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NEWS AND VIEWS

# Altruistic cell death and collective drug resistance

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The Greek myth of Castor and Pollux is a tale about altruism between brothers. Castor and Pollux were twins but they had different fathers. As a son of the god Zeus, Pollux was immortal, but Castor whose father was human, eventually died. Pollux could not bear grief and asked Zeus to share his immortality with his brother or even to give it away and join him in death. Moved by Pollux's altruism, Zeus decided to make them both immortals. In their recent work, Tanouchi *et al* (2012, this issue) examined programmed death in bacterial cells. They show it can too be an altruistic trait, whereby some cells trigger the cell death program and release stress-relieving substances that increase the chances of survival of other cells within the population.

Bacterial drug resistance is a major problem for human health (Taubes, 2008) and recent studies suggest that altruism can play an important role in resistant populations. For example, Lee *et al* observed that most individual bacteria within an antibiotic-resistant population can be significantly more sensitive to the antibiotic than the global population (Lee *et al*, 2010). This paradoxical effect has a surprising explanation: a small number of highly resistant bacteria altruistically protect more vulnerable cells by releasing substances that enhance the growth of the entire stressed population.

In order to generate a population that enables experimental investigation of altruistic cell death in bacteria, Tanouchi *et al* (2012) engineered *E. coli* to carry two extra genetic circuits. The first one is a programmed cell death module where a lytic enzyme can be induced by the beta-lactam antibiotic 6-Aminopenicillanic acid (6-APA). The antibiotic levels can be modulated by experimentalists thus providing a tunable environmental stress. The second module is an IPTG-inducible beta-lactamase (BlaM). BlaM the role of a 'public good' that once released lifts the environmental stress by degrading 6-APA. Importantly, BlaM is produced and stored intracellularly, and is only released from cells upon lysis, thus making cell death beneficial for the remaining survivors.

Using this synthetic system, the investigators show that programmed cell death can indeed be altruistic, at least under specific conditions. The tunability of the system provides furthermore the opportunity to study another surprising phenomenon observed in bacterial populations called the Eagle effect. When the concentration of antibiotic is increased beyond a certain point, the number of bacteria that survive starts to increase instead of decreasing (Eagle and Musselman, 1948). With the help of a mathematical model that captured the dynamics of the system, the authors suggested a plausible mechanism for the Eagle effect. By modulating the two synthetic modules independently they identified experimental concentrations of antibiotic at which populations with altruistic cell death can actually grow better, thanks to a trade-off between the rate of cell death and public good production.

The work by Tanouchi *et al*. (2012) exemplifies the power of synthetic biology to investigate social interactions in microbial communities (Xavier, 2011). Similar modules of altruistic death could in theory help a stressed population regardless of the cell type and the molecular nature of the module implementation (Figure 1). For example, in cancer therapy, radiotherapy-induced apoptosis of cancer and surrounding stromal cells can help the growth of surviving cancer cells and increase population-level resistance (Huang *et al*, 2011). In this specific case, the growth-promoting effect of apoptosis is not due to a passive release of nutrients or growth factors but rather owing to an active biochemical reaction triggered by the apoptosis machinery. Cells lacking Caspase-3, a key apoptotic protease, do not promote tumor growth when killed (Huang *et al*, 2011), reinforcing the idea that altruistic death is not accidental but rather an evolutionary adaptation.

Examples such as these are expanding our view of drug resistance. More than an individual cell trait, resistance can be a collective trait that is potentiated by social interactions. If so, therapies designed to kill individuals may produce undesired population effects such as tumor re-growth. But drug resistance is always an evolutionary process and the evolutionary pressures involved in collective resistance remain, to a large extent, unknown. How can a population evolve altruistic cell death without being exploited by cheater mutants that lack the cell death module but still benefit from the common good released by others? Answering this and other questions will require further investigation.

The answer may come from inclusive fitness theory (Hamilton, 1964), which explains that altruism can be evolutionarily favored if the benefits of its action preferentially benefit relatives, that is individuals more likely to carry a copy of the altruistic gene. Programmed cell death could therefore be favored if its benefits are directed toward related cells that are more likely to carry the cell death program (Reece *et al*, 2011). Directing altruism toward a relative also led to a

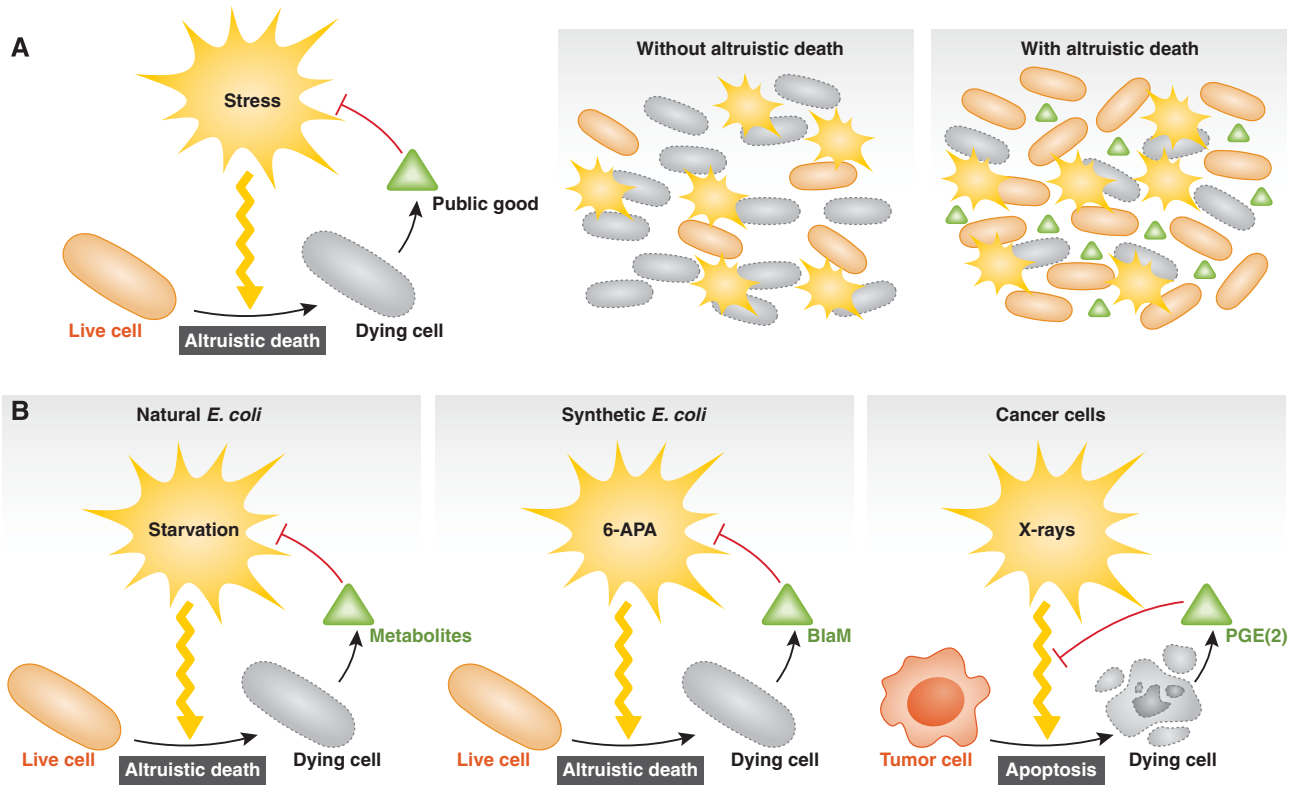


**Figure 1** Altruistic cell death as a social interaction that enhances collective stress resistance. (**A**) Schematic representation of an abstract altruistic death module whereby cells die owing to environmental stress but by doing so they release a stress-relieving public good that helps survivors. (**B**) Examples of actual implementations of this module. *E. coli* dying owing to starvation release metabolites that feed survivors. As shown in this issue by Tanouchi *et al* (2012), the effect can be recapitulated in a synthetic and tunable system. The motif is also found in eukaryotes where apoptotic cells release substances (such as PGE(2)) and enhance population growth (Huang *et al*, 2011).

fortunate conclusion in the myth of Castor and Pollux. Moved by the altruism of Pollux toward his brother, Zeus placed them together in the heavens as the constellation Gemini, the twins.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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