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Review

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Gamete-mediated mate choice: towards a more inclusive view of sexual selection

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'Sperm competition'—where ejaculates from two or more males compete for fertilization—and 'cryptic female choice'—where females bias this contest to suit their reproductive interests—are now part of the everyday lexicon of sexual selection. Yet the physiological processes that underlie these post-ejaculatory episodes of sexual selection remain largely enigmatic. In this review, we focus on a range of post-ejaculatory cellular- and molecular-level processes, known to be fundamental for fertilization across most (if not all) sexually reproducing species, and point to their putative role in facilitating sexual selection at the level of the cells and gametes, called 'gamete-mediated mate choice' (GMMC). In this way, we collate accumulated evidence for GMMC across different mating systems, and emphasize the evolutionary significance of such non-random interactions among gametes. Our overall aim in this review is to build a more inclusive view of sexual selection by showing that mate choice often acts in more nuanced ways than has traditionally been assumed. We also aim to bridge the conceptual divide between proximal mechanisms of reproduction, and adaptive explanations for patterns of non-random sperm–egg interactions that are emerging across an increasingly diverse array of taxa.

1. Introduction

Sexual selection was originally assumed to act exclusively prior to mating (pre-ejaculatory sexual selection), either through direct competition among members of one sex for access to mates (intra-sexual competition) or through mate choice (inter-sexual competition [1]). Many of the 'classic' examples of sexual selection, such as the ritualized mating contests among male red deer, or highly decorated male peacocks competing for female attention, exemplify these forms of sexual selection [2]. However, we now understand that sexual selection can occur at much more subtle levels than originally envisaged by Darwin [3]. Specifically, the prevalence of female multiple mating means that sexual selection will often continue after mating in the form of sperm competition, where ejaculates from different males compete for fertilization [4], and cryptic female choice (CFC), where females bias paternity towards specific males [5,6].

Although numerous potential mechanisms of CFC have been postulated [6], providing unequivocal evidence for the phenomenon continues to be a major challenge in evolutionary biology [7]. Consequently, explicit evidence for CFC is rare and its mechanistic basis remains elusive, particularly where CFC targets cellular- and molecular-level processes that occur just prior to fertilization [8]. Nevertheless, an accumulating body of evidence suggests that CFC has the potential to specifically target pre-fertilization processes that ultimately facilitate mate choice at the cellular level (gamete-mediated mate choice, hereafter GMMC). Our aim here is to review this emerging evidence for GMMC and highlight how these mechanisms are likely to be applicable to a wide range of taxa. Furthermore, we highlight that in many cases sexual selection can be constrained to act exclusively via gamete-level interactions [9,10]. In particular, several recent studies, conducted mainly on externally fertilizing species, have

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revealed that chemically moderated interactions between eggs and sperm can play important roles in moderating conspecific fertilization success and the 'choice' of compatible (or otherwise suitable) reproductive partners (e.g. [11,12]).

These studies on species exhibiting the ancestral reproductive strategy of broadcast spawning are of particular interest to evolutionary biologists because many of the key features of the fertilization process (including gamete interactions) displayed by them are shared by most (if not all) animal species [13]. As such, it has recently been postulated that GMMC may have been an evolutionary precursor for pre-mating sexual selection, culminating in the evolutionary cascade that led to more familiar 'Darwinian'—pre-copulatory—modes of sexual selection [10,14] (see §6). In this review, we explore these cellular-level processes and argue that a better understanding of these mechanisms will offer new insights into sexual selection more generally. Furthermore, we highlight how insights gained in this field of study may have important scientific and clinical benefits in terms of our understanding of reproductive biology and fertility [15].

We commence our review by considering the biochemical and molecular interactions that are fundamental for successful fertilization across sexually reproducing species. We then draw together an accumulating body of evidence that suggests that sexual selection has targeted such interactions to facilitate GMMC. In doing so, we emphasize the evolutionary significance of GMMC, the accumulating evidence for the phenomenon across different mating systems, and highlight some of the possible adaptive functions of mate choice at the cellular level.

2. Chemical communication at the cellular level is critical for fertilization

In sexually reproducing species, fertilization is highly dependent on biochemical interactions occurring between sperm and eggs. In internally fertilizing species, sperm can also 'communicate' with the cells of the female's reproductive tract. These cellular-level modes of communication are mediated by various membrane-bound signalling molecules, such as proteins and carbohydrates, both of which play important roles in fertilization across a wide range of taxa (e.g. [16,17]). Gametes have also been shown to communicate prior to physical contact via chemical signals that are released from the unfertilized eggs, or from the female's reproductive tract [18,19]. In either case, female-derived signalling mechanisms can induce a range of physiological responses in sperm, including capacitation (activation), hyperactivation, structural changes to the sperm plasma membrane and the acrosome reaction (e.g. [13,20]), as well as various behavioural responses, including changes in sperm motility (chemokinesis) and chemo- and thermotaxis towards unfertilized eggs [21].

Sperm cells themselves can also initiate cellular-level interactions between the sexes. For example, in pigs the arrival of sperm in the oviduct initiates a mutual signalling cascade between sperm and the oviduct's epithelium, which modifies oviduct gene expression and protein synthesis, which in turn elicit physiological responses in the sperm (e.g. [22]). In many species, sperm or sperm-derived diffusible factors can also induce oocyte maturation and ovulation [23]. Furthermore, many other (non-sperm) components of the ejaculate can modify various female processes and responses, such as egg production, sexual receptivity, sperm storage and immunity [24]. It has been argued that this complex chemical dialogue between the sexes provides the scope for female-induced sperm recognition and selection, ensuring that only a small subset of sperm cells are able to fertilize the eggs (e.g. [18,25]).

Chemically moderated sperm selection occurs across a range of internally (e.g. [26]) and externally fertilizing taxa [13,27,28], including numerous plants and fungi [10] (see §6). For example, in many externally fertilizing species, the activation of sperm motility is induced by egg-derived soluble factors [29]. Furthermore, fertilization generally takes place in a liquid medium that originates, at least in part, from females, and is known to mediate pre-fertilization chemical communication between the sexes. In mammals, fertilization occurs in the oviduct, where female follicular fluid plays a stimulatory (or inhibiting) role in inducing sperm motility [30]. Similarly, in many externally fertilizing species, changes in sperm motility are induced through interactions with ovarian fluid or egg-derived chemical factors released into the water along with the spawned eggs [31,32]. Such female reproductive fluids are likely to have a strong naturally selected function in sexual reproduction [19]. However, the possible roles that these fluids and female sperm selection mechanisms play in sexual selection (i.e. GMMC) have received much less attention.

3. Why is gamete-mediated mate choice important?

Given the central role that females play in controlling sperm physiology and behaviour during fertilization, an inevitable question is whether they also exploit such mechanisms to facilitate GMMC. As we point out in this prospective review, there is tantalizing new evidence from a range of species that such cellular-level interactions provide the scope for females to exert GMMC.

We present four arguments that in our view emphasize the special importance of studying GMMC. First, sexual selection at the cellular (gamete) level probably arose soon after the evolution of syngamy (fusion of two separate gametes) and thus represents the ancestral form of sexual selection [14]. Second, GMMC potentially enables more accurate—even spermatozoa-specific—gamete selection than any known mechanisms of sexual selection [15]. Thus, by gaining a better understanding of GMMC, we stand to gain a more comprehensive understanding of the overall scope of sexual selection. Third, GMMC provides the only available mechanism of mate choice in species where pre-ejaculatory sexual selection is not possible. Such species include a large number of taxa that lack sexual dimorphism and sufficient sensory capabilities for pre-ejaculatory mate choice, including numerous sessile or sedentary broadcast-spawning animals and plants, where males and females rarely interact directly [9,10]. Thus, the GMMC concept helps to broaden the scope of sexual selection studies to include species that have traditionally been overlooked in sexual selection research [10]. Finally, given the paucity of knowledge about the mechanistic basis of gamete fusion and fertilization [33], elucidating cellular-level processes of mate choice may offer important

new tools for the clarification of molecular-level mechanisms of fertilization and their adaptive functions.

4. Is there any evidence for GMMC?

In this section, we briefly review a range of putative mechanistic processes that have the potential (or demonstrated capacity) to generate intraspecific biases in fertilization success.

(a) The role of female reproductive tract secretions in promoting GMMC

Unfertilized eggs are commonly surrounded by fluids secreted from the female's reproductive tract, such as follicular fluid and oviductal fluid in mammals [30,34], and ovarian fluid in externally fertilizing fish and amphibians [28,31]. In many externally fertilizing species, the high viscosity of ovarian fluid means that it tends to remain in contact with the released eggs in the water [35]. Common to all of these fluids are substances such as proteins, glycoproteins, hormones and nutrients [30,31,36,37], which are present prior to and/or during fertilization [30,35]. These fluids can impose contrasting effects on sperm motility, for example by enhancing sperm motility in some cases [30,35,38] and inhibiting it in others [22,30,39]. In internal fertilizers, follicular and oviductal fluids have also been shown to facilitate sperm release from their oviductal reservoir (both follicular and oviductal fluids [17]), induce capacitation (both fluids [36,40]) or inhibit it (oviductal fluid [41]), induce the acrosome reaction (both fluids [30,36]) or delay it (oviductal fluid [42]), facilitate sperm–zona pellucida binding (both fluids [36,43]) or inhibit it (follicular fluid [44]), and act as a sperm chemoattractant (both fluids [38]).

The evidence for within-species differential responses of sperm to female-derived fluids suggests that the composition of female reproductive fluids may show intraspecific variation. Consistent with this possibility, both organic [45] and inorganic [35] components of these fluids have been shown to differ among individual females within a single species, raising the intriguing possibility that these substances are involved in GMMC. However, we are aware of only a handful of studies that have tested this possibility explicitly [34,46–50] (table 1), five of which show support for the hypothesis [34,46,48–50] (see also [58], for ovarian fluid mediated conspecific sperm precedence). For example, Satake *et al*. [34] demonstrated that in pigs soluble oviductal proteins suppress sperm motility and modify sperm swimming trajectories, and that these effects varied among different males. More explicit evidence for GMMC came from a study by Gasparini & Pilastro [46], who found that in the internally fertilizing poeciliid fish *Poecilia reticulata*, ovarian fluid exerted differential effects on the motility of sperm from related and unrelated males, which ultimately accounted for the fertilization bias towards unrelated males when sperm from related and unrelated males were artificially inseminated into females. Furthermore, Geßner *et al*. [50] recently demonstrated that ovarian fluid mediates fertilization bias against related males in externally fertilizing salmonid fish *Oncorhynchus tshawytscha* (see also [51]). Similarly, in this same species, Rosengrave *et al*. [49] reported evidence for GMMC showing that competitive fertilization success and embryo survival were biased towards the male whose sperm swam fastest in the female's ovarian fluid (see also [59] for ovarian fluid-mediated maintenance of colour polymorphism in *O. tshawytscha*). Finally, Alonzo *et al*. [48] reported that in the externally fertilizing ocellated wrasse *Symphodus ocellatus*, ovarian fluid selectively biased the outcome of sperm competition towards preferred (parental) males by decreasing the numerical advantage that sneaker males would otherwise have during sperm competition.

Other studies have indirectly tested whether GMMC favours sperm from 'compatible' males by testing for the male–female interaction effect of the female ovarian fluid on sperm motility. Three of these studies [52–54] found that the sperm motility of a given male was dependent on the female (ovarian fluid) identity (male–female interaction) while one study failed to find such an interaction [55].

(b) Can egg-derived soluble factors promote GMMC?

Along with the female's reproductive tract, eggs and their surrounding structures (e.g. egg jelly, cumulus cells and zona pellucida) also secrete various soluble factors. Again, all of these factors have been shown either to stimulate or inhibit sperm motility and/or fertilization [18,61,62], and mediate pre-fertilization chemical communication between sperm and egg (or female) [13]. The role that these factors play in influencing chemical communication between gametes is best described in externally fertilizing marine invertebrates [63]. For example, in echinoderms, the egg jelly secretes diffusible chemical substances, called sperm activating peptides (SAP), which elicit behavioural and/or physiological responses by sperm. Until now, several hundred SAPs have been identified, and within individual species SAPs commonly exist in several isoforms. Although the functions of these peptides and their isoforms are largely unknown for most species, SAPs can play an important role in sperm chemoattraction [63]. Sperm chemoattractants have been identified in only a handful of externally fertilizing species, although the basic molecular mechanisms of chemotaxis are likely to be common to all taxa [64]. In addition to chemotaxis, egg-derived soluble factors can serve other functions, such as modifying sperm motility, respiration, capacitation, acrosome reaction and sperm-to-egg binding [19,27,63,65].

The high intra-specific diversity of SAPs suggests that they may be capable of affecting sperm behaviour and physiology in more nuanced ways than currently appreciated. Interestingly, the sperm receptors for egg- and female-derived soluble factors also seem to exhibit considerable intra-specific variation [21,66,67]. Together, these observations raise the intriguing possibility that SAPs (and various other egg-derived soluble factors) play a role in sperm pre-fertilization 'selection', thus potentially facilitating GMMC. Recent evidence from marine mussels (*Mytilus galloprovincialis*) is consistent with such a function [11,12,32] (table 1). In *M. galloprovincialis* sperm migration in the presence of egg chemoattractants was found to be strongly dependent on the specific identities of males and females (male–female interaction) [32], and sperm swam faster towards eggs with which they were ultimately most compatible [11]. Moreover, Lymbery *et al*. [12] have recently shown that egg chemoattractants differentially moderate intraspecific sperm competition in *M. galloprovincialis*, thus confirming the

Table 1. Direct or indirect evidence for GMMC and potential evolutionary implications of the process. SC = sperm competition; + = supporting GMMC; − = no support for GMMC; I = internally fertilizing species; E = externally fertilizing species.

mediating factor	mechanism	outcome	species	implications	GMMC	refs.
female reproductive tract secretions						
soluble oviduct proteins	selective sperm activation	sperm selection?	*Sus scrofa* (I)	unknown	+	[34]
ovarian fluid	selective sperm motility stimulation	fertilization bias	*Poecilia reticulata* (I)	inbreeding avoidance	+	[46]
ovarian fluid	selective sperm motility stimulation	fertilization bias	*Oncorhynchus tshawytscha* (E)	incompatibility avoidance	+	[49–51]
ovarian fluid	general sperm motility stimulation	fertilization bias	*Symphodus ocellatus* (E)	directional selection	+	[48]
ovarian fluid	selective sperm motility stimulation	no fertilization bias	*Oncorhynchus tshawytscha* (E)	—	−	[47]
ovarian fluid	selective sperm motility stimulation	unknown	*Salvelinus alpinus* (E)	unknown	(+)	[52]
ovarian fluid	selective sperm motility stimulation	unknown	*Oncorhynchus mykiss* (E)	unknown	(+)	[53]
ovarian fluid	selective sperm motility stimulation	unknown	*Oncorhynchus tshawytscha* (E)	unknown	(+)	[54]
ovarian fluid	no selective sperm motility stimulation	unknown	*Salvelinus namaycush* (E)	—	(−)	[55]
egg-derived soluble factors						
sperm chemoattractants	differential sperm chemotaxis success	fertilization bias (no SC)	*Mytilus galloprovincialis* (E)	incompatibility avoidance	+	[11,32]
sperm chemoattractants	differential sperm chemotaxis success	fertilization bias (SC situation)	*Mytilus galloprovincialis* (E)	incompatibility avoidance	+	[12]
non-soluble factors/gene-based gamete interactions						
sperm surface protein (bindin)	unknown	assortative fertilization	*Strongylocentrotus purpuratus* (E)	incompatibility avoidance	+	[56]
MHC-dependent fertilization bias	unknown	fertilization bias	*Salmo salar* (E)	hybridization avoidance	+	[57]
sperm surface glycans	differential female immune response against sperm	reproductive incompatibility	Mouse (I)	incompatibility avoidance	+	[58]
sperm surface glycans	differential effect of soluble egg factors on sperm surface	sperm Ca^{2+} influx	*Mytilus galloprovincialis* (E)	incompatibility avoidance	(+)	[20]

role that GMMC plays in ensuring that fertilization occurs between reproductively compatible gametes. While these patterns of selection provide direct evidence for GMMC, the identity of egg-derived chemical factors in this system (and in the majority of other species) needs to be determined.

(c) Non-soluble factors

Gamete surface recognition proteins (GRPs) have been suggested to play an important role in determining the compatibility of sperm and eggs during fertilization [68,69]. Thus, intra-specific functional variation in GRPs is expected to lead to assortative fusion of gametes within populations, but direct evidence for the role of GRPs in GMMC is scant. Interestingly, Stapper *et al*. [56] recently demonstrated that in the sea urchin *Strongylocentrotus purpuratus*, when eggs were given an opportunity to selectively 'pair' with the sperm of several males, eggs non-randomly fused with sperm that had a cell surface protein (bindin) genotypes similar to their own (table 1). This finding accords with earlier evidence from another sea urchin species *Echinometra mathaei*, revealing that competitive fertilization success was biased towards males that share the same bindin genotype as the female [70]. In both cases, the authors concluded that the most likely explanation for their finding was the assortative fertilization mediated by sperm bindin and its egg surface receptor. Non-random gamete fusion based on shared gene (major histocompatibility complex) loci was also reported in Atlantic salmon *Salmo salar* [57]. Although the precise molecular-level mechanisms for such non-random fertilization remain unclear, there is some indirect evidence that sperm surface receptors for MHC peptides may play an important role in the process (see §5).

Along with proteins, gametes (and all other cells) are coated by glycans—an oligo- and polysaccharide shell [71] that forms the outermost layer of the cells. Thus, the first direct interaction between gametes (or any extracellular substances that come into contact with gametes) must occur via this layer. Accordingly, glycans are known to mediate a wide array of cellular-level interactions and have higher structural diversity and regulatory capacity than any other class of biological molecule [71]. Similarly, sperm lectins (proteins that bind to glycans) also exhibit extraordinary intra-specific diversity (e.g. zonadhesin [72]; bindin [71]; lysin [73]; spermadhesin [74]; sperm receptor for egg jelly [75]). Interactions between carbohydrates and lectins play important roles in the binding of sperm both to the surface of the oviduct (e.g. during sperm storage in mammals) and the egg's surface layer prior to fertilization [74]. For example, it has been estimated that in mammals, approximately 80% of the sperm binding sites on the egg surface are carbohydrate dependent, whereas 20% of these sites may rely on protein–protein interactions [62,76,77]. The high diversity of glycans allows highly specific molecular-level interactions between gametes [71]. Indeed, cells of each individual organism have unique ('self') glycan patterns that distinguish them from those from all other ('nonself') organisms. Interestingly, even relatively primitive organisms such as echinoderms have cells that are capable of self-recognition [78]. It seems likely, therefore, that the female reproductive tract and/or egg surface glycans have the capacity to discriminate among sperm from different males, perhaps even at the level of individual spermatozoa [15].

More direct evidence for the role of self-recognition in GMMC comes from a study demonstrating that certain sperm surface glycans cause an immune response in females that leads to reproductive incompatibility between particular males and females that have mismatched cell surface glycans [58]. This evidence, along with other recent findings, suggests that the immune system may play an important role in GMMC (see §5). Furthermore, recent work on the marine mussel *Mytilus galloprovincialis* has revealed that egg-derived chemical factors egg water trigger changes in sperm surface glycans and the sperm acrosome reaction [19], and that the strength of these physiological responses by sperm is strongly dependent on specific male–female interactions [20]. Kekäläinen & Evans [20] also found evidence that these egg water-induced changes in sperm glycans coincide with an influx into the sperm of Ca^{2+}, a key regulator of fertilization from sperm capacitation to gamete fusion [79].

Notwithstanding the findings by Ghaderi *et al*. [58] and Kekäläinen & Evans [20], there is a paucity of direct evidence supporting the idea that glycans can mediate GMMC, although there is tentative indirect support for such a function. For example, the selective binding of sperm to oviductal and egg surface glycoproteins may reduce the likelihood of fertilization by poor quality (low motility, abnormal morphology and abnormal chromatin/DNA structure) sperm [80]. Teijeiro *et al*. [81] uncovered potential mechanisms for this form of selection by demonstrating that the porcine oviductal surface sperm binding glycoprotein is involved in suppressing sperm motility and altering the integrity of the sperm's acrosome. Importantly, Teijeiro *et al*. [81] showed that such inhibiting effects varied across different sperm subpopulations within individual males, indicating that similar processes may also function to selectively favour sperm from different males.

(d) RNA and extracellular vesicles

Mature sperm cells contain complex 'populations' of different RNA subtypes, known to be important for fertilization and early embryo development [82]. Interestingly, it has been suggested that small non-coding RNAs, piRNA and microRNA, may play important roles in the verification of the cytoplasmic and genetic compatibility of gametes prior to fertilization [83]. In this process, non-coding sperm RNAs may recognize their respective binding sites in oocyte RNAs. Conversely, oocyte piRNAs and microRNAs may recognize and 'evaluate' the compatibility of incoming sperm using the same mechanism. During this gamete 'pairing' process, RNAs may either activate or suppress their partner cell, depending on the cytoplasmic and/or genetic compatibility of the gametes. This raises the intriguing (but as yet untested) possibility that these small RNA molecules may facilitate GMMC.

In addition to gamete RNAs, oocytes are also known to emit RNA-containing vesicles (extracellular vesicles; EVs) into the extracellular environment, for example through follicular, oviductal and uterine fluids [84]. Interestingly, EVs emitted by unfertilized oocytes are able to fuse with the sperm, where they can induce the sperm acrosome reaction [84] or moderate gamete fusion [85]. Thus, in principle, an RNA-based mechanism controlling gamete compatibility could occur well before gametes come into physical contact, possibly explaining how remote chemical signalling leads to

assortative fertilizations (e.g. between genetically compatible gametes; see §4a,b). Furthermore, in addition to RNAs, EVs are known to contain a wide variety of other bioactive molecules, such as proteins, lipids, carbohydrates and DNA [84]. Elucidating the possible roles that these molecules play in moderating GMMC offers an exciting challenge for future research in this area.

5. Immune system—a potential universal mediator of GMMC?

The evolution of the immune system is traditionally attributed to natural rather than sexual selection [86]. However, recent evidence suggests that immunity and reproductive function may be closely associated processes. For example, both immunity and reproduction involve cellular-level communication and critically depend on the recognition of particular cell types in a highly specific manner [87]. Furthermore, in many internally fertilizing species, the presence of ejaculates can trigger immune responses in females [86,88,89], eventually leading to the destruction of spermatozoa that are not required for fertilization (leucocyte reaction [90]). Interestingly, males also show considerable individual variation in their ability to elicit female responses and polymorphism in genes regulating these responses [86,91]. Additionally, changes in female gene expression that are induced through mating depend on the specific combination of males and females [92]. Thus, female post-mating immune responses may have evolved to facilitate GMMC [86], allowing females to bias fertilization towards compatible or otherwise preferred male partners [93].

The mechanisms by which the female's immune system may mediate GMMC have yet to be established formally (e.g. [93]). However, in mammals, for example, seminal fluid, follicular fluid and egg secretions are all known to contain various immune molecules, including cytokines and chemokines (immune system signalling molecules), as well as major histocompatibility complex (MHC) antigens (proteins responsible for the regulation of the immune system) [65,94–97]. Follicular fluid cytokines (and possibly also soluble MHC peptides; see [98]) are known to regulate sperm motility and chemotaxis via sperm surface receptors [95], and are predictive of oocyte fertilization [99]. Similarly, male seminal fluid cytokines, as well as soluble MHCs, are predictive of sperm quality and fertility [96,97]. Interestingly, it has recently been demonstrated that male reproductive tissues and possibly sperm cells express olfactory receptors for various MHC peptides [21], which may serve the function of signalling the MHC haplotype and thus 'self' (identity) of the spermatozoa [98]. Given that it is well known that body odours associated with MHC can mediate mate choice prior to gamete release (e.g. [100]), this finding raises an intriguing possibility that MHC peptides and their receptors could play important roles in reinforcing such mating preferences at the level of gametes.

Morrow & Innocenti [86] predicted that sexual selection via female post-ejaculatory immune responses should play a particularly important role in internally fertilizing species, where ejaculates are in direct contact with the female reproductive tract. However, there is no reason why female immune responses should not mediate post-ejaculatory sexual selection in externally fertilizing taxa as well. For example, immune proteins and glycoproteins are also present in the gametes and surrounding fluids in externally fertilizing species (e.g. [101,102]), suggesting that immune responses could potentially occur after gamete release in the surrounding environment. Furthermore, despite the fact that acquired immune systems (and thus immunoglobulins) exist only in jawed vertebrates, immune systems can be surprisingly sophisticated in many other taxa. For example, self-recognition ability—a potentially important prerequisite for GMMC [58]—is almost universal, existing in nearly all metazoans [103]. Finally, females from both internally and externally fertilizing species tend to have more powerful immune responses than males [104], which suggests the potential for sexual selection to drive sex differences in immune function. Taken together, these observations suggest that the immune system may represent a universally important mediator of GMMC across a broad diversity of taxa.

6. Taxonomic breadth of GMMC

Pre-fertilization mate choice can be studied most readily in species that release their gametes into the external environment. Accordingly, much of the evidence for GMMC has come from externally fertilizing taxa, notably broadcast-spawning invertebrates (table 1), although it is likely that these processes are common to a broad range of species. For example, in mammals, post-ejaculatory cellular-level interactions occur in a highly 'controlled' environment inside the reproductive tract of the female [15], which indicates that putative mechanisms of GMMC are also likely to be widespread in internally fertilizing taxa. Supporting this view, several studies on mammals have shown that mixed inseminations with semen of multiple males frequently lead to highly skewed fertilization outcomes (reviewed by [15]). It is also likely that the taxonomic breadth of GMMC extends beyond animals, for example to many plants and fungi, where the mechanisms underlying selective fertilization are strikingly similar to those operating in many animals. Beekman *et al*. [10] have recently argued that the female reproductive secretions commonly reported across plant, animal and fungi kingdoms (e.g. ovarian fluids, chemoattractants, pheromones etc.) may serve a common role in terms moderating gamete interactions that differentiate prospective mates after gamete release. Indeed, in the case of plants, polyandry and pollen competition are widespread, and females are therefore likely to benefit by exploiting mechanisms that enable them to bias the paternity of their seeds towards compatible or otherwise 'preferred' males [105]. Interestingly, Lankinen *et al*. [106] recently showed that in the hermaphroditic mixed-mating plant *Collinsia heterophylla*, siring success under competitive pollination depended on the specific combination of males and females (i.e. male-by-female interaction). One potential explanation for this finding is that the pistils of the females conduct GMMC towards compatible males. Although this anecdotal evidence for GMMC is suggestive, far more work on non-animal species is needed to better understand whether GMMC is a general phenomenon in these taxa [10,107].

7. Evolutionary significance of GMMC

The accumulating evidence that females exploit cellular- and molecular-level processes to exert biases in competitive fertilization success strongly suggests that GMMC is adaptive for

females [7,15]. However, it is also important to note that post-ejaculatory signalling is not a one-way process (see §§2, 4d and 5), and involves a complex chemical dialogue between the gametes from both sexes. It is likely, therefore, that males also benefit from GMMC, particularly where GMMC depends on male–female compatibility (reviewed by [7]). In principle, GMMC may result either in (i) directional selection, where GMMC biases fertilization towards certain (presumably high quality) individual phenotypes, or (ii) non-directional selection, where preference criteria of GMMC will differ across different male–female combinations (e.g. depending on the genetic compatibility of males and females). To date, most of the available evidence for GMMC is consistent with non-directional selection, through incompatibility, inbreeding or hybridization avoidance (table 1; but see [48]). However, further studies incorporating a range of different mating systems are required to assess the generality of these patterns.

8. Conclusion

Post-ejaculatory cellular-level communication between the sexes is a critical component of sexual reproduction across a diverse array of taxonomic groups. Until recently, the primary (naturally selected) function of these forms of communication was thought to be limited to ensuring the successful fertilization of oocytes. However, a growing number of studies indicate that these communication processes may also allow highly specific discrimination among individual sperm cells on the basis of their quality or compatibility with the egg (or female). Thus, we argue that an additional adaptive explanation for these communication processes is to moderate GMMC. Given that some form of gamete-level communication almost certainly occurs in all sexually reproducing species, a better understanding of the mechanistic processes of gamete communication within a framework that recognizes the potential for GMMC will have a great potential to pave the way towards a more inclusive view of sexual selection and reproduction. In our view, a unified framework that combines these largely disparate disciplines of study is highly desirable, both from a fundamental perspective but also in more applied areas of study.

From a fundamental perspective, we envisage that a closer focus on GMMC will help broaden the sexual selection concept to species in which traditional (pre-ejaculatory) sexual selection mechanisms cannot operate [9,10]. As we highlight in this review, there has already been considerable progress in this regard, and we envisage that the insights gained from studies of these 'neglected' taxa will continue to promote research into GMMC in more familiar taxa (e.g. [15,46,49,58], reviewed by [10]). Such approaches will no doubt improve our understanding of the nuanced ways in which sexual selection operates in 'higher-order' taxa, where post-ejaculatory sexual selection has been recognized for decades [3,7,108,109]. We also anticipate that by identifying the scope of mechanisms underlying GMMC, we can hope to gain a better understanding of the evolutionary origins of more overt forms of mate choice and mating competition [14].

From an applied perspective, we see a range of potential benefits of understanding the mechanisms that ultimately determine whether sperm from a given male will successfully fertilize eggs from a particular female, and the potential flow-on effects in terms of offspring development and survival. For example, current clinical infertility diagnoses partition causes of infertility into male- or female-dependent factors [110], and therefore ignore the possibility that parental incompatibility, possibly expressed through gametes and reproductive fluids (and thus via GMMC), may play an important role in the process. Gamete-level incompatibilities may explain, at least in part, why infertile couples often fail to conceive even after multiple rounds of treatment, which for 30–40% of cases remain unexplained [111]. Thus, we envisage that the integration of the GMMC concept with current fertilization research may offer novel solutions for more efficient infertility diagnostics methods and development of new (e.g. male) contraceptives.

Data accessibility. This article has no additional data.

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Competing interests. We declare we have no competing interests.

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