

1 **Supplementary material**

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3 **Supplementary methods**

4 **Systematic review process**

5 As we wanted to identify publications that research the interactions between the
6 three components, the MHC, the microbiota, and odor, we carried out a combinatorial
7 approach using search strings that included two of the components in different
8 combinations as well as all three of them together. We conducted the search up to
9 30th January 2020 in both Web of Science and PubMed, excluded reviews, and
10 selected studies written in English. We excluded human studies as the majority
11 focused on single MHC variants or specific microbiota related to diseases.
12 Furthermore, human studies include cultural, technological, and socioeconomic
13 features unique to humans (reviewed in Winternitz and Abbate 2015), such as
14 contraceptives, perfume, and the use of antibiotics, which could influence the
15 microbiota, odor, and behavior of an individual, impeding comparison with other,
16 particularly wild, species. Additionally, we focused on vertebrates only (as non-
17 vertebrates are not relevant for MHC effects) and excluded non-empirical modelling
18 and ex-vivo studies. We excluded studies investigating only a single or genetically
19 modified MHC genotype, except for studies working with knock-out variants, as they
20 enable the investigation of the mechanisms through which the MHC works. In a
21 similar fashion, studies targeting only single microbiota strains were excluded, as
22 these studies do not allow determination of the effects of different MHC genotypes on
23 odor or the microbiota to help unravel the relationship between MHC, odor and
24 microbiota. For studies investigating odor, we excluded those that use
25 preference/discrimination experiments providing more cues to the choosing individual

26 than odor alone as this impedes determination of the role of odor cues. In general,
27 we only kept studies investigating the unidirectional influence of the MHC on the
28 microbiota, of the MHC on odor, and of the microbiota on odor. Studies investigating
29 relationships other than the one-way interactions proposed in Figure 1 have been
30 excluded. For the remaining studies, we recorded study species, MHC locus,
31 odor/microbiota source, methods and study type, hypotheses, results, as well as
32 sample size.

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34 **Systematic review – search strings**

35 We used the following search terms:

36 (MHC OR "major histocompatibility complex") AND (odor OR scent OR preen) NOT
37 human

38 (MHC OR "major histocompatibility complex") AND (microbiome OR microbiota) NOT
39 human

40 (odor OR scent OR preen) AND (microbiome OR microbiota) NOT human

41 (MHC OR "major histocompatibility complex") AND ((odor OR scent OR preen)
42 AND (microbiome OR microbiota)) NOT human

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44 **Supplementary results**

45 To validate the comprehensiveness and unbiasedness of our search strings, we
46 carried out additional searches using the snowballing or chain referral method often
47 used in sociological research (reviewed in Biernacki and Waldorf 1981), checking
48 recent reviews and publications on this topic and carried out manual searching on

49 Google Scholar. We retrieved 64 relevant studies by using our search strings and
50 filtering approach. Through further searching, we found nine additional studies that
51 were not retrieved by our search strings. However, we argue that our search strings
52 are sufficiently comprehensive as well as unbiased, since three out of those nine
53 additional publications were neither indexed in PubMed nor Web of Science. Another
54 two of the missing studies were not recovered by our search strings, as they included
55 the word 'human' in their abstract (which led to exclusion due to the search term
56 'NOT human'). Nonetheless, we argue for comprehensiveness of our search strings,
57 as removing the term 'NOT human' from the search strings increases the number of
58 results from 216 to 515 for all searches combined in PubMed and from 457 to 8601
59 in Web of Science (duplicates between search engines not yet removed). The
60 remaining 4 publications could have been retrieved by including additional search
61 terms in three of the four searches (microbiota & odor: add 'OR bacterial', MHC &
62 microbiota: add 'OR 'microbial communities'', MHC & odor: add 'R 'olfactory
63 signals''). However, this would have further increased the results from 515 to 1712
64 for the searches in PubMed and from 860 to 2069 for the searches in Web of
65 Science. We argue that it is not feasible to carry out a systematic search with so
66 many hits in a reasonable time span. Consequently, we agree with Nakagawa and
67 Lagisz (2019) that comprehensiveness of a systematic review can be impracticable
68 or even impossible to achieve. Instead, requirements of a good systematic review are
69 unbiasedness and transparency in the search process. This can be achieved by
70 conducting the searches in at least two data bases and predefining search and data
71 extraction strategies (Nakagawa et al. 2017). Since we fulfill these prerequisites of a
72 good systematic review, we contend that our systematic search is of appropriate
73 quality and defend the usage of our search strings despite missing six studies.

74 However, to be comprehensive we included the relevant studies that had not been
75 retrieved with our search strings in the tables and marked them with asterisks.

76 **Tables and figures**

77 **Table S1.** Results of the systematic review – microbiota and odor. * indicates publications that were not retrieved by the systematic
 78 search but were included in the table due to relevance.

| Article | Study species | Sample size | Odor/ microbiota source | Methods and study type | Hypothesis | Results |
|------------------------|--|-------------------------------------|-------------------------------|--|---|---|
| Brunetti et al. 2019 * | South American tree frog (<i>Boana prasina</i>) | 8 males and one female | Dorsal skin | Solid-phase microextraction (SPME), GC-MS, bacterial culture, experimental study | Microbiota might produce volatiles found in the chemical profile | A symbiotic bacterial species found on the skin produced volatile compounds present in the chemical profile |
| Whittaker et al. 2019 | Dark-eyed junco (<i>Junco hyemalis hyemalis</i>) | 4 males and 6 females per treatment | Uropygial gland, preen oil | Antibiotic treatment, GC-MS, 16S rRNA sequencing, correlational and experimental study | Microbiota might be involved in shaping the volatile profile and alteration of the microbiota with antibiotics influence the odor profile | (i) Volatile profile compounds were related to the relative abundance of specific bacterial OTUs, (ii) cultivated bacteria isolated from preen oil produced volatiles present in preen oil, (iii) abundance of volatile compounds differed between treatments |
| Yamaguchi et al. 2019 | Bengal cat (<i>Felis catus x Prionailurus bengalensis</i>) | 1 | Anal sac secretion | 16S rRNA sequencing, bacterial cultivation and volatile analysis via GC-MS, experimental study | Bacteria present in anal sac secretions produce volatiles | Bacteria isolated produce volatile compounds also found in anal sac secretion |
| Jacob et al. 2018 | Great tits (<i>Parus major</i>) | 65 | Uropygial gland secretions | 16S rRNA sequencing using a next generation sequencing approach (NGS), gas chromatography – mass spectrometry (GC-MS), correlational study | (i) Gland chemicals might either specifically hinder the growth of certain bacteria or support the growth of commensals, (ii) host chemicals might have broadband effects on microbiota | (i) No significant effects of chemicals on specific bacterial taxa, (ii) chemical modules did not significantly correlate with overall microbiota composition |

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| Leclaire et al. 2017 | Meerkats (<i>Suricata suricatta</i>) | (i) males: n = 15, females n = 15, (ii) 42 samples, (iii) 31 pure and 24 mixed secretions | Anal gland secretions | GC-MS, 16S rRNA sequencing (NGS), correlational study | (i) Odor cues are linked to microbiota composition, (ii) the microbiota should contain odor producers and fermenting bacteria, (iii) mixed secretions should contain more low molecular weight (LMW) compounds compared to pure secretions due to bacterial degradation/fermentation | (i) Chemical composition significantly covaried with bacterial composition in males, (ii) anal gland secretions contained bacteria known from to produce odor, (iii) within individuals, LMW component richness was significantly higher in mixed secretions compared to pure ones |
| Buesching et al. 2016 * | European badger (<i>Meles meles</i>) | 66 | Subcaudal gland secretion | Terminal restriction fragment length polymorphism (T-RFLP), 16S rRNA cloning and sequencing, gas chromatography (GC), correlational study | If the microbiota is involved in generating compounds of the chemical profile, there should be a correlation between microbiota composition and chemical profile | An overall significant correlation between terminal restriction fragments of 16S rRNA genes and chemical composition of the secretions was observed |
| Goodwin et al. 2016 * | African elephants (<i>Loxodonta africana</i>) | 3 | Urine | GC-MS, 16S rRNA sequencing, bacterial culture, protein sequencing, experimental study | Investigate the role of bacteria in the increased abundance of certain compounds in exogenously aged urine | Removal of bacteria from the urine stopped exogenous production of chemical compounds previously found to increase during aging |
| Whittaker et al. 2016 | Dark-eyed junco (<i>Junco hyemalis carolinensis</i>) | 9 females, 8 males, 27 nestlings | Uropygial gland, cloaca and preen oil | 16S rRNA sequencing, GC-MS, correlational study | Microbial and volatile profiles might covary | Volatile profiles did not covary with microbiota profile structure or composition |
| Theis et al. 2013 | Spotted hyenas (<i>Crocuta crocuta</i>), striped hyenas (<i>Hyaena hyaena</i>) | 40 spotted and 33 striped hyenas | Subcaudal scent pouch | Volatile fatty acid (VFA) analysis using GC-MS, 16S rRNA gene sequencing, correlational study | (i) Mammalian scent gland secretions should contain fermentative, odor-producing bacteria, (ii) bacterial and odor profiles should covary | (i) Both spotted and striped hyena microbiota were dominated by fermentative anaerobes, (ii) VFA and microbiota composition covaried significantly in spotted hyenas |
| Martín-Vivaldi et al. 2010 * | European hoopoe (<i>Upupa epops</i>), green woodhoopoes | N = 19 in total, 3 treatment groups with 6-7 individuals each | Preen gland secretion | GC-MS, antibiotic treatment, experimental study | Microbes might produce antimicrobial volatiles in preen secretions | Microbial clearance through antibiotic treatment resulted in the depletion of 7 out of 10 volatile compounds in the |

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| | <i>(Phoeniculus purpureus)</i> | | | | | chemical profile |
| Gorman et al. 1974 * | Indian mongoose (<i>Herpestes auropunctatus</i>) | 2 males | Anal pocket | Gas-liquid chromatography, bacterial culture, antibiotic treatment, experimental study | Investigate the role of microbiota in producing scent compounds | The antibiotically treated anal pockets did not contain all chemical compounds that were present in the untreated ones |

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81 **Table S2.** Results of the systematic review of MHC and odor. * indicates publications that were not retrieved by the systematic search
 82 but were included in the table due to relevance. ** indicates the publication investigating all the link between MHC and odor and MHC
 83 and microbiota.

| Article | Study species | Sample size | Odor source | MHC | Methods | Hypothesis | Results |
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| Grieves et al. 2019 | Song sparrow (<i>Melospiza melodia</i>) | 36 | Preen oil | MHC-II | GC-MS, odor preference tests, MHC genotyping via NGS, correlational study | Similarity of the chemical profile of preen oil is linked to MHC-II similarity | Positive correlation between pairwise dissimilarity of preen oil chemical profile and genetic distance at the MHC ((i) amino acid distance, (ii) chemical dissimilarity) |
| Grogan et al. 2019 * | Ring-tailed lemurs (<i>Lemur catta</i>) | 57 donor animals and 27 recipients | Genital gland secretions | MHC-II DRB | GC-MS, behavioral bioassays, experimental study | Investigate if chemical similarity is linked to MHC-II DRB similarity in | (i) Both sexes signal MHC-II DRB diversity and |

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| | | | | | | both sexes | pairwise similarity, but in a sex- and season-dependent manner, (ii) the sexes discriminate MHC diversity in genital odors of opposite-sex conspecific |
| Gahr et al. 2018 | Three-spined sticklebacks (<i>Gasterosteus aculeatus</i>) | 14 river and 12 lake subject animals | Synthetic MHC peptide ligands | MHC-IIB | Odor preference tests, genotyping via RSCA, experimental study | Test role of MHC peptide ligands as a source of odor in female mate choice | Females prefer synthetic MHC peptide mixtures with the optimal allele number of the population they originated from |
| Leclaire et al. 2017 | Blue petrel (<i>Halobaena caerulea</i>) | Subject animals: Females: 20 individuals and 26 tests; males: 7 individuals and 11 tests. Donor animals: 14 males and 14 females | Back, rump, wings, chest and head | MHC-IIB | Odor preference tests, MHC genotyping via NGS, experimental study | Blue petrels might use odor cues to assess MHC dissimilarity | Incubating males prefer the odor of less MHC-similar females, whereas incubating females prefer the odor of more MHC-similar males |
| Slade et al. 2016 | Song sparrows (<i>Melospiza melodia</i>) | 60 (19 females, 41 males) | Preen wax | MHC-II Exon 2 | GC-MS, NGS, correlational study | Chemical composition of preen wax correlates with MHC-II β genotypes | (i) pairwise chemical distance reflected amino acid distance for male-female but not for same sex dyads, (ii) chemical diversity and richness did not reflect MHC-II β diversity |

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| Leclaire et al. 2014 | Black-legged kittiwake (<i>Rissa tridactyla</i>) | Male-male dyads: n = 210, male-female dyads: n = 378, female-female dyads: n = 153 | Preen gland secretions | MHC-II DRB | GC-MS, MHC genotyping via PCR, cloning and sequencing, correlational study | Preen gland secretions signal MHC-relatedness | MHC amino acid distance was positively correlated to chemical distance in male-male and male-female dyads |
| Hinz et al. 2013 | Zebrafish (<i>Danio rerio</i>) | 42 | Synthetic MHC peptides | MHC-I and -II | Olfactory choice test, experimental study | MHC peptides might act as olfactory signals for imprinting in zebrafish | Zebrafish larvae raised with MHC peptides prefer kin over non-kin |
| Cutrera et al. 2012 | Talas tuco tucos (<i>Ctenomys talarum</i>) | 16 | Urine | MHC-II DRB Exon 2 | Odor preference tests, genotyping via PCR, cloning and sequencing, experimental study | Test whether females prefer odors of males that differ more strongly at the MHC from their own genotype | No difference in the preference of male odors regarding amino acid distance detected |
| Eizaguirre et al. 2011 | Three-spined sticklebacks (<i>Gasterosteus aculeatus</i>) | (i), (ii) N = 17/20 | Tank water | MHC-IIB | Odor preference tests, genotyping via reference strand-mediated conformation analysis (RSCA), experimental study | River and lake population might have different MHC alleles pools (i) and females might prefer sympatric males (ii) | (i) Individuals from river population carried on average a higher number of MHC alleles and the allele pools between river and lake population show a dissimilarity of 96.2%. (ii) Females prefer the odor of sympatric males |
| Setchell et al. 2011 | Mandrills (<i>Mandrillus sphinx</i>) | 88 swab samples (45 individuals, 1 to 4 replicates per individual), 89 hair samples (43 individuals, 1 to 4 | Hair and swabs taken from the sternal gland | MHC DRB | GC-MS, MHC-genotyping via NGS, correlational study | Differences in MHC-similarity and overall genetic relatedness are linked to body odor | MHC dissimilarity increases with difference in the chemical profile |

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| | | replicates per individual) | | | | | |
| Milinski et al. 2010 | Three-spined stickleback (<i>Gasterosteus aculeatus</i>) | (i) 7 pairs in the non-reproductive and (ii) 6 pairs in the nest-maintaining males test | Tank water | MHC-IIB | Odor preference tests, experimental study | Females should prefer MHC-optimal males' odor over MHC-optimal males' odor that has been artificially modified to be super-optimal when MHC composition is signaled via odor | (i) Females prefer the spiked odor in non-reproductive males over that of an optimal male, (ii) females tend to prefer the optimal, non-spiked odor in males that maintain their nest |
| Kwak et al. 2009 | Laboratory mice | 23 and 19 individuals per strain, N _{total} = 42 | Urine | H2 | GC to extract only volatile components, odor discrimination trials, experimental study | Test evidence for a peptide-free volatile signal of MHC in mouse urine | Mice trained to distinguish between odors of congenic mice can generalize this ability to the peptide-free odor solution |
| Zomer et al. 2009 ** | Laboratory mice (<i>Mus musculus domesticus</i>) | 28 mice (from 4 different strains) | Scent marks | H2 | GC-MS, denaturing gradient gel electrophoresis, correlational study | MHC- and background genes influence volatile and microbiota profiles of scent marks | Genetic strain influences both microbiota and volatile profile. MHC has a clearly visible but lower trend in influencing microbiota and volatile profile than strain |
| Kwak et al. 2008 | Laboratory mice | 16 | Urine | H2 | Odor discrimination trials, experimental study | MHC odor profiles should remain relatively stable and discriminable despite dietary variation | Differences in dietary odor are more striking than MHC odor differences, but differences in MHC-related odor can be |

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| | | | | | | | discriminated despite variation in odor caused by dietary changes |
| Radwan et al. 2008 | Bank voles (<i>Myodes glareolus</i>) | 20 MHC-dissimilar and 20 MHC-similar donor animals | Soiled bedding | MHC-II DRB | Odor preference test, experimental study | Test females for a preference of MHC-dissimilar males | Females prefer odors of MHC-dissimilar over those of MHC-similar males |
| Novotny et al. 2007 | Laboratory mice (congenic, recombinant, mutant, transgenic) | 7 strains, N = 73 (with 5 to 8 individuals per strain) | Urine | both MHC classes | GC-MS, experimental comparison | Variations in the odor profile linked to the MHC are mainly of quantitative nature | Excretion of substances differed significantly even for strains differing in only a few amino acids in the peptide binding region of a single MHC-I gene |
| Röck et al. 2007 | Laboratory mice | 50 (15 per strain plus 5 control pools) | Urine | MHC-I | GC-MS, experimental comparison | MHC-I depletion leads to undistinguishable urine volatiles | Urine of MHC-I depleted laboratory mice could still be distinguished, strain differences could be correlated to the provenance and genetic distance rather than the MHC-I |
| Knapp et al. 2006 * | Ring-tailed lemurs (<i>Lemur catta</i>) | 6 adults and 2 juveniles | Brachial gland and tail scent samples | MHC-II DRB | GC-MS, correlational study | MHC sequences and volatile composition of odor correlate | not statistically significant, but relationship between the absence of certain MHC sequences and the concentration of |

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| | | | | | | | volatile compound |
| Rajakaruna et al. 2006 | Atlantic salmon (<i>Salmo salar</i>) and brook trout (<i>Salvelinus fontinalis</i>) | (i) 20 Atlantic salmon (AS), 20 brook trout (BT), (ii) 15 AS, 20 BT, (iii) 16 AS, 20 BT | Tank water | MHC-II b1 exon of the DAB | Odor preference tests, experimental study | Atlantic salmon and brook trout distinguish kin based on differences at the MHC locus | (i) fish prefer kin sharing both alleles over kin sharing none, (ii) fish prefer non-kin sharing alleles over kin sharing none, (iii) fish prefer kin sharing no alleles over non-kin sharing none |
| Willse et al. 2006 | Laboratory mice | 6 different genotypes (3 per strain) | Urine | H2 | GC-MS, odor discrimination trials, experimental study | MHC-odortypes should be discriminable against a varying genetic background | Laboratory mice were able to generalize the discrimination of MHC with varying genetic background, despite the varying background's influence on odor profiles |
| Hurst et al. 2005 | Laboratory mice | 53 | Urine | H2 | Countermarking experiments, experimental study | Markings from mice differing from the subject at the MHC should elicit a countermarking response | MHC was not used for individual recognition of scent marks in territorial behavior |
| Willse et al. 2005 | Laboratory mice | Two strains with 5 and 6 pools (consisting of samples of 3-4 individuals) respectively | Urine | H2 | GC-MS, observational study and method description | MHC-dependent differences in the concentration of volatiles in congenic mice should be detectable via GC-MS | 80 compounds discriminating the MHC-congenic samples have been identified and the significant differences were all quantitative |

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| Häberli and Aeschlimann 2004 | Three-spined sticklebacks (<i>Gasterosteus aculeatus</i>) | 15 subjects, 12 male donor and 13 female donor animals | Tank water | MHC-IIB | Odor preference tests, genotyping via SSCP, experimental study | Gravid females might choose their mate based on MHC-odor preferences | Gravid females preferred males that had not yet built a nest over females when the males had less MHC alleles than females |
| Wysocki et al. 2004 | Laboratory mice | 8 treated and 6 sham mice | Urine | H2 | Surgical removal of the vomeronasal organ and odor discrimination trials, experimental study | The vomeronasal organ is involved in discrimination of MHC-odortypes | Mice without a vomeronasal organ were able to learn to discriminate the odor of MHC-congenic mice |
| Aeschlimann et al. 2003 | Three-spined sticklebacks (<i>Gasterosteus aculeatus</i>) | 11 subject animals | Tank water | MHC-IIB | Odor preference tests, single-strand conformation polymorphism (SSCP), experimental study | Test ability of females to use self-referencing to optimize their offspring's MHC-genotype | Females use a self-referencing mechanism to optimize the number of alleles and prefer MHC-dissimilar males |
| Olsson et al. 2003 | Sand lizard (<i>Lacerta agilis</i>) | 20 | Femoral pores | MHC-I | Odor preference test, genotyping via restriction fragment-length polymorphism (RFLP), experimental study | Females might be able to assess MHC genotype through odor for precopulatory mate choice | Females did not prefer males with more RFLP bands for the MHC-I over males with less bands |
| Carroll et al. 2002 | Laboratory mice | (i) 19, (ii) 20, 28, 28 (for the different F ₂ segregants) | Urine | H2 class I | Habituation-dishabituation trials, experimental study | (i) Test ability of untrained mice to distinguish natural variants differing at a single locus (ii) Test for a detection threshold for detecting odor differences | (i) Untrained laboratory mice can distinguish between natural variants of class I H2 differing only at a single locus, (ii) F ₂ segregants can only be distinguished with |

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| | | | | | | | a minimum amino acid difference at the PBS |
| Olsén et al. 2002 | Arctic char (<i>Salvelinus alpinus</i>) | 6 subject animals, 5 donor animals per experiment | Tank water | MHC-II | Odor preference test, MHC genotyping via DGGE, experimental study | Odors important for kin discrimination might be influenced by the MHC and the response could be learned or innate | (i) Fish did not discriminate between the odors of siblings with identical MHC. (ii) The fish preferred MHC-identical siblings over MHC-differing siblings. (iii) They did not show a discriminative response towards an MHC-identical non-sibling and an MHC-different sibling. (iv) Fish isolated since fertilization did not discriminate between MHC-identical and non-identical siblings. |
| Schaefer et al. 2002 | Laboratory mice | between 8 and 6 for each of the 4 genotypes, 3 for the control, N _{total} = 32 | Urine | H-2K class I | GC-MS, in situ hybridization of mRNA expression in the main olfactory bulb, experimental study | Single genetic differences might alter the volatile profile and its representation in the main olfactory bulb | Urine odors differing at a single gene evoked unique activation patterns in the olfactory bulb |
| Ehman and Scott 2001 | Laboratory mice | (i) 20 subject animals (10 animals per strain), 20 different pairs of donors, (ii) 10 subject | Urine | H2 | Odor discrimination trials, experimental | (i) Test MHC-preferences of females in urinary odors in female conspecifics, (ii) test a female preference for MHC-disparate males | (i) Females did not show a preference for MHC-similar or MHC-disparate females, (ii) No preference |

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| | | animals (5 per strain), 20 different pairs of donors | | | | | for MHC-dissimilar or MHC-similar males detected |
| Janssen et al. 2001 | Laboratory rats (Lewis rats, Brown Norway rats) | (i) 16, (ii) 4 | Urine | MHC-I | (i) Habituation-dishabituation trials, (ii) GC-MS, experimental study | Injection of recombinant allogenic soluble MHC molecules might alter urinary odor | Brown Norway rats were able to discriminate between urinary odors of Lewis rats with different recombinant soluble MHC molecules |
| Reusch et al. 2001 | Three-spined stickleback (<i>Gasterosteus aculeatus</i>) | (i) 29, (ii) 21 | Tank water | MHC-IIb | Odor preference tests, genotyping via SSCP, experimental study | Females might prefer males with higher numbers of MHC alleles (i) and odors of MHC-dissimilar males (ii) | (i) Females showed a preference for males with a higher number of MHC alleles over those that only have few alleles, (ii) There was no female preference of MHC-dissimilar over MHC-similar males |
| Bard et al. 2000 | Laboratory mice | 5 sensor mice | Urine | MHC I | Odor discrimination trials, experimental study | MHC I molecules have a role in shaping odor profiles | MHC-I influences odor, as loss of MHC-I expression makes odor of laboratory mice distinguishable from otherwise genetically identical conspecific |
| Yamazaki et al. 2000 | Laboratory mice | (i) 19 (105 pups) and 21 (122 pups) litters per strain | Soiled bedding | H2 | Odor discrimination trials, experimental study | Pups discriminate familiar MHC-odortypes from another MHC- | (i) Pups discriminate their familiar, syngenic |

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| | | respectively (two strains), (ii) 20 (102 pups) and 15 (79 pups) litter per strain (two strains) | | | | congenic odor and cross-fostering might impact this preference | odor from MHC-congenic odor and (ii) cross-fostering impacts their preference |
| Eklund 1998 | House mice (<i>Mus musculus</i>) | 10 female and 19 male subject animals, 2 MHC-congenic donor strains | Soiled bedding | H2 | Odor preference tests, genotypes known for lab strains serving as odor donors, experimental study | Test for MHC-based mate choice preference (only initial testing for experiments) | No odor preference for either strain by males or females. |
| Olsén et al. 1998 | Arctic char (<i>Salvelinus alpinus</i>) | 31 | Tank water | MHC-IIB | Odor preference test, MHC genotyping via denaturing gradient gel electrophoresis (DGGE), experimental study | Kin recognition and sibling discrimination might be influenced by the MHC | Juvenile arctic char can discriminate between self and non-self MHC genotypes of siblings |
| Pearse-Pratt et al. 1998 | Laboratory rats | 2 per genotype, N _{total} = 6 | Urine | MHC-I | (i) Habituation-dishabituation trials, (ii) X-ray crystallography, experimental study | Injection of purified MHC-I molecules into the circulation of laboratory rats should alter the urinary odor and render it discriminable | (i) Laboratory rats were able to discriminate between the odors of injected and non-injected congenic rats, (ii) structural changes in the MHC molecule occur between membrane bound state and soluble state in urine |
| Penn and Potts 1998 | House mice (<i>Mus musculus domesticus</i>) | 5 subjects, 30 odor donors | Urine | H2 | (i) Odor discrimination trials, (i) habituation-dishabituation trials, experimental study | (i) Wild mice should be able to distinguish odors of MHC-congenic mice after training, (ii) Untrained wild mice should be able to distinguish different MHC | (i) Wild mice could learn discrimination of MHC-congenic odors, (ii) wild mice could discriminate MHC- |

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| | | | | | | types | congenic odors without prior training, but they also discriminated between individuals of the same strain |
| Schellinck et al. 1997 | Long-Evans rats, PVG rats | 6 and 7 subject rats for experiment 1 and 2 respectively, 8 and 7 donor rats for each of the two strains respectively, N _{total} = 15 | Urine | MHC class Ia | Odor discrimination trials, experimental study | Dietary cues might influence the ability of Long-Evans rats to discriminate between odors of MHC-congenic rats | Strain differences did not disrupt discrimination of diet, but when both strain and diet differed then rats trained to distinguish odor fail |
| Singer et al. 1997 | Laboratory mice | 12 urine samples from each of two congenic panels | Urine | H2 | Anion exchange chromatography and odor discrimination trials with the fractions obtained via gas chromatography, experimental study | MHC-determined urinary odor is produced by a mixture of volatile carboxylic acids and their relative concentration | Mice could distinguish between the retained ion exchange fractions |
| Brown et al. 1996 | Long-Evans rats | 6 | Urine | MHC-IA | Odor discrimination trials, experimental study | MHC-dependent odor cues should be stable and distinguishable over dietary changes | Long-Evans rats can distinguish dietary cues in mice urine more easily than MHC-dependent cues |
| Beauchamp et al. 1994 | Laboratory mice | 5 for the maternal and 3 for the paternal fetal genotype | Urine | H2 | Odor discrimination trials, experimental study | MHC molecules expressed in utero can be sensed in urine of the pregnant mouse before birth | The fetal haplotype is present from at least day 9-12 of fetal age and enables urine discrimination |
| Yamazaki et al. 1994 | Laboratory mice | 109 (split into 4 strains) | Urine | H2 | Odor discrimination trials, experimental | Background genetic effects influence | Mice were able to discriminate MHC |

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| | | | | | study | discrimination of MHC-odortypes by mice | differences in outbred mice |
| Schellinck et al. 1993 | Long-Evans rats/laboratory mice | 4 subject rats, 8 donor individuals for each of the three strains, $N_{total} = 24$ | Urine | H-2K locus | Odor discrimination trials, experimental study | Long-Evans rats should be able to discriminate the odors of MHC- and Y-congenic mice | Changing the diet in the donor rats disrupted the ability of the subject rats to discriminate the learned odor |
| Singer et al. 1993 | Laboratory mice | 40-60 MHC-congenic donor pairs | Urine | H2 | Odor discrimination trials, dialysis, and lyophilisation for the fractioning of urine samples, experimental study | Volatile compounds of the odors of MHC-congenic mice play an important role in discrimination | Protein-free MHC-congenic urine odors can still be distinguished by mice |
| Yamazaki et al. 1992 | Laboratory mice | 4 adult mice (2 males, 2 females) | Litter odor and urine | H2 | Odor discrimination trials, experimental study | MHC-odortypes are already expressed by infants | Adult mice were able to discriminate the urine of infant mice differing at the MHC from day 1 and litter odor from day 14 onwards |
| Schellinck et al. 1991 | Laboratory rats (Long-Evans rats and PVG rats) | 8 subject animals, 5 donor animals per condition | Urine | MHC-IA | Odor discrimination trials, experimental study | MHC and microbiota influence odors and rats can be trained to detect odor differences between (i) outbred conspecifics, (ii) MHC-congenic rats, (iii) two germ-free raised rat strains, and (iv) individuals of the same conventionally housed rat strains | All four odor combinations (i-iv) were discriminable but learning patterns differed. Task (iii) and (iv) were most difficult, tasks (ii) was discriminated most easily. |
| Yamazaki et al. 1990 | Laboratory mice | 3 mice of each of the two strains | Urine | H2 | Odor discrimination trials, experimental study | Microbiota should be necessary for the production and discrimination of MHC- | Germ-free rearing of donor mice did not disrupt the discrimination of |

| | | | | | | dependent odors | their odor |
|-----------------------|--|--|-------|---------------------------------------|---|--|---|
| Brown et al. 1989 | Laboratory rats (PVG) | (i) 32, (ii) 24, (iii) 24, (iv) 16, (v) 16 | Urine | all three regions (IA, II B/D, I C/E) | Habituation-dishabituation trials, experimental study | Rats should be able to distinguish differences in the different MHC loci of MHC-congenic rats via odor | MHC dissimilarity increases with difference in the chemical profile |
| Brown et al. 1987 | Laboratory rats (Lister hooded, PVG, and Wistar albino rats) | 10 donor animals per strain, $n_{total} = 20$; subject animals: PVG $n = 24$, Wistar = 8, Lister = 11 and 36 | Urine | MHC-IA | Habituation-dishabituation trials, experimental study | The MHC might control cues important for odor discrimination | MHC-congenic PVG rat odors could be discriminated, however this could not be repeated in a second round. Serum of MHC-congenic mice could not be distinguished, nor the isolated MHC-IA protein. Urine with the MHC-IA protein removed could be distinguished |
| Beauchamp et al. 1985 | Laboratory mice and rats (Wistar/Furth) | 5 males and 3 female subject rats | Urine | H2 | Odor discrimination trials, experimental study | MHC-based odor signals might be discriminable across species barriers | Rats can discriminate odors of MHC-congenic mice |

| | | | | | | | |
|--------------------------|-----------------|---|-------|------|--|--|--|
| Yamazaki et al. 1982 | Laboratory mice | 5 | Urine | H2-K | Odor discrimination trials, experimental study | Genetic differences at the K end of the H2 region of mice might be discriminable by conspecifics | Genetic differences at the K end of the H2 region can be discriminated by mice |
| Yamaguchi et al. 1981 | Laboratory mice | 4 | Urine | H2 | Odor discrimination trials, experimental study | Urine might signal MHC-dissimilarity in mice | Mice could discriminate MHC-congenic mice based on urine as an odor source |

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88 **Table S3.** Results of the systematic review – MHC and microbiota. * indicates publications that were not retrieved by the systematic
 89 search but were included in the table due to relevance.

| Article | Study species | Sample size | MHC | Microbiota source | Methods and study type | Hypothesis | Results |
|------------------------|---|---------------------------------|---------|--|---|---|--|
| Leclaire et al. 2019 | Blue petrel (<i>Halobaena caerulea</i>) | 36 | MHC-IIb | feather microbiota samples at 4 different body sites | Genotyping and 16s rRNA sequencing via NGS, correlational study | (i) MHC dissimilarity positively correlates with dissimilarity of microbiota, (ii) higher MHC diversity should result in lower microbiota diversity | (i) Distance in microbial community varied with MHC diversity among individuals, (ii) higher MHC diversity was linked to lower microbiota diversity in preen feathers, but not in ventral, dorsal, or neck feathers |
| Wadud Khan et al. 2019 | Laboratory mice | 6 genotypes with 5 animals each | H2 | Fecal samples | 16S rRNA sequencing, experimental study | MHC heterozygosity influences taxonomic composition and functional gene content of the microbiota | (i) Microbiota diversity differed between hetero- and homozygotes, (ii) microbiota composition was more dissimilar in heterozygotes compared to homozygotes, (iii) no difference in alpha and phylogenetic diversity, (iv) no difference |

| | | | | | | | |
|-----------------------------|---|--|------------------|--|--|--|---|
| | | | | | | | between homo- and heterozygotes in the functional gene content of the overall microbiota |
| Derakhshani et al. 2018 | Holstein dairy cows | 24 and 25 cows for each variant | BoLA-DRB3 Exon 2 | Mammary gland (colostrum and milk) | Genotyping via PCR-RFLP, 16S rRNA sequencing via Next Generation Sequencing (NGS), correlational study | Relationship between BoLA-DRB3 polymorphism and intramammary microbiota composition in cows during the first week of lactation | Significant difference in microbiota diversity and composition between the two variants only on day 0 |
| Hernández-Gómez et al. 2018 | Ozark hellbenders (<i>Cryptobranchus alleganiensis bishopi</i>), eastern hellbenders (<i>C. a. alleganiensis</i>) | 21 eastern and 28 Ozark hellbenders | MHC-IIb | Skin | 16S rRNA sequencing and MHC genotyping via NGS, correlational study | Skin microbial community might be linked to the diversity of MHC-II genes | Relationship between MHC-II amino acid distance and skin community richness: positive for the eastern hellbender and not significant for the Ozark hellbender |
| Pearce et al. 2017 * | Leach's storm petrel (<i>Oceanodroma leucorhoa</i>) | 22 | MHC-IIb DAB2 | Skin and feathers near uropygial gland | 16s rRNA gene sequencing, MHC genotyping, correlational study | MHC diversity influences microbiota diversity | In males, DAB2 homozygosity explains 72% of variation in microbial community structure |
| Kubinak et al. 2015 | Laboratory mice | (i) Flow cytometry: n = 6-8 per genotype (n _{total} = 21) ELISA: n = 11 per | H2 | Fecal samples | 16S rRNA sequencing, experimental study | MHC polymorphism influences the microbial community | (i) MHC genotype significantly influenced antibody responses against |

| | | | | | | | |
|---------------------|---|--|---------|-------|---|--|---|
| | | genotype, n _{total} = 33 (ii)+(iii) WT (n = 4), B2M ^{-/-} (n = 6), and MHCII ^{-/-} (n = 6), (iv) 5 heterozygotes and 5 homozygotes of each genotype | | | | | commensal bacteria in the gut, (ii) Lack of MHC class I and II-mediated antigen presentation led to alterations in microbiota composition and structure, (iii) Class II plays a more important role in forming the microbial community, (iv) MHC heterozygotes do not have a more diverse microbiota, but heterozygosity influences microbiota composition |
| Bolnick et al. 2014 | Three-spined sticklebacks (<i>Gasterosteus aculeatus</i>) | 150 | MHC-IIb | Gut | 16s rRNA gene sequencing, MHC genotyping, correlational study | Association between MHC and microbiota composition: individuals with different MHC-II genotypes can recognize different microbiota causing covariation of gut microbiota composition and MHC | Individuals with more divergent MHC motifs had less diverse microbiota, small number of significant pairwise associations between MHC and microbial families was observed |
| Wegner et al. 2012 | European plaice (<i>Pleuronectes</i>) | 40 | MHC-IIB | Gills | Genotyping and 16s rRNA | There might be a link between MHC | Significant weak overall correlation |

| | | | | | | | |
|----------------------|-------------------|---------------------------------------|----|-------------|--|---|--|
| | <i>platessa</i>) | | | | sequencing via NGS, correlational study | genotype and bacterial colonization | between MHC matrix and pathogen abundance matrix |
| Lanyon et al. 2007 * | Laboratory mice | 9 per strain, N _{total} = 36 | H2 | Scent marks | 16S rRNA sequencing using DGGE, experimental study | MHC and background genotype contribute to microbiota community regulation | DGGE profiles of scent mark microbiota can be distinguished between the congenic strains and both MHC and background genotype influence it |

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93 **Table S4.** Components and processes involved in immune response. Presented are
 94 the humoral and cellular components and immunological processes and their
 95 corresponding involvement in immune response. Components can either act in both
 96 elimination and tolerance or affect only one outcome.

| Component | Role in inflammation | Role in tolerance |
|--------------------------------|--|---|
| Antigen presenting cells (APC) | Antigen recognition, processing, and presentation <ul style="list-style-type: none"> • Influence peptide recognition causing elimination of the peptide | Antigen recognition, processing, and presentation <ul style="list-style-type: none"> • Influence peptide recognition causing tolerance to the peptide |
| B cell | Can act as APCs and produce antibodies <ul style="list-style-type: none"> • Influence peptide recognition and can facilitate inflammation | Can act as APCs and produce antibodies <ul style="list-style-type: none"> • Influence peptide recognition and can temper inflammation |
| Immunoglobulin A (IgA) | Neutralize, coat and agglutinate peptides <ul style="list-style-type: none"> • Causing inactivation and elimination of the peptide | Coat peptides <ul style="list-style-type: none"> • Facilitate passage through epithelium and thus production of bacteria specific IgA Neutralizes toxins and bacterial epitope expression <ul style="list-style-type: none"> • Reduces immunogenicity |

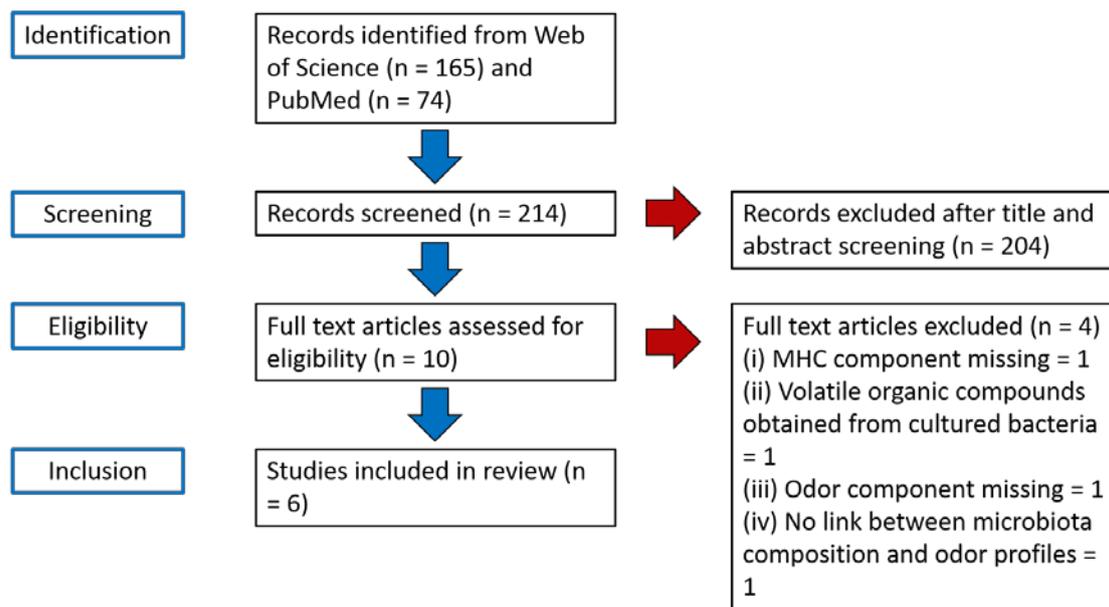
| | | |
|--|--|---|
| Innate lymphoid cells (ILCs) | Produce cytokines that orchestrate immune response | Promote homeostasis by inducing cell death of T cells acting against commensal bacteria |
| Regulatory T cell (Treg cell) | | Regulate IgA diversity Temper inflammatory response |
| Major histocompatibility complex class II (MHC-II) | Present peptides to T cells MHC-II-peptide complex causes elimination in the presence of costimulation Might influence the T cell receptor repertoire and thus peptide recognition | Present peptides to T cells MHC-II-peptide complex causes tolerance in the absence of costimulation Might influence the T cell receptor repertoire and thus peptide recognition |
| Microbiota diversity | Can cause inflammatory responses that facilitate clearance from the antigenic source | Influences Treg reg cells and thus IgA Can promote itself by feeding into this positive feedback loop |

98 **Table S5. Glossary of key terms**

| Abbreviation/term | Meaning |
|--------------------------|---|
| APC | Antigen presenting cell, initiate immune response |
| B cell | Immune cell bearing MHC-II molecules, B stands for bone marrow |
| CD4 | Cluster of differentiation 4, receptor on the surface of immune cells, such as T helper cells |
| Congenic | Describes organisms that differ genetically only at a single locus |
| Cytotoxic T cell | T cells that can initiate the death of malignant, infected, or damaged cells |
| DGGE | Denaturing gradient gel electrophoresis |
| GC-MS | Gas chromatography – mass spectrometry |
| H2 | Mice equivalent of the MHC |
| IgA | Immunoglobulin A, antibody type that is prevalent at mucous body surfaces |
| ILC | Innate lymphoid cell |
| MHC | Major histocompatibility complex |
| NGS | Next generation sequencing, high throughput sequencing method |
| RSCA | Reference strand-mediated conformation analysis |
| PBS | Peptide binding site |
| T cell | immune cell, T stands for thymus, includes Th cells |
| TCR | T cell receptor, receptor on the surface of T cells |
| Th cell | T helper cell, facilitates inflammation, CD4+ (cluster of differentiation, describes surface glycoproteins) |
| Treg cells | Regulatory T cell, temper inflammation |
| RFLP | Restriction fragment-length polymorphism |
| SSCP | Single-strand conformation polymorphism |
| Syngenic | Describes genetically identical organisms |

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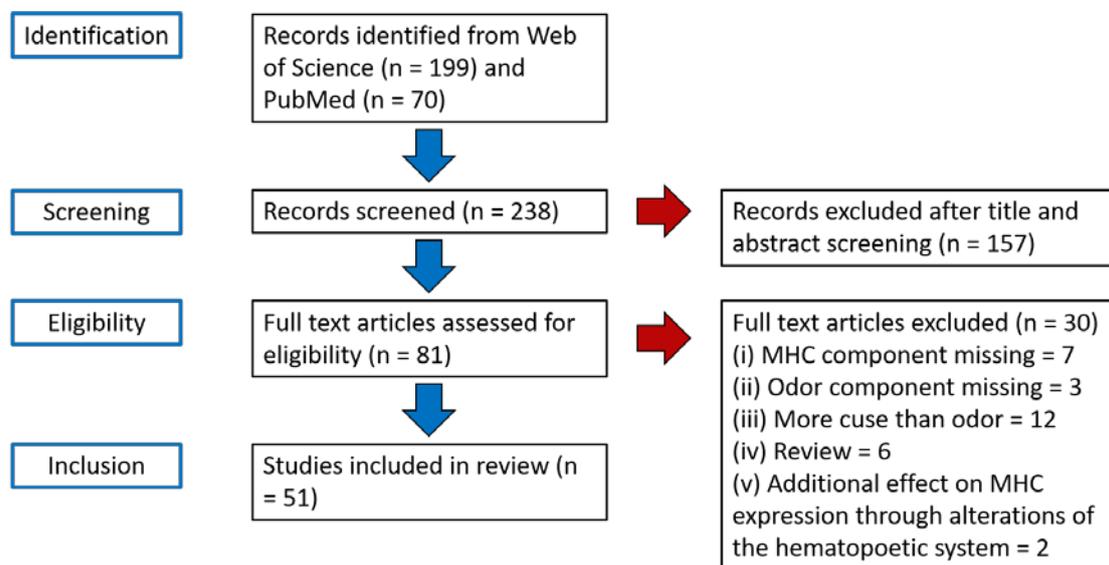
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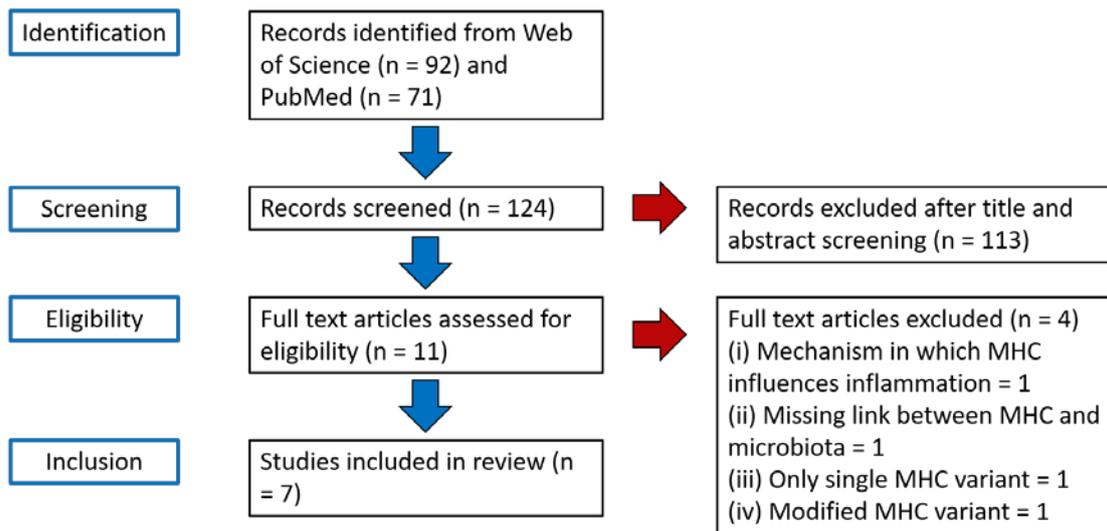
102 **Figure S1.** PRISMA flowchart for the systematic review on microbiota and odor
 103 interaction.

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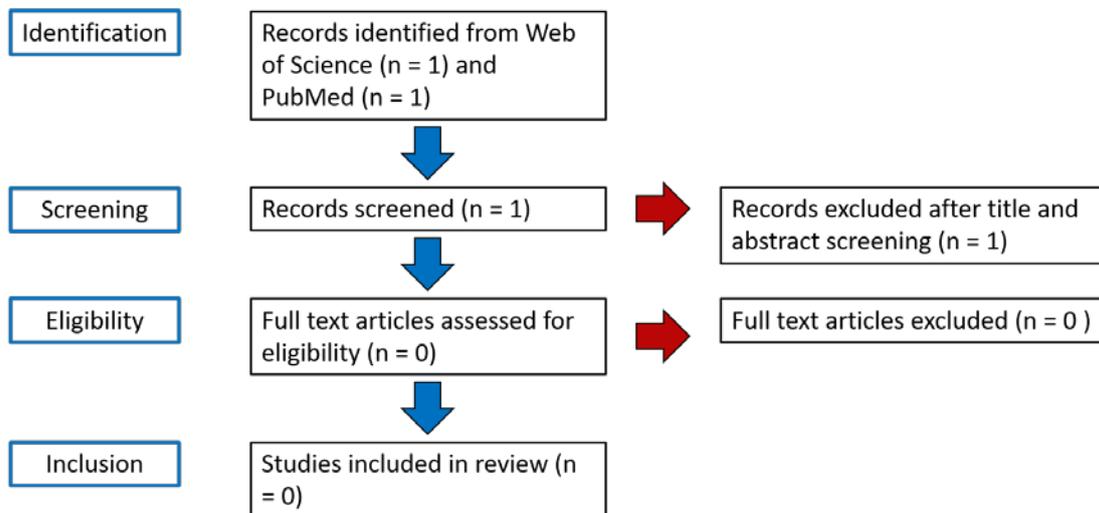
106 **Figure S2.** PRISMA flowchart for the systematic review on MHC and odor
 107 interaction.



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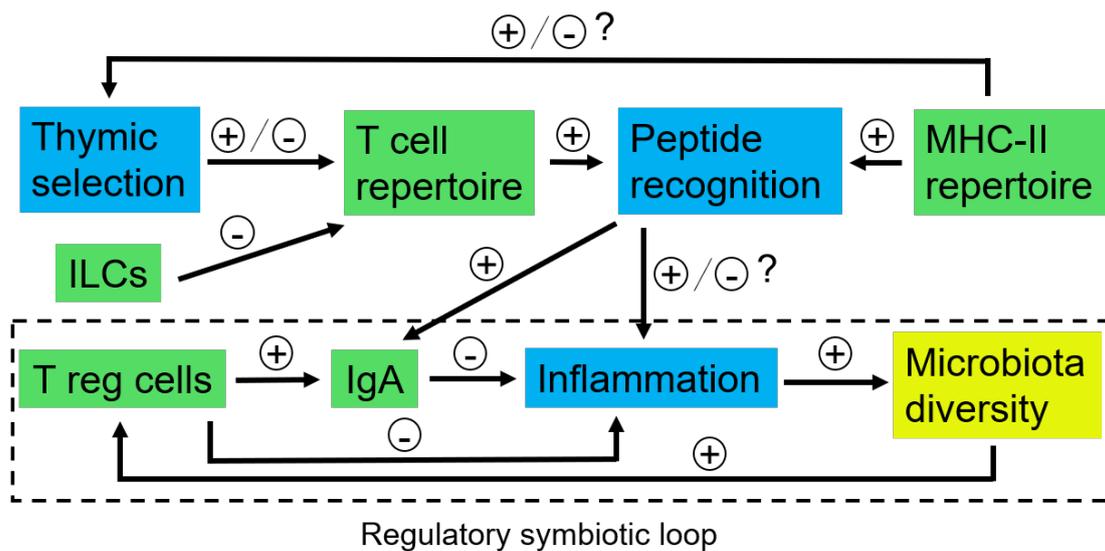
109 **Figure S3.** PRISMA flowchart for the systematic review on MHC and microbiota
 110 interaction.

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113 **Figure S4.** PRISMA flowchart for the systematic review on MHC, microbiota, and
 114 odor interaction.



■ processes
■ cellular/humoral components of the immune system

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116 **Figure S5.** Agents of the immune system affecting microbiota diversity. Arrows
 117 indicate the direction of the agent's effect with + or - describing whether higher
 118 diversity/amount of the agent is enhancing or limiting to the component being
 119 affected by the agent. Both + and - simultaneously (+/-) describes that the effect an
 120 agent has on another component has not yet been fully revealed or can have both
 121 outcomes, depending on other factors. Peptide recognition might both limit or
 122 increase inflammatory responses, depending on the mechanism acting between
 123 MHC-II and the commensal microbes, and MHC-II diversity could theoretically both
 124 reduce or increase the T cell repertoire during thymic selection. Processes are
 125 represented in blue, whereas cellular and humoral components are depicted in
 126 green. Microbiota diversity is presented in yellow. The dashed line marks the
 127 regulatory symbiotic loop governing inflammation and thus microbiota diversity.

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