

Review

Learning to get along despite struggling to get by

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Abstract

How cooperation can evolve by natural selection is important for understanding the evolutionary transition from unicellular to multicellular life. Here we review the evolutionary theories for cooperation, with emphasis on the mechanisms that can favor cooperation and reduce conflict in multicellular organisms.

Altruism occurs when individuals behave in ways that reduce their own survival or reproduction and provide a fitness benefit to others. While it is often studied in the context of societies or animal behavior, some of the most powerful examples in the biological world are found inside a multicellular organism. From apoptosis-induced suicide to the presentation of foreign antigens by cells that target them for death, it is clear that the cells of a multicellular organism cooperate and behave altruistically. Less obvious, however, is how acts of selflessness can evolve by natural selection if they reduce the fitness of the individuals which perform them, and how they persist despite the immediate benefits of behaving more selfishly.

Social evolution addresses the benefits that cooperation among individuals provides and how it can be maintained in the face of opportunities to cheat. An important goal is to understand how potential conflicts are resolved to give rise to stable societies, whether the society consists of a group of animals or the cells of a body [1-3]. Of course, genetic variation is the raw material upon which natural selection acts, and thus an obvious way to stamp out selection is to limit genetic variation. Indeed, many multicellular organisms develop from a single cell, and conflict is partly reduced by this and other mechanisms that limit genetic heterogeneity within the individual [3-5]. Much of social evolution theory, however, was developed around studies of animal societies, such as social insects, where interactions routinely take place between individuals which vary in their

relatedness [5,6]. These studies have not only revealed strategies to direct the benefits of costly actions towards relatives, but also mechanisms to enforce cooperation, such as policing and punishment of rogue individuals whose selfish interests threaten the functioning of the colony [7,8]. For example, in some species of bees, ants and wasps, worker-laid eggs are sought out and destroyed by the queen or other workers (Figure 1). Worker policing reduces the benefits that accrue to individuals who selfishly invest in their own reproduction rather than working to benefit that of the queen [9].

Here we review mechanisms that reduce conflicts and promote cooperation in taxonomically diverse organisms. We highlight why selfish behaviors sometimes arise and persist, and we argue that minimizing the opportunities for selfish behaviors may have played a vital role in many aspects of multicellular biology, both within the lifespan of the individual and across generations. We discuss these mechanisms from different viewpoints - from basic life-history features, such as unicellular bottlenecks during development, to the genetic and molecular bases of altruistic behaviors and how they might function to stabilize cooperation among different cells.

Relatedness and the unicellular bottleneck

Many multicellular organisms start as a single cell, which undergoes successive cell divisions to produce all of the cells

**Figure 1**

Worker policing in the wasp *Dolichovespula saxonica* [69]. Classic examples of altruism occur in the social insects, where workers forego their own reproduction to raise the queen's offspring. Hamilton's inclusive fitness theory (also referred to as kin selection theory) showed that individuals might give up their personal fitness if it enhances that of their relatives (Box 1) [12,13]. Nevertheless, additional mechanisms can also be important for enforcing cooperation and preventing selfish behaviors [1,7,8,70]. Here, a worker that lays an egg (left) has that egg eaten by another worker (right). Photo courtesy of Kevin Foster, Harvard University.

of the body. This 'unicellular bottleneck', or passage through a single-cell stage each generation, is thought to be an adaptation that ensures that all the cells of the body are highly related, thus minimizing conflict over which cells adopt the somatic cell fate - and die in the current generation - and which cells contribute to the next generation through reproduction (the germline) [2,10,11]. In this view, somatic cells can be selected to perform acts of altruism because, by improving the survival and reproduction of the organism as a whole, they enhance the fitness of the germline cells that carry their genes into the next generation. Kin selection theory explains why individuals might behave altruistically if their actions benefit their relatives (Box 1) [12,13].

In addition to increasing relatedness between cells, the unicellular bottleneck can also help to purge selfish variants from the population if they entail a fitness cost in the absence of their victims [3,10,11]. For example, selection might favor genetic variants that are predisposed to adopt the germline fate, but a unicellular bottleneck would prevent them from attaining prevalence if they failed to form an adequate soma in the absence of compensation by other cells. Development from a single cell may have additional advantages in reducing the threat of selfish behavior. In higher metazoans, germline cells are sequestered early in development, reducing the number of divisions that they undergo before transmission and limiting the opportunities

Box 1. Kin selection theory and the evolution of altruism

Kin selection was formulated by Hamilton to explain the evolutionary logic underlying altruism: why individuals behave in ways that reduce their personal fitness and provide a fitness advantage to others [12,13]. Kin selection theory demonstrates that organisms can evolve to perform costly actions if they benefit their relatives, who carry (and thus pass on) their genes. Although we usually think of kin selection in terms of individuals behaving altruistically towards their blood relatives, it is more straightforward to explain the theory from the perspective of the gene that confers the costly behavior. Such a gene can increase in frequency only if the costly behavior it causes in some is more than offset by the fitness benefit it confers in others. Several corollaries of kin selection theory follow more naturally from this gene-centered explanation. First, individuals would ideally direct the benefits of their costly behavior to other individuals who carry the same gene - thus, the ability to discriminate kin from non-kin, called kin discrimination, is thought to be important for the evolution of such a costly trait. Second, 'relatives' are really those who carry the same gene. They do not necessarily have to be genetically similar throughout the entire genome, although altruism that runs counter to relatedness across the genome could provoke a coevolutionary response to suppress its effects [67,68]. In practice, knowing to whom you are related via shared ancestry may be an easy way of approximating true (gene-specific) relatedness: high average relatedness across the genome owing to a recent common ancestor also means a high probability of relatedness at any given locus, including the one responsible for the altruism. Finally, with respect to a costly ('altruism') gene becoming established in a population by natural selection, relatedness is relative to the scale at which competition between alleles occurs. Strictly speaking, the cells of the body do not behave altruistically towards one another because they are genetically similar, but because they are on average more genetically similar to one another than they are to cells from other individuals. By the same token, if competition occurs primarily among the cells within the individual rather than between individuals, then selection may no longer favor acts of altruism and instead promote the evolution of more selfish behaviors.

for selfish mutations to arise and propagate. Plants do not sequester a germline during embryonic development, although it has been argued that the immobility of plant cells reduces the need for such protections [3]. In rare cases, when somatic cells have circumvented the germline route to transmission, the outcome can be devastating. Canine transmissible venereal tumor (CTVT) is a cancer that is infectious transmitted between dogs [14]. The tumor cells are transferred through direct contact, primarily during copulation, but also through other forms of contact, such as

biting and grooming. Phylogenetic analyses indicate a single origin of the cell lineage, somewhere between 200 and 2,500 years ago, making it the oldest known continuously propagated somatic cell line [14]. Contagious tumors have also been reported in hamsters and the Tasmanian devil - in the latter, the spread of the disease is threatening the survival of the species [15-17].

Conflict can emerge in the gametes

Although the diploid cells of metazoans are genetically identical to one another (somatic mutations notwithstanding), intercellular genetic heterogeneity occurs in the gametes as a result of meiosis. The resulting variability in the extent to which different gametes contain or transmit different alleles provides the traction for selection to take hold, favoring those genes that maximize their transmission to the next generation. Not surprisingly, nearly all examples of selfish genetic elements in higher eukaryotes can be traced back to conflicts that originate during this stage of the life cycle, with some examples described below. The ensuing conflict is thought to explain some of the most fundamental aspects of organismal biology, from mechanisms of sex determination to sexual reproduction and speciation [18,19].

Conflict arises because selection can favor genes that prevent the transmission of their competitors, a phenomenon called meiotic drive. Meiotic drive occurs in many taxa, from *Segregation Distorter (SD)* in *Drosophila melanogaster* to t-haplotypes in mice, which kill or inactivate, respectively, their competitors - those sperm that do not carry them [20,21]. What prevents selfish genes from taking over a population? In some cases, distorting genes will be subject to counter-selection by other genes in the genome whose own transmission suffers as a result of the distortion. Leigh refers to this process as the “parliament of genes”, because the common interest of the many can act to suppress the “cabals of the few” [22,23]. For example, cytoplasmic male sterility (CMS) is a condition that affects numerous species of flowering plants (Figure 2). CMS is caused by selfish mitochondrial variants that interfere with the production of the male reproductive portions of the flower, effectively converting a self-fertile hermaphrodite (producing both ovules and pollen) into a female. Reducing allocation to male reproduction can be beneficial to the mitochondria and other genes that are uniparentally inherited through the female. However, it can be deleterious to nuclear genes that are transmitted in both pollen and ovules. Indeed, CMS in natural populations is often countered by evolutionary changes in nuclear genes that suppress its effects and restore male fertility [24-26].

Many selfish genes, however, may produce no obvious phenotypic effect or fitness cost, in which case, they may experience little opposition from the other genes in the genome, limiting the coevolutionary response to alternative



Figure 2

Nuclear-mitochondrial conflict in the bladder campion *Silene vulgaris*. Populations of gynodioecious plants such as *S. vulgaris* consist of females (pictured here) and hermaphrodites, the latter producing both seeds and pollen [24,26]. Females are produced from hermaphrodites by mitochondrial variants that interfere with the development of the stamens, called cytoplasmic male sterility (CMS). Because they are primarily transmitted through ovules but not pollen, the mitochondria gain a fitness advantage from reducing allocation to male reproduction. CMS variants, however, are often subject to counter-evolutionary changes in nuclear-encoded genes that suppress their effects and restore male fertility. Photo courtesy of Doug Taylor, University of Virginia.

alleles at the same locus and those linked to them. For this reason, ‘epidemics’ of selfish genetic elements are thought to occur frequently, but go unnoticed because they are either swept to fixation or rapidly suppressed [26]. Once fixed, but not forgotten, they can later reveal themselves in the form of incompatibilities between populations. In *Drosophila pseudoobscura*, for example, male hybrid sterility occurs in crosses between two geographically distinct populations [27]. Sterility is caused by a cryptic segregation distorter in one of the populations that is ‘silenced’ by an autosomal suppressor [28]. Thus, whereas the two populations can produce phenotypically normal males by themselves, partial sterility arises when they are crossed because the suppressor is not fully dominant. The reduction in hybrid fitness is an important illustration of how the within-population dynamics of selfish genetic elements can generate incompatibilities that contribute to speciation [28].

The enemy of my enemy is my friend

Genetic variability does not always favor conflict over cooperation. Genetically distinct gametes sometimes display complex forms of cooperation, and possibly altruism

[29-31]. In some rodents, sperm group together to form long trains, a form of cooperation that promotes efficient swimming towards the egg, but reduces the probability of fertilization for any given sperm [32]. Some sperm undergo morphological changes that prevent them from fertilizing the egg, but their presence improves the success of other sperm, enhancing their survival in the presence of natural spermicides in the female reproductive tract [33-35]. The key to understanding whether selection will lead to cooperation or conflict requires knowing whether the gametes of an individual compete primarily against one another or against gametes of other individuals. Thus, in organisms where sperm from different males encounter one another in the female reproductive tract, there may be an advantage for sperm of a single male to join forces. In other words, cooperation may evolve more readily in the face of a common enemy. Such a notion exemplifies the kin selection concept of relatedness, in that it measures not just how genetically similar individuals are, but how similar they are relative to their competitors (see Box 1).

Sources of chimerism in multicellular organisms

Selfish behaviors are expected to emerge at even the slightest hint of intra-individual genetic heterogeneity, so it is curious that truly chimeric organisms exist. However, in some multicellular organisms, different individuals can fuse or exchange cells. *Botryllus schlosseri*, for example, is a marine tunicate that is closely related to vertebrates (reviewed in [36]). It spends its infancy as a motile larva and its adulthood as a brightly colored sessile colony. During the adult stage, neighboring colonies can fuse and the germ cells of one colony can take over the germline of another [37]. Similarly, in ascomycete fungi, multicellular filaments called hyphae fuse to form a vast network of interconnected cells - the mycelium [38]. Hyphal fusions occur between hyphae within a single colony, as well as between different colonies when they come into contact. The shared cytoplasm of the mycelium is cooperative, in that it allows resources to be transported to the growing tip, resulting in rapid outward growth. In other organisms, multicellularity results from aggregation of the constituent cells. In the amoeba *Dictyostelium discoideum*, for example, cells aggregate in groups of 100,000 when starved to form a multicellular organism. Nearly 20% of the cells in the initial aggregate eventually die to form a rigid stalk. The remaining amoebae crawl up the stalk and differentiate into viable spores. The death of the stalk cells is thought to provide a fitness benefit to the spores by lifting them out of the soil or increasing their chances of dispersal [39,40].

These model organisms demonstrate that remarkable acts of cell cooperation and altruism occur even in organisms that form chimeric structures. However, many of these organisms also possess mechanisms that restrict chimerism to closely related individuals (Figure 3). Individuals of

B. schlosseri fuse only if they share alleles at a highly polymorphic fusion-histocompatibility (FuHC) locus, and other loci dictate which cell line dominates after fusion [37,41]. Genetically different strains of *Dictyostelium discoideum* initiate multicellular development together, but then separate partially to form distinct fruiting bodies [42]. And the same filamentous fungi that form multicellular mycelia also possess, multi-allele, multi-locus recognition genes that prevent fusion with unrelated individuals [38]. Thus, these potential exceptions to the primacy of kin selection may in the end provide some of its strongest support, demonstrating high relatedness to be a defining feature of nearly all of multicellular life. Nor is chimerism restricted to lowly creatures. In marmosets, for example, 95% of pregnancies result in twins that exchange some cells *in utero*, resulting in chimerism of most tissues, including the germline [43].

Molecular mechanisms that maintain cooperation

To date, much of the social evolution literature has focused on identifying whether selection favors cooperation in any given circumstance, with far less attention paid to the genetic bases of such behaviors and how they might promote or restrict cooperation. The discovery of social behaviors at the cellular level in genetically tractable model organisms, however, has opened the door to probing the molecular basis of cooperative and altruistic behaviors [44]. The description of gene-regulatory circuits has also given rise to the idea that they can exhibit basic design features, characteristic structures that reflect the requirements of the phenotypes they instill [45-47]. For example, positive feedback loops amplify small differences in initial states and can be important for the establishment and maintenance of divergent cell types [48]. For example, in the Gram-positive bacterium *Bacillus subtilis*, a positive feedback loop is critical for the development of competence in a minority of the cell population at the onset of stationary phase [49]. More generally, the structure of the gene-regulatory network has an impact not only on what phenotypes are observed but also their robustness, or lack thereof, to different types of perturbation. Is it possible that altruistic behaviors will also be found to have characteristic design features - attributes that ensure that they robustly generate the altruistic phenotype, while safeguarding against the most common opportunities to cheat?

Savageau's Demand Theory illustrates how such evolutionary safeguards can be achieved, in this case, through differences in gene regulation [50,51]. The theory was formulated as an explanation of why bacteria often exhibit positive regulation for resources they commonly encounter and negative regulation for resources they rarely encounter. Positive regulation refers to transcription that is initiated in response to a stimulatory element, whereas negative regulation refers to transcription that is initiated by the removal of

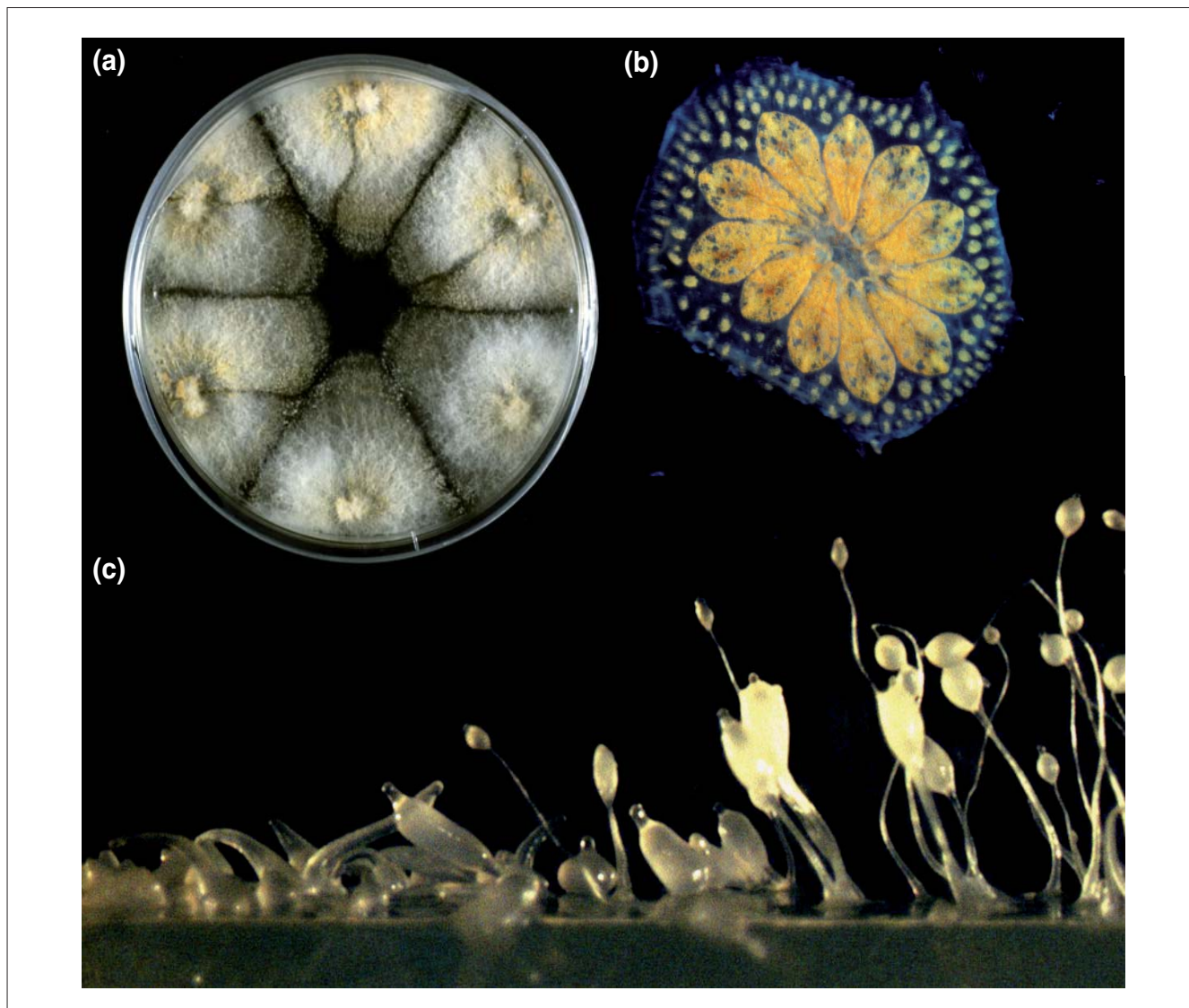


Figure 3

Who's who in multicellularity. Self-nonsel self recognition in multicellular organisms that form chimeras. **(a)** *Cryphonectria parasitica*, the causal agent of chestnut blight. Hyphal fusion is restricted to strains that match at all vegetative incompatibility loci [71,72]. Incompatible reactions result in localized cell death and the formation of a barrage zone. Of the six pairings shown, only two (bottom right) are compatible. **(b)** In the marine tunicate *Botryllus schlosseri*, fusion or rejection is controlled by a highly polymorphic locus containing multiple immunoglobulin domains (FuHC) [41]. A single population can contain hundreds of different alleles. **(c)** In the social amoeba *Dictyostelium discoideum*, thousands of cells aggregate (far left) and subsequently develop into a fruiting body (far right). Cells of genetically different individuals can partially separate during multicellular development [42]. *C. parasitica* photo by Kent Loeffler, courtesy of the Department of Plant Pathology and Plant-Microbe Biology at Cornell University. *B. schlosseri* photo courtesy of Tony de Tomaso, University of California, Santa Barbara. *D. discoideum*, courtesy of Gerda Saxer, Rice University.

a repressing element. Both modes of regulation serve the same proximate function - they insure that expression of the relevant catabolic pathways occurs only when the resource is present. Savageau postulated that for resources in high demand, mutations causing loss of expression would be more strongly counter-selected than those causing constitutive expression. The opposite would be true for resources in low demand: mutations causing constitutive expression would be more strongly counter-selected than those causing

loss of expression. Assuming that random mutations tend to disrupt a function, greater evolutionary stability could therefore be achieved if bacteria were to use positive regulation for common resources and negative regulation for rare resources, which corresponds well to what is observed [51].

The broader significance of Savageau's theory is that we might consider not just how regulatory circuits serve their immediate function, but also their evolutionary stability in

the face of common genetic and environmental perturbations. In the case of the genes encoding altruistic traits, evolutionary stability might be achieved in part by safeguarding circuits against common ways to cheat. Indeed, evolutionarily distinct mechanisms of programmed cell death have the common feature of defaulting to altruistic rather than selfish outcomes when perturbed. For example, much of the apoptosis machinery is constitutively expressed by default and inhibited from taking effect until the withdrawal of extracellular signals occurs - the cells are thus constantly primed for death [52,53]. Programmed cell death in bacteria and some simple eukaryotes also seems to default to being 'on'. For example, many bacteria carry toxin-antitoxin genes, called addiction molecules [54]. Because the toxin is constitutively expressed, the bacteria face the constant threat of death: its deadly effects can only be counteracted through the simultaneous and constitutive expression of the linked antitoxin.

Toxin-antitoxins were originally found on plasmids, leading to the supposition that they function as selfish genetic elements that ensure plasmid maintenance. However, the discovery of toxin-antitoxin genes on the bacterial chromosome, regulated by stress-response genes, suggests that they could function in programmed cell death of bacteria in response to stress [55-57]. Others have argued that the buildup of the toxin can have a reversible bacteriostatic effect rather than a bacteriocidal effect - and thus, that these systems primarily improve an individual cell's survival during times of stress rather than cause its altruistic suicide [54,58]. A similar explanation is applicable to the tumor suppressor gene p53, which has conflicting roles on the induction of autophagy (and subsequent cell death) depending on its location in the nucleus or cytoplasm [59]. Similar to toxin-antitoxin systems in bacteria, some have questioned whether p53 would be better characterized as a cell-death or a cell-survival gene [59,60].

If altruism genes provide a fitness advantage to the individual under some conditions, then it may be easier to understand their evolutionary maintenance in a different context - that is, why selfish mutants that lack these genes are not rampant in populations. Pleiotropy, which occurs when one gene affects multiple traits, could restrict the mutations that give rise to selfishness because they must also not disrupt the other functions of the gene [61-64]. Indeed, the possibility that pleiotropy will restrict the evolutionary paths to cheating has been suggested previously [65]. Here we also suggest that the benefits of pleiotropy may be best accomplished by linking an individual-level (selfish) fitness advantage to a group-level (altruistic) fitness advantage of the same gene. If true, pleiotropy might also be important in maintaining altruistic traits that are only rarely expressed by providing protection from mutation accumulation [66].

Prospects: integrating evolutionary and genetic approaches to cooperation

One of the themes of social evolution theory is that competition is the driving force behind both cooperation and conflict. Perhaps one of the best illustrations of this principle comes from the reality TV series *Survivor*. Each season, individuals initially form two tribes that compete primarily against one another. Consistent with between-tribe competition, individuals within a tribe behave altruistically towards one another, sacrificing their personal success in competitions to promote the victory of a tribe member. Eventually, however, the tribes merge. In the absence of external competition, individuals within the tribe compete primarily against one another, and cooperation soon gives way to conflict. Similarly, predicting whether the cells of a multicellular organism are likely to cooperate requires identifying the relative importance of internal versus external sources of competition, as well as knowing how the biology of organisms suppresses competition and promotes the evolution of cooperative and selfless behaviors. As Maynard Smith and Szathmáry have emphasized, the major transitions in evolution required that conflicts at lower levels of biological organization be minimized so that the evolutionary potential of these higher-level units could be achieved [2,10].

Finally, we wish to emphasize the molecular mechanisms of social behaviors, especially putatively altruistic behaviors such as programmed cell death. Regardless of the long-term benefits that cooperation and altruism entail, they will always be threatened by the immediate selective advantages afforded by cheating, even when these evolutionary changes are ultimately short-sighted. The strong potential for short-sighted evolution in genes encoding altruistic phenotypes means that selection should favor molecular mechanisms that are evolutionarily resistant to change and robust in the face of common selfish mutations. Recent development of model organisms for the study of altruistic behaviors in genetically tractable systems means that these behaviors can now be dissected by standard molecular techniques. For example, a recent screen in *Dictyostelium discoideum* identified genes that, when mutated, cause the mutant strain to preferentially form spores and avoid becoming stalk [44]. Whole-genome sequencing will also allow the reconstruction of the evolutionary history of these traits. Through an integration of these approaches, we can begin develop a fuller understanding of how cooperation and altruism became codified in the biology of so many organisms.

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