteeing specific resistance to that stimulus. Immunity thus also seems to be regulated in a specific way, respective to the particular trigger. Take the cases of small RNA responses in *C. elegans* as an example. Even though there are slight differences in implementing immunity against a virus or starvation, the mechanisms concur at the relevant level—they engage the same effector proteins and install immunity through the same principle (complementary binding). For the case of starvation-induced gene expression changes, the change in RNA-state seems more straightforward, as, given the wide-reaching physiological impact of starvation and the many gene-regulatory changes it requires, numerous species of small RNA molecules change concentration (Rechavi et al. 2014). This is, however, also the case for the virus example. An increase in one particular species of small RNAs, in this case, virus-derived small RNAs, leads to changes in overall concentrations (Sarkies et al. 2013). Given that small RNA effectors are limited resources, an increase in one small RNA species leads to, for example, fewer small RNAs of a different species. Thus, both responses—the one following the biotic and the one following the abiotic triggers—converge at the level of small RNA pool changes. In conclusion, small RNA-based immunity to biotic and abiotic triggers is equally caused by specific changes to small RNA states.

Is mechanistic convergence, however, sufficient to lift the distinction between responses to biotic and abiotic triggers? Mechanistic convergence is a fairly common phenomenon that might not on its own justify drawing deep analogies. Two intuitions about the distinctness of biotic triggers immediately come to mind: (1) The interactions of organisms with biotic triggers are distinct because of the versatility of the biotic, the complexity of the interactions, and the evolutionary arms race engaging the host and the pathogen. (2) The nature of the functioning of the immune system is deeply rooted in its interaction with biotic triggers: immune systems respond to biotic threats, a threat that goes into the body, replicates, and persists.

The first intuition concerns biological individuality. Interactions of the host with biota shape the target organism in particular ways over evolutionary timeframes. The arms race between the organism and its biotic environment brings about specific innovations (Anderson et al. 2010; Stern and Sorek 2011; Hoffmann et al. 2015): if we look at evolutionary timeframes, the biotic/abiotic distinction becomes empirically adequate. It is possible to reject this concern by separating the evolutionary and the physiological individual (Pradeu 2016). While from an evolutionary perspective there might be differences between interactions with biota and abiota, the same might not be valid for the physiological, immunological perspective focused on one generation.

It is not, however, necessary to give in as much. Abiotic stimuli had tremendous effects on the evolution of organisms. The most dramatic example is probably the great oxygenation event (Dorado et al. 2010). The effects of interactions with abiotic environments over evolutionary timeframes are, however, studied in different disciplines, such as genetics or paleontology. Given that some small RNA-based responses to environmental triggers persist transgenerationally (Rechavi 2014) (a topic not central to this article's arguments), the evolutionary importance of the immune system's interactions with abiota does not seem entirely off the table. RNA-based immune systems, thus, might not only bridge the biotic/abiotic divide but also physiological and evolutionary perspectives (Veigl 2022a, b). In addition, as I shall discuss in more detail below, the mechanistic and evolutionary convergence of (abiotic) stress responses and immune signaling is currently also discussed in vertebrate immunology (Swiatczak 2020). In conclusion, interactions with biota or abiota cannot be strictly separated by the extent they affect the organism.

The second intuition is functionalist: shouldn't we understand immune systems by how they function, the most

explicit characteristic of their functioning being responding to a biotic threat located inside the body? Biota are characterized by particular emergent properties, such as metabolism and reproduction. It is precisely these properties that guarantee immune interactions: they are signals of presence, replication, and persistence. In short, the way the immune system functions is through interactions with unique properties of the living. Current developments in immunology and its philosophy, however, dissuade this perspective. For instance, recent critiques of the self/nonself model are primarily rooted in finding the idea of the organism (self) fending off pathogens (nonself) empirically inadequate. Instead, the philosophy of immunology favors a view of the immune system as one that is not triggered by interactions with exogenous substances and pathogens but by the context of the interaction (i.e., the trigger's degree of discontinuity). Immunogenicity is thus not solely explainable by the threat posed by biota or the "foreign." Rather, immunity becomes a more contextual property. While the abiotic environment has so far been acknowledged as part of the background producing a particular context, small RNA-based responses suggest that they might also have more active engagements with the immune system. The small RNA state produced through the convergence of biotic and abiotic small RNA signaling pathways (and other "physiological" small RNAs) provides a readout of the organism's current interactions with the environment.

Given that reasons to distinguish biota and abiota entirely in immunology a priori are not too immediate, it is now upon me to question why the distinction is in place in invertebrate and plant immunology. Furthermore, it is necessary to carve out how exactly the distinction is operational, given that abiotic triggers are not entirely neglected but admitted as "fine-tuners" of the immune system.

How the "Soft" Biotic/Abiotic Divide Came to Operate on Small RNA Responses in Invertebrate Immunology

If I have been successful in arguing that the mechanistic convergence of small RNA-based responses to biota and abiota justifies both types of responses being understood as immune responses, it is now necessary to investigate why the biotic/abiotic divide is upheld within *C. elegans* and *A. thaliana* immunology.

Small RNAs were Born in a Biochemistry/Genetics Background

In previous sections, I argued that while small RNAs are recognized as immune effectors in plant and invertebrate immune systems, they are often not incorporated into general musings about immune systems but are instead dealt with in separate articles. Nevertheless, the implicit separation of responses to biotic and abiotic triggers is carried through in these articles, considering only those small RNAs responding to viruses, bacteria, helminths, and so on as immune responses. It thus seems necessary to ask: why doesn't the mechanistic convergence of responses to biotic and abiotic triggers induce a discussion or questioning of the biotic/abiotic distinction in these research fields?

To answer this question, we have to look at the disciplinary history of small RNA research. Small RNAs are somewhat new to immunological discourse. Even though, particularly in plants, RNAs have been hypothesized to be involved in defense mechanisms for almost a century (McKinney 1929; Sela and Applebaum 1962), their success story started in the late 1990s (Fire et al. 1998; Ruiz et al. 1998).[1] While the involvement of small RNAs with immune functions, particularly virus defense, was early to be established after the discovery of RNAi, the small RNA research field was primarily a geneticist and biochemist endeavor (Veigl 2021).

With the embeddedness of the small RNA field in these settings also comes a particular way of how small RNA responses to environmental triggers are discussed. Small RNA responses are embedded in the language of genetics. They are often considered "adaptive" in a genetic sense, that is, as potentially contributing to differential fitness, but not as "adaptive" in the immunological sense of the word. In the "genetic" literature on small RNA responses, the biotic/abiotic distinction is not operational: if small RNA contributions to adapting to specific environmental conditions are discussed, small RNA-based responses to heat, starvation, and virus infection are mentioned within one sentence, without invoking conceptual separations. In this background, the environment thus seems to be considered in its entirety. In addition, as argued before, even though there are specialized effector molecules for particular small RNA pathways, the interconnectedness of different small RNA pathways contributing to small RNA states is a guiding principle of small RNA biology (in their genetics/biochemistry situatedness) and further dissuades treating small RNA responses to biota or abiota separately.

The conceptual distinction of small RNAs into those that respond to biotic and those that respond to abiotic stressors in the immunological discourse was thus not imported from the original disciplinary context. In addition, many of the effects of small RNAs considered immune effector functions were not discovered in the disciplinary context of immunology. For instance, the most cited works on small RNA-based

[1] In fact, the fact that RNAs could trigger immune responses in the jawed vertebrate immune system was an important background hypothesis in the discovery of RNAi (Fire et al. 1998).

defense against viruses and bacteria were conducted in plant and invertebrate genetics and not initiated by an immunological/medical research objective.[2] Small RNA-based immunity was thus imported from a different disciplinary context and is not "native" in an immunological context. One trace of this "transfer" is that small RNA-based responses are often dealt with separately in the immunological discipline rather than in connection with other, more established immune effectors.

When it comes to discussing small RNAs and immune systems, a process of de- and re-situation takes place; small RNA-based effects are appropriated to fit immunological discourse. When importing small RNAs into immunology, only those small RNA responses launched against biotic stimuli were appropriated. Small RNA responses to biota were incorporated in the invertebrate and plant immunological literature. What counts as an immune response was predetermined by the presuppositions of the target discipline. It is, thus, necessary to enquire why invertebrate and plant immunologies presuppose that interactions with abiotic triggers do not fully qualify as immune responses.

Is There a "Soft" Biotic/Abiotic Distinction in Vertebrate Immunology?

While immune systems of all species are studied within immunology, it is fair to say that there is an extreme emphasis on the immune systems of jawed vertebrates. Invertebrate or plant immune systems, for instance, do not make it into the most influential immunology textbooks (e.g., Abbas 2017). As discussed in previous sections, many accounts of *C. elegans* and *A. thaliana* immune systems describe these systems referencing their similarities and dissimilarities from jawed vertebrate immune systems. On the one hand, they describe these systems in terms of "lack of," for instance, cell-based immunity. On the other hand, most reviews focus on those effectors that are somewhat comparable to jawed vertebrate immune systems, such as (protein) receptor-based signaling, and specifically those signal molecules that are homologous to effector molecules in mammals. When discussing invertebrate and plant immune systems in the literature, there is thus a strong tendency to appropriate immune phenomena in a discourse shaped by the properties of the jawed vertebrate immune system, in a way that suggests the biggest symmetry possible. Given this polarized perspective present in accounts of invertebrate and plant immune systems, it seems necessary to ask whether presupposing the biotic/abiotic distinction is also due to perspectives polarized towards vertebrate immunology.

Vertebrate adaptive immunity is usually viewed as an evolved property that sets apart jawed vertebrate immune systems from the immune systems of invertebrates, plants, and other eukaryotic and prokaryotic lifeforms (Flajnik and du Pasquier 2004; Netea et al. 2019), with the recent exception of CRISPR-Cas9-based immune systems in bacteria and archaea (Koonin 2019; Pradeu 2019). Entangled with the differentiation of adaptive and innate immune systems is the notion of specificity (Podolsky and Tauber 1997).[3] In general, specificity refers to the phenomenon that an immune response to a pathogen is targeted towards that pathogen (exclusively). The capacity to specifically respond to, and after a certain time, re-respond to a particular stimulus is reserved for adaptive immune systems.[4]

Immunological specificity is a good starting point to enquire about the biotic/abiotic distinction. Can an abiotic trigger be specifically recognized and re-recognized by the effectors of the adaptive immune system? And, does that response lead to "immunity" specific to that particular abiotic stimulus? Upon interaction with an antigen, B- and T-cells have the capacity to recognize this trigger through the match between their receptor and a specific "epitope," a molecular structure specific to that trigger presented to them by antigen-presenting cells (APCs). The capacity of B- and T-lymphocytes to recognize specifically almost any epitope is realized through a process called V(D)J recombination (Sakano et al. 1980). By recombining those parts of DNA that code for receptor fragments, each matured lymphocyte can recognize a molecularly unique epitope. Epitopes can, however, be recognized by several distinct receptors with varying degrees of affinity and avidity. Epitope binding alone, however, does not trigger an immune response, but a second trigger, such as costimulatory triggers from an APC, is needed.

How B- and T-cells interact with epitopes makes it hard to conceptualize how certain interactions with abiotic triggers

[2] There is one particular species of small RNAs, miRNAs, that attracted much attention after it was discovered that they have homologues in vertebrates, and, even better, mammals: miRNAs (for a short time called stRNAs) (Pasquinelli et al. 2000). Since then miRNAs were found to contribute to many developmental and disease phenotypes and have somewhat separated from the genetic/biochemical small RNA fields. Thus, with the "disease-relevant" small RNAs (at least in the vertebrate context) separated from the field, the genetic situatedness of remaining small RNA-types gets even stronger.

[3] At this point it is important to differentiate immunological from genetic specificity (Woodward 2010). While the notion of genetic specificity was initially imported from immunology and histochemistry (Kay 1989; Morange 2020) the notions are particularly situated within their disciplines and not coextensive. Roughly, immunological specificity describes a response that is particular to a trigger.

[4] There are exceptions such as trained immunity. Authors seem to agree, however, that such exceptions do not realize the phenomenon of adaptive immunity fully, but only some aspects of it (Pradeu and du Pasquier 2018).

would work. Many abiotic triggers are not corporeal. Rather than being entities, they are vectors, acting upon an entity. What translates into an epitope of "it is too cold" or "it is too hot"? How to interact with "there are too few food sources" or "it has been too salty"? Even more so, how could such exposures and reactions to these exposures be extinguished and subsequently relaunched?

At this point, it is necessary to specify different kinds of abiotic triggers. Amongst abiotic triggers, we have to distinguish between corporeal and non-corporeal triggers: Corporeal triggers exist because there is a body as a material realizer, whereas non-corporeal triggers do not have bodies as material realizers.[5] Corporeal triggers can be organic or inorganic triggers: those corporeal triggers whose molecular structure is determined by one or more carbon atoms are organic, whereas those corporeal triggers whose material realizers are composed of structuring elements other than carbon atoms are inorganic.

In the previous sections on small RNA-based immune responses in *Arabidopsis* and *C. elegans*, I have primarily examined non-corporeal triggers, such as, for example, temperature. How can the immune system specifically recognize coldness? Non-corporeal abiotic triggers do not have epitopes, *stricto sensu*. Given what is taken to make the adaptive immune system special, it is unclear how its specific memory of certain triggers could translate to non-corporeal abiotic triggers that are environmental conditions. How could the adaptive immune system ensure that after repeated heat shock, radiation, or starvation, the organism launches a more efficient response to these stimuli? The processes leading to adapting to these stressors are instead studied in genetics or epigenetics and thus concern different evolutionary timeframes.

How therefore does jawed vertebrate immunology deal with abiotic triggers? Immune cells must be responsive to abiotic stimuli. There are many substances, such as dead bacteria, immune stimulants like alum, deleterious crystals, RNAs, or synthetic antigens used within vaccines that can produce specific resistances (Sela 1983; Ulmer et al. 2006; Pardi et al. 2018). Also, immunologists study "sterile inflammation," meaning inflammation in the absence of pathogens, caused by, for example, cell death and tissue damage (Chen et al. 2007; Chen and Nunez 2010). Finally, given conditions such as fever, or temperature discrepancies between central and peripheral parts of the human body, immune cells are exposed to almost 10 ℃ in temperature variation. There must thus be a way that immune cells respond to and accommodate abiotic triggers.

To investigate this topic, it is essential to distinguish between immunogens and antigens. An immunogen is a trigger that causes an immune response. An antigen is a substance that can interact with immune receptors (antibodies, T-cell receptors). Immunogens can be biotic but antigens are not "living," since they are relatively small molecules. However, in the case of immune reactions to pathogens, antigens are derived from a living pathogenic trigger. They are, in a way, corporeal traces of the living.

While popularized and pedagogic texts about jawed vertebrate immune systems and many review articles describe the jawed vertebrate immune system as one that exclusively responds to biotic triggers and maybe mention corporeal abiotic triggers, ongoing research also studies responses to non-corporeal abiotic triggers. For instance, temperature is sensed by particular T-cells and induces several gene-expression changes, probably to prime them to activity in peripheral sites, where the body temperature is below 37 ℃ (Xiao et al. 2011). Stress-associated signals such as heat shock proteins can also induce the production of second signals. Other examples include osmolarity changes that can induce T-cell inflammatory responses to cellular and tissue stress conditions (Eddie and Medzhitov 2015) and nutritional status impacting immune cell metabolism and function (Alwarawrah et al. 2018). Finally, sterile inflammation involves cases where the trigger is neither biotic nor abiotic as in the case of wounds: here, inflammation is related to the absence of the corporeal. Of course, such scenarios are complex in that wounds also involve biotic corporeal triggers such as dying cells. Within vertebrate immunology there is, thus, no hard, explicit biotic/abiotic distinction since many different abiotic triggers' interactions with the immune system are being studied. Furthermore, non-corporeal abiotic triggers are considered for their effects on and the fine-tuning of other canonical immune effector functions.

There is, however, one area of immune system functioning where abiotic non-corporeal triggers have so far not been considered: adaptive immune memory. Also in these scenarios abiotic non-corporeal triggers are considered important fine-tuners (e.g., Appenheimer and Evans 2018), but adaptive immunity against abiotic non-corporeal triggers is (currently) not discussed. This, of course, necessitates the question whether it would even "make sense" for jawed vertebrates to guarantee adaptive immunity against abiotic non-corporeal triggers. There are certainly other phyla which have to deal with abiotic changes in the environment differently. Plants, for instance, cannot change location if environmental conditions are not favorable. Also, for organisms with shorter lifecycles than jawed vertebrates, such as *C. elegans*, any environmental fluctuation would last for a significant amount of time in the life of a roundworm. In

[5] I use corporeal in the above sense and not in the sense of "derived from a body." For instance, I consider synthetic proteins corporeal since they are materially realized by a body. A distance, for example, would be non-corporeal since it has no body as a physical realizer, but is material.

conclusion, it is empirically adequate to state that while there is no “hard” biotic/abiotic distinction operating in vertebrate immunology, there is a “soft” distinction, in that abiotic non-corporeal triggers are not currently investigated for their capacity of eliciting adaptive immune memory. This “soft” distinction, however, is not an unwarranted presupposition, but corresponds to current understandings of jawed vertebrate immune systems. It now remains to ask whether this particular understanding of the role of abiotic non-corporeal triggers in vertebrate immune interactions affects conceptualizations of immune responses in the invertebrate and plant contexts.

Disciplinary and Taxonomic Polarizations Govern Clashes of Representational Spheres

In previous sections, I illustrated how small RNA responses in invertebrates and plants converge at a mechanistic level and that, if we are prepared to consider small RNAs as immune effectors in general, there are no straightforward reasons for considering only small RNA responses to biotic triggers as immune responses. In the case of invertebrate and plant immune systems, both small RNA responses to biotic and (non-corporeal) abiotic triggers provide specific responses and confer specific resistance to the organism against a second trigger. The resistance is guaranteed in the same way given the mechanistic convergence of both pathways. Nevertheless, in the immunological literature on *A. thaliana* and *C. elegans*, non-corporeal abiotic triggers are only considered influences on, or fine-tuners of the immune system. Given the overwhelming dominance of jawed vertebrate immunity in the field of immunology, both historically and currently, and given how invertebrate and plant immunologists seem to make their discussions fit the jawed-vertebrate perspective, we have reason to speculate that they also adopted the jawed-vertebrate specific way of treating non-corporeal abiotic responses—as not capable of engaging in specific interactions that induce immune memory.

Let me thus propose a particular dynamics between the representational scopes of MOs in basic and applied research and how they interact if brought together (Fig. 1). It concerns particularly the sphere where basic research produced in invertebrate model organisms and applied, medical knowledge produced in vertebrate model organisms meet. The range of phenomena that will be studied when invertebrate MO basic knowledge gets transferred into a more "applied" subject such as immunology will be determined by the dominant MO, often representing the core objective of the discipline (e.g., understanding diseases of the human body), in the applied field. While processes studied in organisms such as worms and plants are often treated in basic research contexts as representing processes in "more complex" organisms, only those processes that correspond to processes studied in the more applied field and the "more complex" MO are admitted into the applied discipline, in our case, immunology. It is a clash of representational spheres that is determined by the institutional conditions of the target discipline. The MO of the target discipline repolarizes the organization of the phenomena of the source organism. Similarly to how other aspects of plant and invertebrate immune systems are discussed in regards to and whether they match processes in jawed vertebrate immune systems, the parts that are dissimilar to jawed vertebrate systems were left out in the small RNA case as well. Particularly, specific immune memory to non-corporeal, abiotic triggers is not considered.

In invertebrate and plant fields, there are, however, good reasons to challenge or change this perspective and explore ways of including (non-corporeal) abiotic responses as equal, stand-alone ways of immune function. As immune effectors, small RNAs provide specific responses to (non-corporeal) abiotic triggers that cause (prolonged) resistance to this trigger. In this section, I have traced why small RNA-based responses to abiotic stimuli in plants and invertebrates are not considered immune responses. I have also shown that the distinction between biota and abiota is complicated to wrestle with when it comes to immunological discourse. A full-blown biotic/abiotic distinction is neither explicit nor operational. Also, the distinction does not seem to be an “actor’s category”—a way practicing immunologists conceptualize their findings. Non-corporeal abiotic stressors are not ignored. But the immune system is not viewed as a system that guarantees specific resistance against a non-corporeal abiotic trigger after first having specifically interacted with that very same trigger. This perspective towards non-corporeal abiotic triggers seems empirically adequate in vertebrate immunology but influences the conceptual repertoire of other branches of immunology where evidence points into a different direction.

Towards an Eco-Immunological Perspective on the Immune System’s Interactions with Abiota

In the previous section, I investigated why in plant and invertebrate MOs, despite mechanistic convergence, small RNA-based responses to abiota are not considered immune responses. I have argued that even though this convergence obtains, it currently does not affect conceptualizations in invertebrate immunology. In this section, I will argue why this mechanistic convergence not only *obtains* but also *matters*, that is, it has significant consequences for several conceptual questions in immunology and its philosophy. I will particularly query into three interrelated subjects. Given the incorporation of non-corporeal abiotic triggers as immune

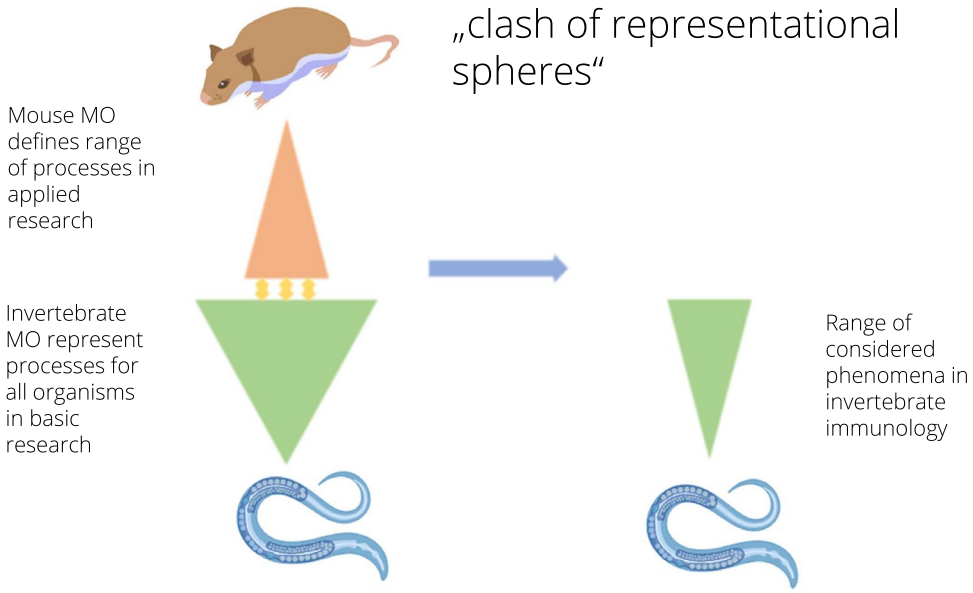

Fig. 1 Clash of representational spheres between basic and applied research contexts. Only the range of phenomena established in the "basic research" context that matches the phenomena studied in the "applied research" context is able to trespass disciplinary boundaries

responses, how is the conceptual border of what an immune phenomenon is reshaped? Do cognitive metaphors extend to "recognition" of non-corporeal abiotic triggers by small RNAs? How do small RNA responses to abiota sit with conceptions of immunity that dissuade agential thinking, such as eco-immunity? Considering response to abiota as part of the immune response, I will show, yields a fuller picture of the notion of "environment."

While organism–environment interactions represent one key area of interest in the current philosophy of immunology (Gilbert and Tauber 2016; Pradeu 2016; Suárez and Stencel 2020; Schneider 2021), interactions of the organism with the abiotic parts of the environment have not yet attracted much attention. Let me thus discuss what is at stake when expanding immune responses to the abiotic. Adding non-corporeal abiotic triggers as triggers the immune system can interact with suggests a conception of immunity that regards immune reactions as those reactions that enable the organism to become an integrated constituent of an environment. This perspective on immunology is labeled eco-immunology, calling for integration of immunology, developmental biology, and ecology (Demas and Nelson 2011). While eco-immunology has so far primarily considered environments as environments that house particular microbes, abiotic conditions are necessarily part of the environment. The question is whether they are in the background, or come to the front.

A more thorough consideration of responses to abiota also corresponds with recent trends in plant immunology, calling for integrating responses to abiotic environmental factors in the study of plant–microbe interactions (Saijo and Loo 2020). While considering abiotic factors conceptually expands the operational notion of environment in immunology and its philosophy, the inclusion of abiotic factors still maintains a precise notion of what an immune interaction is. Even more so, it is in line with systemic perspectives on immune interactions, which are currently popular within the philosophy of immunology (e.g., Pradeu 2011). Such perspectives regard the interactions of immune systems with environments as continuous. An immune response is triggered if there is a disturbance (i.e., a change in the continuity of the interactions). Including responses to abiota as immune responses still preserves immune triggers as results of continuous (i.e., embedded in the environment) interactions separated from those that are discontinuous, resulting from actions and/or agents. In short, it preserves the distinction between immune response and avoidance behavior. Similarly to how an immune reaction might be triggered if a change in the composition of the microbiome is too substantial in a certain context (the immune interactions are too discontinuous compared to those in a previous (steady) state), an immune reaction is triggered if a temperature increase or decrease is too sharp (i.e., discontinuous). Just as the immune system interacted at both time points with microbes, it also interacted at both time points with the outside temperature. The types of interaction partners are continuous, because they are embedded in the environment, and they are predefined as stimuli the immune system has the capacity to interact with, but changes in quantity or quality of these stimuli cause discontinuity and thus an immune reaction.

Nevertheless, the conceptual tie between immune systems and cognition and agency is a deep one, not only reflected in the use of cognitive metaphors in immunology but also through the ever-increasing number of reports on the interconnectedness of the immune and the neurological system (Koren et al. 2021; but also for small RNAs in *C. elegans* see Posner et al. 2019). However, despite including reactions

to non-corporeal abiotic triggers, a demarcation remains intact through the criteria of specificity and resistance. For instance, a fly that reacts to a flyswatter being swung would not be considered to be reacting specifically to the flyswatter (as opposed to a whack of my hand or a boulder rolling down the hill, towards the fly), or being resistant (through learning) to further exposures. This is because, as already primed in the previous paragraph, interactions between environmental components and the organism require degrees of correspondence between them. A flyswatter and the fly immune system cannot inform each other since the immune system can neither represent nor present the flyswatter. The above considerations suggest that we have a particular notion of certain "spheres" of encounter we believe cannot directly interact with each other because sufficient correspondence is not given. Nevertheless, the question remains whether the cognitive metaphor still obtains in interactions in a sufficiently similar sphere, namely whether the immune system "cognizes" abiota similarly to biota.

Tauber (2013) points out that there are two different theories of cognition that are employed in immunology—the representational and the nonrepresentational (presentational). Representational perspectives require cognitive mediation between the immune system and the antigen. The antibody can represent the antigen because both correspond, the immune system can be "informed" of the other. Presentational perspectives do not differentiate between the recognizer and the recognized; perception is locked into a system with no cognitive hierarchy. Thus "agency as a function of a subject processing data is replaced with perception conceived as the system's disturbance" (Tauber 2013, p. 246). The antigen is not a representation but a component (that breaks linkages/causes disequilibrium).

Corresponding with its fit with an eco-immunological perspective, the small RNA-based responses fit with the presentational take on the cognitive metaphor. According to Gibson, perception requires resonance between cognitive structures and sensory data—environment is already organized as meaningful, the world is already seen as a direct presentation (Gibson 1979). This view also presents an alternative to the self/nonself model because meaning arises within the system itself. "When selfhood frames immune functions, coupling agency to representational modes of perception completes a portrait of the biological subject, who navigates the world with a cognitive apparatus borrowed from human models" (Tauber 2013, p. 255). Another related approach argues that immune "learning," "memory," "recognition," and so on, are functions of the entire organism (Maturana 2002); the cells and molecules comprising the immune system are not themselves cognitive except as used metaphorically in their physical descriptions. This point has also been made elsewhere regarding genes and agency, arguing that many biological terms are just metaphoric extensions of ourselves (Wilson 2005).

Particularly with abiotic non-corporeal triggers, the representational model seems not applicable—is the correspondence between organism and world ensuring the informing of the immune system, leading to higher-order processing? Can any immune effector "represent" increased temperature similarly to how an antibody represents an antigen to the immune system (Tauber 2013, p. 243)? Self-ness also requires a certain correspondence between the cognizer and the cognized, making it difficult to understand how a particular temperature could be more or less self than a different temperature. The idea of the small RNA state moves away from this perspective. Instead, the presentational version of the cognitive metaphor aligns with the small RNA state and the idea of mechanistic convergence. No single entity can represent the environmental trigger. Changes in small RNA equilibria present the current status of the system; the system knows but is not informed, because the small RNA state continuously mediates between organism and environment. Thus, it also seems no surprise that it is precisely the level of the small RNA state on which responses to biota and abiota converge, as this is also the place where immune "cognition" operates in the ecological rendering of the metaphor.

In this section, I have argued that incorporating small RNA responses to (non-corporeal) abiota as immune responses because of their mechanistic convergence suggests an eco-immunological perspective. Adopting the presentational reading of the cognitive metaphor, it is exactly the small RNA state—shaped by small RNA responses to biotic and abiotic triggers—that presents the organism's interaction with the environment. Consequently, both agential perspectives on immune systems that rest on the creation of selfhood and individuality are dissuaded and "acknowledged as products of the third person point of view" (Tauber 2013, p. 259).[6]

[6] Buying into the ecological reading of the cognitive metaphor also bears on another central issue in immunology and its philosophy, namely individuality. The eco-immunological perspective dissuades a version of immunological individuality that is based on self-nonself discrimination but regards individuality as embedded in and continuously renegotiated with the (biotic and abiotic) environment. While notions of the environment in eco-immunological discourse usually focus on biota, particularly bacteria composing the holobiont, the mechanistic convergence of small RNA responses to biota and abiota might provide a way to include a fuller notion of the environment in the eco-immunological perspective. The full bearing of considering abiota in configuring physiological individuality, however, needs to be dealt with elsewhere.

Conclusion

In this article I have examined the salience of the biotic/abiotic distinction within the immunological discipline. I have questioned why a particular set of phenomena in an invertebrate and a plant MO—small RNA-based responses to environmental triggers—are not treated as a cohesive set of processes but are separately discussed: small RNA-based responses to stress from the biotic part of the environment as immune responses, small RNA-based responses to stress from the abiotic part of the environment as generalized stress responses. I have asked whether and why a distinction between biota and abiota is operational in invertebrate and plant immunology. I have argued that a clash of representational spheres (between the dominant MO of immunology and the dominant MOs in "basic research" disciplines in which the phenomena were uncovered initially) that is governed by strong taxonomic polarities leads to the application of the soft biotic–abiotic divide—that non-corporeal abiotic triggers are not considered capable of priming immune memory towards them—in plant and invertebrate immunology.

While prominent in other parts of (the philosophy of) biology, such as evolutionary biology, the biotic/abiotic distinction is not as explicit in immunology. Textbooks on immunology do not commence with differentiations of what lives and what does not live, what is corporeal and what is non-corporeal, and neither do review articles mention this distinction when introducing immune systems. Nevertheless, the distinction is implicitly operational: researchers focus on how non-corporeal abiotic triggers might affect or fine-tune the immune system but do not investigate whether the immune system can specifically respond to the non-corporeal abiotic trigger, so the organism acquires resistance to that trigger.

Thus, while non-corporeal abiotic triggers are not absent from immunological discourse, they cannot be accommodated by one function we consider essential for immune systems: trigger-specific response, re-response, and resistance. Thus, while this qualified version of the biotic/abiotic distinction is not as explicit as in other fields and is empirically adequate in vertebrate immunology, it does some conceptual heavy lifting within plant and invertebrate immunology. To confront the distinction, it is, however, necessary to bring it to the forefront.

It is not trivial for an epistemic object to travel between disciplines. Deeply embedded conceptual presuppositions in the target discipline reshape the travelling set of phenomena. It is thus hard to maintain a comprehensive view of "immunity." Indeed, if immunity is considered beyond the vertebrate case in plant and invertebrate MOs, there is a mechanistic basis for a small RNA-based system to realize immunity to non-corporeal abiotic stressors. Small RNA-states present interactions with the environment. Even though in the vertebrate and the invertebrate/plant scenario, abiotic triggers are immunogenic and not antigenic (i.e., they can trigger an immune response but cannot themselves specifically interact with immune receptors), there are dedicated mechanisms in invertebrates and plants that channel the trigger into a small RNA-based immune response that subsequently guarantees resistance to that very trigger.

Accepting small RNA-based responses to abiota as part of immune responses emphasizes the organism's constant interactions with and embeddedness in the environment. It also helps move towards a fuller picture of the ecological perspective on immunity, including environmental microbiota and non-corporeal environmental abiota as specific interaction partners. In so doing, it is in line with dissuading the representational version of the cognitive metaphor and with it the emphasis on agential thinking and mechanisms of insularity.

The convergence of biotic and abiotic stress responses is not limited to small RNA pathways in plants and invertebrates. How (generalized) stress signaling and immune signaling relate is also a question central to vertebrate immunology. For instance, those molecular mechanisms ensuring diversification following certain environmental conditions as an evolutionary adaptation in prokaryotes are believed to have been co-opted by the adaptive immune system to guarantee these diversification processes within the physiological individual (Swiatczak 2020). Also for the innate part of the immune system, co-adaptive evolution of stress and immune responses has been proposed (Zhang et al. 2015). As a result, many call for an integrative perspective towards stress signaling and immune responses when studying diseases (Andreassen and Vestbo 2003; Muralidharan and Mandrekar 2013). In this respect, it might prove extremely interesting to further investigate how small RNAs play a role in vertebrate immune signaling, since they might also play a role in bridging stress and immune responses in jawed vertebrates as small RNA-based immune responses are considered to have evolved prior to cell-based immunity and thus, there might be pathways where both types of effectors converge. Small RNA-based effects, amongst other immune effectors such as heritable maternal antibodies, are also important candidates for another aspect of the convergence of (evolutionary) stress response pathways and (physiological) immune responses: adaptive, heritable immune responses might be considered cases of “Lamarckian” inheritance. This further blurs the line on what is a genetic process, and what is an immune response.

In conclusion, investigating any conceptual distinction brings to light the many ways that particularities of biological processes, disciplinary histories, applied versus basic

research, MO repertoires, and the situatedness of concepts and practices all contribute to a particular way of dividing aspects of the world into grand classes. If these contingent norms obstruct specific investigative strategies, if they obstruct particular perspectives that would be fruitful, that would help to see specific systems differently, then we need to question contingent norms and contingent disciplinary lines. In this article, I hope to have demonstrated that a "soft" version of the biotic/abiotic distinction in immunology—specifically, that there is no (adaptive) immune memory against non-corporeal abiotic triggers—causes the exclusion of certain phenomena in plant and invertebrate immune interactions that could otherwise be considered part of the immune system. To denaturalize such distinctions and question their applicability, generality, and fruitfulness it is important to rely not only on the models central to a particular discipline in order to ask what is an immune response and whether a comprehensive answer can be given.

Funding Open access funding provided by University of Vienna. This research was funded through the Interuniversity Program in the History and Philosophy of the Life Sciences, supported by the Humanities Fund of the Israeli Council of Higher Education.

Declarations

Conflict of interest The author declared no conflict of interest.

References

Abbas A et al (2017) Cellular and molecular immunology, 9th edn. Elsevier, Amsterdam

Alcázar R, Parker JE (2011) The impact of temperature on balancing immune responsiveness and growth in *Arabidopsis*. Trends Plant Sci 16(12):666–675

Alwarawrah Y, Kiernan K, MacIver NJ (2018) Changes in nutritional status impact immune cell metabolism and function. Front Immunol. https://doi.org/10.3389/fimmu.2018.01055

Anderson JP, Gleason CA, Foley RC, Thrall PH, Burdon JB, Singh KB (2010) Plants versus pathogens: an evolutionary arms race. Funct Plant Biol 37(6):499–512

Andreassen H, Vestbo J (2003) Chronic obstructive pulmonary disease as a systemic disease: an epidemiological perspective. Eur Respir J 22(46 suppl):2s–4s

Ankeny RA (2001) The natural history of *Caenorhabditis elegans* research. Nat Rev Genet 2(6):474–479

Ankeny RA, Leonelli S (2011) What's so special about MOs? Stud Hist Philos Sci Part A 42(2):313–323

Ankeny RA, Leonelli S (2016) Repertoires: a post-Kuhnian perspective on scientific change and collaborative research. Stud Hist Philos Sci Part A 60(18–28):24

Ankeny R, Leonelli S (2020) MOs. Cambridge University Press, Cambridge

Bentham AR, De la Concepcion JC, Mukhi N, Zdrzałek R, Draeger M, Gorenkin D et al (2020) A molecular roadmap to the plant immune system. J Biol Chem 295(44):14916–14935

Cai Y, Yu X, Hu S, Yu J (2009) A brief review on the mechanisms of miRNA regulation. Genomics Proteomics Bioinform 7(4):147–154

Chen GY, Nuñez G (2010) Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol 10(12):826–837

Chen CJ, Kono H, Golenbock D, Reed G, Akira S, Rock KL (2007) Identification of a key pathway required for the sterile inflammatory response triggered by dying cells. Nat Med 13(7):851–856

Cullen BR, Cherry S (2013) Is RNA interference a physiologically relevant innate antiviral immune response in mammals? Cell Host Microbe 14(4):374–378

Demas GE, Nelson RJ (eds) (2011) Ecoimmunology. Oxford University Press, Oxford

Dong X, Jiang Z, Peng YL, Zhang Z (2015) Revealing shared and distinct gene network organization in *Arabidopsis* immune responses by integrative analysis. Plant Physiol 167(3):1186–1203

Dorado G, Rey I, Rosales TE, Sánchez-Cañete FJS, Luque F, Jiménez I et al (2010) Biological mass extinctions on planet Earth. Archaeobios 4:53–64

Durand PM (2020) The evolutionary origins of life and death. University of Chicago Press, Chicago

Eddie Ip WK, Medzhitov R (2015) Macrophages monitor tissue osmolarity and induce inflammatory response through NLRP3 and NLRC4 inflammasome activation. Nat Commun 11(6):6931

Engelmann I, Pujol N (2010) Innate immunity in *C. elegans*. In: Söderhäll K (ed) Invertebrate immunity. Advances in experimental medicine and biology. Springer, Boston, pp 105–121

Ermolaeva MA, Schumacher B (2014) Insights from the worm: the *C. elegans* model for innate immunity. Semin Immunol 26(4):303–309

Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC (1998) Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. Nature 391(6669):806–811

Flajnik MF, Du Pasquier L (2004) Evolution of innate and adaptive immunity: can we draw a line? Trends Immunol 25(12):640–644

Gibson JJ (1979) The ecological approach to visual perception. Houghton Mifflin, Boston

Gilbert SF, Tauber AI (2016) Rethinking individuality: the dialectics of the holobiont. Biol Philos 31(6):839–853

Godfrey-Smith P (2009) Darwinian populations and natural selection. Oxford University Press, Oxford

Griesemer J (2014) Reproduction and scaffolded developmental processes: an integrated evolutionary perspective. In: Minelli A, Pradeu T (eds) Towards a theory of development. Oxford University Press, Oxford, pp 183–202

Hamilton AJ, Baulcombe DC (1999) A species of small antisense RNA in posttranscriptional gene silencing in plants. Science 286(5441):950–952

Hoffmann HH, Schneider WM, Rice CM (2015) Interferons and viruses: an evolutionary arms race of molecular interactions. Trends Immunol 36(3):124–138

Islam W, Noman A, Qasim M, Wang L (2018) Plant responses to pathogen attack: small RNAs in focus. Int J Mol Sci 19(2):515

Jones JD, Dangl JL (2006) The plant immune system. Nature 444(7117):323–329

Kaletsky R, Moore RS, Vrla GD, Parsons LR, Gitai Z, Murphy CT (2020) *C. elegans* interprets bacterial non-coding RNAs to learn pathogenic avoidance. Nature 586(7829):445–451

Kasamatsu J (2013) Evolution of innate and adaptive immune systems in jawless vertebrates. Microbiol Immunol 57(1):1–12. https://doi.org/10.1111/j.1348-0421.2012.00500.x. (PMID: 22924515)

Katagiri F, Tsuda K (2010) Understanding the plant immune system. Mol Plant Microbe Interact 23(12):1531–1536

Kay LE (1989) Molecular biology and Pauling's immunochemistry: a neglected dimension. Hist Philos Life Sci 11(2):211–219

Koonin EV (2019) CRISPR: a new principle of genome engineering linked to conceptual shifts in evolutionary biology. Biol Philos 34(1):1–30

Koonin EV, Starokadomskyy P (2016) Are viruses alive? The replicator paradigm sheds decisive light on an old but misguided question. Stud Hist Philos Sci Part C 59:125–134

Koren T, Amer M, Krot M, Boshnak N, Ben-Shaanan TL, Azulay-Debby H et al (2021) Insular cortex neurons encode and retrieve specific immune responses. Cell 184(24):5902–5915

Leonelli S (2007a) Arabidopsis, the botanical *Drosophila*: from mouse cress to MO. Endeavour 31(1):34–38

Leonelli S (2007b) Growing weed, producing knowledge: an epistemic history of Arabidopsis thaliana. Hist Philos Life Sci 29(2):193–223

Li H, Zhou Y, Zhang Z (2017) Network analysis reveals a common host–pathogen interaction pattern in Arabidopsis immune responses. Front Plant Sci 8:893

Liu HH, Tian X, Li YJ, Wu CA, Zheng CC (2008) Microarray-based analysis of stress-regulated microRNAs in *Arabidopsis thaliana*. RNA 14(5):836–843

Malone CD, Hannon GJ (2009) Small RNAs as guardians of the genome. Cell 136(4):656–668

Maturana H (2002) Autopoiesis, structural coupling and cognition: a history of these and other notions in the biology of cognition. Cybern Hum Knowing 9(3–4):5–34

McKinney HH (1929) Mosaic diseases in the Canary Islands, West Africa, and Gibraltar. J Agric Res 39:557–578

Millet AC, Ewbank JJ (2004) Immunity in *Caenorhabditis elegans*. Curr Opin Immunol 16(1):4–9

Morange M (2020) The black box of biology: a history of the molecular revolution. Harvard University Press, Cambridge

Muralidharan S, Mandrekar P (2013) Cellular stress response and innate immune signaling: integrating pathways in host defense and inflammation. J Leukoc Biol 94(6):1167–1184

Nejat N, Mantri N (2017) Plant immune system: crosstalk between responses to biotic and abiotic stresses the missing link in understanding plant defence. Curr Issues Mol Biol 23(1):1–16

Netea MG (2013) Training innate immunity: the changing concept of immunological memory in innate host defence. Eur J Clin Invest 43(8):881–884

Netea MG, Schlitzer A, Placek K, Joosten LA, Schultze JL (2019) Innate and adaptive immune memory: an evolutionary continuum in the host's response to pathogens. Cell Host Microbe 25(1):13–26

Nicholas HR, Hodgkin J (2004) Responses to infection and possible recognition strategies in the innate immune system of *Caenorhabditis elegans*. Mol Immunol 41(5):479–493

Nimchuk Z, Eulgem T, Holt Iii BF, Dangl JL (2003) Recognition and response in the plant immune system. Annu Rev Genet 37(1):579–609

Nishimura MT, Dangl JL (2010) *Arabidopsis* and the plant immune system. Plant J 61(6):1053–1066

Nobori T, Tsuda K (2019) The plant immune system in heterogeneous environments. Curr Opin Plant Biol 50:58–66

Padmanabhan C, Zhang X, Jin H (2009) Host small RNAs are big contributors to plant innate immunity. Curr Opin Plant Biol 12(4):465–472

Parameswaran P, Sklan E, Wilkins C, Burgon T, Samuel MA, Lu R et al (2010) Six RNA viruses and forty-one hosts: viral small RNAs and modulation of small RNA repertoires in vertebrate and invertebrate systems. PLoS Pathog 6(2):e1000764

Pardi N, Hogan M, Porter F et al (2018) mRNA vaccines—a new era in vaccinology. Nat Rev Drug Discov 17:261–279

Pasquinelli AE, Reinhart BJ, Slack F, Martindale MQ, Kuroda MI, Maller B et al (2000) Conservation of the sequence and temporal expression of let-7 heterochronic regulatory RNA. Nature 408(6808):86–89

Podolsky SH, Tauber AI (1997) The generation of diversity: clonal selection theory and the rise of molecular immunology. Harvard University Press, Cambridge

Posner R, Toker IA, Antonova O, Star E, Anava S, Azmon E et al (2019) Neuronal small RNAs control behavior transgenerationally. Cell 177(7):1814–1826

Pradeu T (2011) The limits of the self: immunology and biological identity. Oxford University Press

Pradeu T (2016) Organisms or biological individuals? Combining physiological and evolutionary individuality. Biol Philos 31(6):797–817

Pradeu T (2019) Philosophy of CRISPR-Cas: Introduction to Eugene Koonin's target paper and commentaries. Biol Philos 34(1):16

Pradeu T (2020) Philosophy of immunology. Cambridge University Press

Pradeu T, Cooper EL (2012) The danger theory: 20 years later. Front Immunol 3:287

Pradeu T, Du Pasquier L (2018) Immunological memory: what's in a name? Immunol Rev 283(1):7–20

Rader KA (1998) The "mouse people": murine genetics work at the Bussey Institution, 1909–1936. J Hist Biol 31:327–354

Ramegowda V, Da Costa MVJ, Harihar S, Karaba NN, Sreeman SM (2020) Abiotic and biotic stress interactions in plants: a cross-tolerance perspective. In: Priming-mediated stress and cross-stress tolerance in crop plants. Academic Press, London, pp 267–302

Rechavi O, Minevich G, Hobert O (2011) Transgenerational inheritance of an acquired small RNA-based antiviral response in *C. elegans*. Cell 147(6):1248–1256

Rechavi O, Houri-Ze'evi L, Anava S, Goh WSS, Kerk SY, Hannon GJ, Hobert O (2014) Starvation-induced transgenerational inheritance of small RNAs in *C. elegans*. Cell 158(2):277–287

Ren Z, Ambros VR (2015) Caenorhabditis elegans microRNAs of the let-7 family act in innate immune response circuits and confer robust developmental timing against pathogen stress. Proceedings of the National Academy of Sciences USA 112(18):E2366–E2375

Rozzi R (2019) Taxonomic chauvinism, no more!: antidotes from Hume, Darwin, and biocultural ethics. Environmental Ethics 41(3):249–282

Ruiz MT, Voinnet O, Baulcombe DC (1998) Initiation and maintenance of virus-induced gene silencing. Plant Cell 10(6):937–946

Saijo Y, Loo EPI (2020) Plant immunity in signal integration between biotic and abiotic stress responses. New Phytol 225(1):87–104

Saleem M, Meckes N, Pervaiz ZH, Traw MB (2017) Microbial interactions in the phyllosphere increase plant performance under herbivore biotic stress. Front Microbiol 8:41

Sarkies P, Ashe A, Le Pen J, McKie MA, Miska EA (2013) Competition between virus-derived and endogenous small RNAs regulates gene expression in Caenorhabditis elegans. Genome Res 23(8):1258–1270

Saxena S, Jónsson ZO, Dutta A (2003) Small RNAs with imperfect match to endogenous mRNA repress translation: implications for off-target activity of small inhibitory RNA in mammalian cells. J Biol Chem 278(45):44312–44319

Schneider T (2021) The holobiont self: understanding immunity in context. Hist Philos Life Sci 43(3):99

Sela M (1983) From synthetic antigens to synthetic vaccines. Biopolymers 22(1):415–424. https://doi.org/10.1002/bip.360220155

Sela I, Applebaum SW (1962) Occurrence of antiviral factor in virus-infected plants. Virology 17(4):543–548

Seo JK, Wu J, Lii Y, Li Y, Jin H (2013) Contribution of small RNA pathway components in plant immunity. Mol Plant Microbe Interact 26(6):617–625

Shriram V, Kumar V, Devarumath RM, Khare TS, Wani SH (2016) MicroRNAs as potential targets for abiotic stress tolerance in plants. Front Plant Sci 7:817

Stern A, Sorek R (2011) The phage-host arms race: shaping the evolution of microbes. BioEssays 33(1):43–51

Suárez J, Stencel A (2020) A part-dependent account of biological individuality: why holobionts are individuals and ecosystems simultaneously. Biol Rev 95(5):1308–1324

Swiatczak B (2020) Genomic stress responses drive lymphocyte evolvability: an ancient and ubiquitous mechanism. BioEssays 42(10):2000032

Tajima Y, Loo EPI, Saijo Y (2020) Plant physiological and molecular mechanisms in cross-regulation of biotic-abiotic stress responses. In: Hossain MA, Liu F, Burritt D, Fujita M, Huang B (eds) Priming-mediated stress and cross-stress tolerance in crop plants. Academic Press, London, pp 21–34

Tauber AI (2013) Immunology's theories of cognition. Hist Philos Life Sci 35(2):239–264

Troudet J, Grandcolas P, Blin A, Vignes-Lebbe R, Legendre F (2017) Taxonomic bias in biodiversity data and societal preferences. Sci Rep 7(1):1–14

Ulmer J, Valley U, Rappuoli R (2006) Vaccine manufacturing: challenges and solutions. Nat Biotechnol 24:1377–1383

Veigl SJ (2017) Use/disuse paradigms are ubiquitous concepts in characterizing the process of inheritance. RNA Biol 14(12):1700–1704

Veigl SJ (2021) Small RNA research and the scientific repertoire: A tale about biochemistry and genetics, crops and worms, development and disease. Hist Philos Life Sci 43(1):1–25

Veigl SJ (2022a) Adaptive immunity or evolutionary adaptation? Transgenerational immune systems at the crossroads. Biol Philos 37(5):41

Veigl SJ (2022b) Do heritable immune responses extend physiological individuality? Hist Philos Life Sci 44(4):67

Wilkins C, Dishongh R, Moore SC, Whitt MA, Chow M, Machaca K (2005) RNA interference is an antiviral defence mechanism in *Caenorhabditis elegans*. Nature 436(7053):1044–1047

Wilson RA (2005) Genes and the agents of life: the individual in the fragile sciences biology. Cambridge University Press, Cambridge

Woodward J (2010) Causation in biology: stability, specificity, and the choice of levels of explanation. Biol Philos 25(3):287–318

Xiao B, Coste B, Mathur J, Patapoutian A (2011) Temperature-dependent STIM1 activation induces Ca2+ influx and modulates gene expression. Nat Chem Biol 7(6):351–358

Zhang B (2015) MicroRNA: a new target for improving plant tolerance to abiotic stress. J Exp Bot 66(7):1749–1761

Zhang L, Li L, Guo X, Litman GW, Dishaw LJ, Zhang G (2015) Massive expansion and functional divergence of innate immune genes in a protostome. Sci Rep 5(1):8693