Cheating Cells Get the Boot

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Any cooperative system is vulnerable to cheaters, who receive benefits without contribution. Cooperation takes place between similar individuals contributing and receiving identical benefits (homotypic cooperation) or between populations sharing and receiving distinct benefits (heterotypic cooperation). Cheaters are therefore at a competitive advantage compared to cooperators, who pay the cost of producing benefits. To avoid being overrun by cheaters, cooperative systems engage in positive assortment, wherein cooperative, benefit-supplying members of the system interact preferentially with other cooperative individuals.

There are two primary means of protecting cooperation against cheaters. In partner choice, cooperators recognize and exclude or punish cheaters. In partner feedback, cooperators and cheaters engage in repeated interactions, and helping a cooperator leads to receiving greater benefit, ensuring repeated, mutually beneficial interactions. To study protection of cooperation from cheating, postdoctoral fellow Dr. Babak Momeni and graduate student Adam James Waite in the lab of Dr. Wenying Shou (Basic Sciences Division) made use of the budding yeast Saccharomyces cerevisiae. "In natural cooperative systems, it is often unclear which (or both) mechanisms operate, and it has been difficult to study each mechanism in isolation of the other mechanism. To investigate how partner feedback by itself could benefit heterotypic cooperation, we used a combination of engineered yeast strains and mathematical models which were free from recognition mechanisms," says Dr. Momeni.

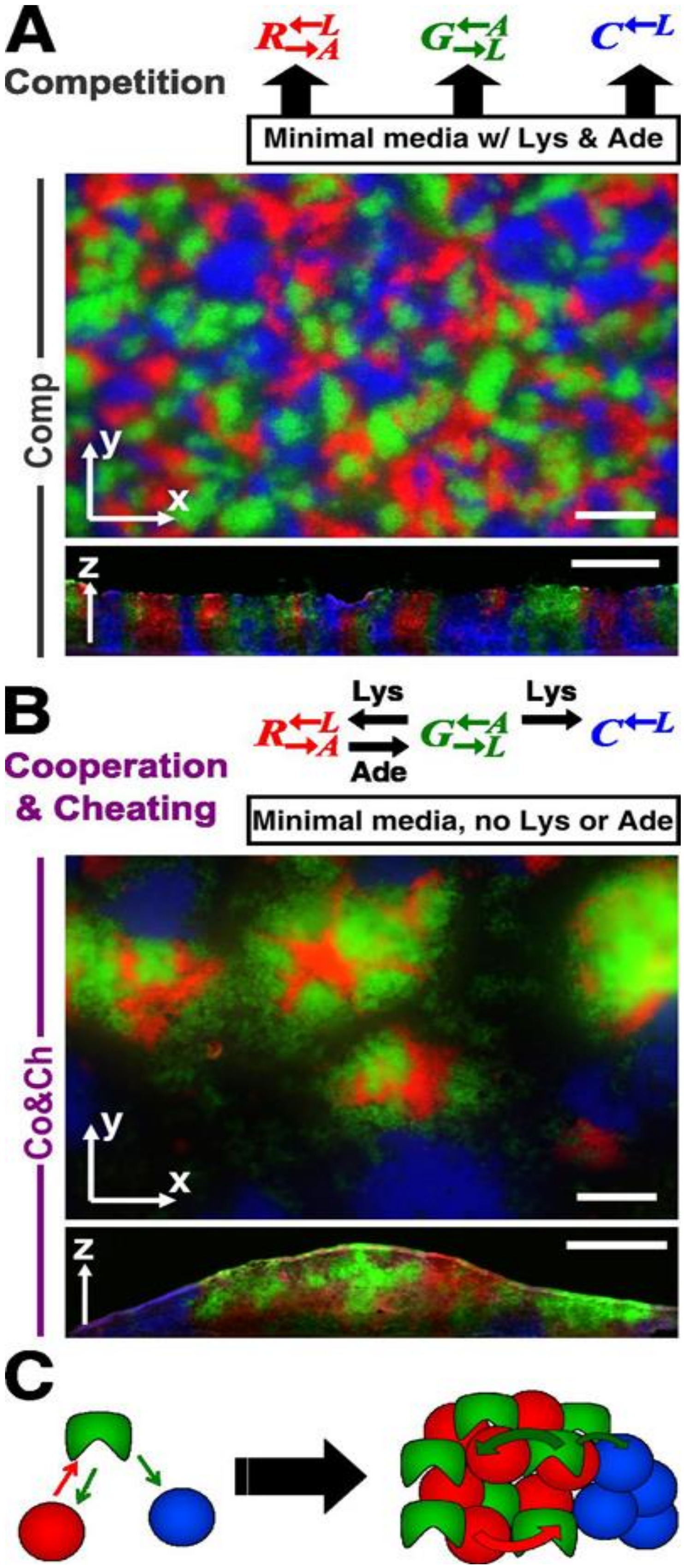
The authors used a system consisting of three yeast strains: (1) a green fluorescent strain (G) requiring the nucleobase adenine and releasing the amino acid lysine (2) a red fluorescent strain (R), requiring lysine and releasing adenine (3) a cyan fluorescent (C) strain requiring lysine and not releasing adenine. As G and R cooperate by exchanging distinct metabolites, these strains are considered heterotypic cooperators. These strains displayed different interactions depending on their environment. In minimal medium supplemented with adenine and lysine, supporting independent growth of all three strains, the strains compete for commonly required nutrients such as glucose and nitrogen, as well as the limited space in the culture. In minimal medium lacking adenine and lysine, G and R exchange essential adenine and lysine, while C consumes lysine without releasing adenine and shows a growth advantage of ~2%. Without lysine or adenine, a culture of G and R (cooperators) grows well, while a culture of G and C (cooperator and cheater) fails to grow. In summary, in the absence of adenine and lysine, R and C compete for the lysine supplied by G, and cooperator R reciprocates by releasing lysine, while cheater C does not.

The researchers tested whether such a heterotypic cooperative environment was protected from cheaters in a spatial arrangement, which facilitates repeated interactions between neighboring individuals. In unmixed communities lacking adenine and lysine, the cooperator R was favored, while in mixed communities, cooperator R was no longer favorted. To test how a spatial arrangement might promote heterotypic cooperation, the authors performed microscopy to assess the three-dimensional structure of yeast communities. This revealed that, during cooperation and cheating, the cooperators G and R grew in close proximity, while the cheater C was spatially excluded (see figure). This emergence of non-random patterns from initially random distributions of cells driven by cell-cell interactions internal to the system rather than by external forces is known as self-organization. When cooperators, cheaters, and their beneficial partners interact,Thus, self-organization benefits cooperators by allowing cooperators to gain more access to beneficial partners than cheaters do. reducing the access of cheaters to cooperative benefitsself-organize to maximize benefits and minimize the deleterious effects of cheating on growth.

They next tested what factors drive spatial organization in a heterotypic cooperative system. Heterogeneity in the initial distribution of cells, through occasional random interaction between cooperative partners, facilitated but was not required for self-organization. Rather, it was found that asymmetric fitness effects (that is, the capacity to reciprocate benefits to a partner) and growth into open space were required for self-organization.

"We show that when in a spatially structured environment, cooperators and cheaters "self-organize" such that despite an initially random spatial distribution, cooperators gained more access to the partner than cheaters did. By depriving the cheater of access to the partner, this self-organization allows cooperators to thrive despite their intrinsic disadvantage compared to cheaters. Self-organization arises from the interactions among cooperators, cheaters, and their heterotypic partners as they grow toward open space. This mechanism protects cooperation from cheaters so that more sophisticated recognition mechanisms can evolve," says Dr. Momeni.

Momeni B, Waite AJ, Shou W. 2013. Spatial self-organization favors heterotypic cooperation over cheating. eLife 2:e00960.


A
Competition
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Ade
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Image provided by Dr. Babak Momeni.

A cheater-isolating spatial organization emerges in yeast communities. Three strains of yeast were engineered such that R required lysine and released adenine, G required adenine and released lysine, and C consumed lysine without releasing adenine. Starting from a random initial distribution of R, G, and C populations the patterns of communities were examined in top-views (xy) and vertical cross-sections (z) of the community. (A) In an environment where adenine and lysine were amply provided, the three strains engaged in competition for shared resources. This competition showed no preferential association among populations in top-views and columnar segregated features in vertical cross-sections. (B) When no lysine and adenine was provided in the media, R and G engaged in heterotypic cooperation, while C cheated by consuming lysine without contributing to the production of adenine. In this case, a particular organization emerged in the community where R and G populations were highly associated with each other whereas C was isolated. (C) Schematically, starting from a random initial state, self-organization drives a spatial ‘order’ in communities containing cooperators and cheaters. The very acts of cooperation and cheating lead to a situation where cooperators have more access to their heterotypic cooperating partners, but cheaters are excluded. Yeast strains in the empirical tests were engineered to express green, red, or cyan fluorescent proteins so that they could be discriminated optically. Vertical cross-sections were obtained by cryosectioning the yeast communities. Scale bars = 100 microns.