Gamete Fusion: Key Protein Identified

Is there a common mechanism of eukaryotic sex? Two recent reports highlight an ancient and widely distributed protein that is key to gamete fusion and is a potential target for malaria vaccines.

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Sex defines us — not as individuals or as a species but as eukaryotes. Reductive meiotic division to produce haploid gametes, and the subsequent fusion of these two cells allow for two vital processes: the reassortment of alleles through recombination, and the regeneration of decrpet bodies by reversion to a single-celled state followed by new cell growth. Sex has undoubtedly been a key to the success of eukaryotes, but it’s a tricky thing to do. The gametes must recognize each other, then fuse; and both of these processes must be managed carefully as failures are disastrous. Despite the fundamental nature of this process, pulling back the veil to get a peek at the molecular mechanisms controlling gamete fusion hasn’t been easy, in stark contrast to the exquisite detail in which the processes of intracellular membrane fusion have been described. But vesicle fusion within a cell has little in common with the union of two intact cells, and only very recently have some of the proteins involved in gamete fusion in plants and animals been identified (reviewed in [1]). Still lacking is a basic understanding of the exact role these proteins play in the complex series of events that leads to fertilization. This deficiency in understanding stems in part from the complex nature of gamete development, which limits the availability of tractable in vitro experimental systems, and also from the difficulty in observing and manipulating the processes of fertilization in vivo [1].

Two new papers — one in a recent issue of Current Biology by Hirai et al. [2] — have made significant strides towards understanding the fundamental process of gamete fusion [2,3]. Both focus on a protein, known either as GCS1 (generative cell specific 1) or HAP2 (hapless2), that was first identified in screens for male-fertility mutants defective in pollen tube growth in the plants Arabidopsis [4] and Lilium [5], then again in a screen for mutants compromised at later stages of gamete interaction in the green algae Chlamydomonas reinhardtii [3]. GCS1 thus has a clear role in plant and algal fertilization, but genome searches have also revealed homologues in malaria parasites (Plasmodium), African sleeping sickness parasites (Trypanosoma brucei), slime moulds, ciliates, choanoflagellates and cnidarians [5], suggesting that GCS1 is an ancient and highly conserved component of the gamete fusion apparatus. Hirai et al. [2] and Liu et al. [3] now provide elegant support for this hypothesis.

The fact that both groups chose to work with malaria parasites to investigate GCS1 function marks something of a coming of age for...
Plasmodium as a model system. Typically, doing anything in the lab with malaria parasites is very difficult, but studying malaria parasite sex is a notable exception. Gamete production in malaria parasites commences immediately after the parasites are taken up in a mosquito blood meal (Figure 1), but gametogenesis can be initiated in vitro by simply taking parasites cultured in blood and altering temperature and pH to mimic conditions found in the mosquito midgut [6]. Moreover, Plasmodium gametes lack the complex extracellular matrix that surrounds the gametes of most other organisms [7], providing direct access to the action. Loss of the GCS1 gene in microgametes (the male gamete in Plasmodium) reveals its requirement for successful fertilization. Deletion of GCS1 blocked zygote formation and subsequent parasite development in the mosquito host, effectively stopping the transmission of the disease. Importantly, GCS1 is apparently exposed on the surface of the male gamete [3], raising the possibility of targeting this molecule as part of a transmission blocking strategy. The idea here is to create a so-called ‘Good Samaritan’ vaccine that prevents people from passing on the infection by inducing antibodies that block development of the parasite only after it leaves the human host and enters the insect [8]. GCS1 is a promising target candidate for such a vaccine.

Liu et al. [3] took the investigation of GCS1 function a step further, pursuing the exact timing of GCS1 function in Chlamydomonas. Their evidence indicates that GCS1 acts in the few seconds between gamete adhesion and fusion, strongly suggesting a role in the fusion process itself [3]. A post-adhesion function was also indicated for GCS1 in Plasmodium. It is interesting to note that the molecules involved in the pre-fusion adhesion processes in Chlamydomonas and Plasmodium are unrelated, suggesting that GCS1 may perform an essential function, such as membrane fusion, that has been conserved between these widely divergent species, even though other components of the process became highly specialized.

Although GCS1 first emerged in plants and algae, and malaria parasites are known to have a plastid of endosymbiotic algal origin [9], there is no suggestion that GCS1 was acquired from the endosymbiont. Indeed, the presence of GCS1 homologues in a wide variety of eukaryotes argues for a deep ancestry, and phylogenetic analysis of the GCS1 genes is congruent with accepted evolutionary relationships, supporting vertical inheritance. So, it appears that GCS1 has ancient origins, most likely being conserved since the divergence of all eukaryotes [2,3].

Given its ancient origins and widespread distribution, it is intriguing that GCS1 has apparently disappeared in higher animals. This is somewhat at odds with its apparent role in the fundamental process of gamete fusion. The only obvious homologue among insects is in the flour beetle Tribolium castaneum, but the region of homology to GCS1 is confined to the amino terminus, and the carboxyl terminus of the flour-beetle protein has more similarity to a family of calcium transporters involved in neural signaling [10]. Understanding the function of this gene (a homologue of which is also found in honey bees [3]) awaits further investigation.

Paradoxically, the genomes of many recently diverged animals lack obvious GCS1 homologues [2,3]. If GCS1 is indeed an important part of the ancestral gamete fusion apparatus, this might suggest that complex, multicellular organisms have invented novel forms of gamete fusion. An example of one of these experiments in fertilization is found in Drosophila, where canonical gamete fusion is replaced by a process in which an intact sperm enters the egg [11] and fertilization occurs only after degradation of the male gamete’s plasma membrane, a process that results in the release of the genetic contents [12]. Mammals retain a more typical process of gamete fusion but apparently lack GCS1 and presumably replaced it with unique proteins not yet thoroughly described [1]. The novel adaptations in these organisms raise intriguing questions. Is evolutionary experimentation with new methods of fertilization unique to animals or has it occurred in other kingdoms?

What drove the novel adaptations in...
gamete fusion? Was it the loss of GCS1, or did other evolutionary changes make GCS1-mediated gamete fusion deleterious? It could be argued that the elaborate courtship rituals and the internal insemination and gamete fusion of animals might reduce the need for strictly regulated gamete fusion, but it appears more likely that these mating strategies might lower the stringency of the species recognition machinery, which Liu et al. [3] have elegantly demonstrated does not involve GCS1 [3]. Thus, other explanations for the loss of GCS1 in animals must be sought.

Understanding the functions and distribution of GCS1 in a range of organisms should shed light on the role of changes in the mechanisms of fertilization in the evolution of eukaryotes. Analysis of GCS1 might also be useful in figuring out when sex first evolved in eukaryotes [13]. For instance, GCS1 is apparently lacking in Giardia lamblia, a pathogenic eukaryote held by some to be a very early (perhaps pre-sexual) eukaryote, but the absence of GCS1 in other later emerging lineages (fungi and most animals for instance) makes it hard to establish the real significance of the lack of GCS1. A role for GCS1 in gamete fusion is now clear, but how sex arose at the dawn of eukaryotes is still to be revealed.

References

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