CANCER EVOLUTION

Resistance games

A game theory study supported by in vitro experimental data shows that drug treatment of non-small-cell lung cancer cells causes the cells to switch between evolutionary games they play among each other. Moreover, the work calls into question standard assumptions on the fitness costs of drug resistance to cancer cells.

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Originating from Von Neumann and Morgenstern[1] in the 1950s, game theory has become the mathematical theory of decision making in situations where an individual entity's outcome may depend not just on its own behaviour, but also on the behaviours of others. Initially, game theory focused on conflict and cooperation in economics and social sciences. In the 1970s, Maynard Smith and Price pioneered its application to evolutionary dynamics[2], creating the field of evolutionary game theory (EGT). In EGT, players often inherit, rather than choose, their (proliferation and survival) strategies[3], and of interest are the eco-evolutionary consequences of these inherited strategies. EGT of cancer emerged about 20 years ago[4,5], allowing tumourigenesis to be studied in a manner in which cancer cells play an evolutionary game among each other, possibly with healthy cells as well. More recent works on EGT of cancer[6–9] have focused on investigating whether (and how) the cancer evolutionary game could be altered by treatment choices so that a more desirable patient outcome is achieved. Writing in *Nature Ecology & Evolution*, Kaznatchev et al.[10] have now applied EGT to study evolution of drug resistance in human non-small-cell lung cancer cells.

More specifically, Kaznatchev et al. focus on the resistance of H3122 cells to the drug alectinib, with and without cancer-associated fibroblasts (CAFs), which are considered the main non-malignant component of the tumour microenvironment and possibly a key contributor to drug resistance in tumour cells. Kaznatchev et al. model the competition between treatment-naïve (parental) cells and resistant (daughter) derivative cancer cells as a matrix evolutionary game, estimating the game parameters through the best fit of measurements obtained from in vitro co-culture experiments. In this way, the authors accurately approximate the (possibly more complex) game that the cancer cells of the two types play among each other.

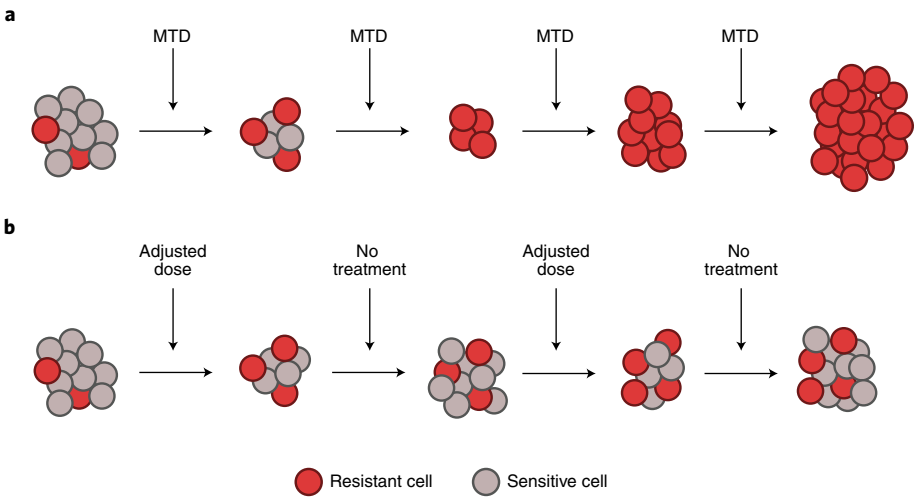

Fig. 1 | Cancer treatment strategies. a, Current standard cancer therapy involves repeated application of a drug or drug combination at the MTD. This strategy is likely to select strongly for drug resistance in the cancer cells. **b**, An alternative approach is evolutionary therapy, in which the dosing regime is designed to target resistance evolution. The underlying assumption is that resistance has a cost: although cancer cells resistant to treatment are fitter than sensitive cells when the treatment is applied, they are less fit without the treatment. The Kaznatchev et al. study challenges this assumption by suggesting that resistance may not always be costly.

The authors observe a striking difference in the qualitative properties of four games that they analyse, in the presence or absence of alectinib and CAFs — differences including the relation of the growth rates of resistant cells and initial proportion of the parental cells in the co-culture.

These observations strongly support the concept that treatment influences the character of the resistance response in cancer cells and that this response must be carefully considered before the treatment is put in place[6–9]. This is particularly important for treatment of metastatic cancers, where the current standard of care is repetitive application of a drug or drug combination at the maximum tolerable dose (MTD), continuously or in identical and a priori decided cycles, until unacceptable toxicity or tumour progression occur. The MTD approach seems to be evolutionarily unwise, as it may strongly select for resistance in cancer cells. An alternative to MTD is 'evolutionary therapy', which is designed to target the evolution of treatment-induced resistance in cancer cells[6–9] (Fig. 1; adapted from original figure in ref. [7]). Different forms of evolutionary therapies for metastatic cancers are currently being proposed and tested in the (pre-) clinical setting. This is a consequence of the success of the (still ongoing) clinical trial on evolutionary abiraterone therapy of metastatic castrate-resistant prostate cancer[7], during which the mean life expectancy of the patients has at least tripled. Kaznatchev and colleagues' combination of experiments with game theory provides a better understanding of the evolution of resistance, and they challenge assumptions standardly adopted when proposing evolutionary therapies for metastatic cancers.

For example, the standard assumption of game-theoretical models of evolutionary

therapies is that resistance comes at a cost (Fig. 1). Kaznatchev et al. suggest this may not always occur. In their co-culture experiments, the researchers observe that resistant cells always have a higher fitness, regardless of whether the treatment is applied. Although the duration of these experiments was relatively short and it is therefore still possible that a resistance cost would demonstrate itself over a longer time period (for example, in the form of carrying capacity), their observations conflict with a classic assumption of cancer biologists that resistant cells have a fixed lower growth rate than the growth rate of sensitive cells when no treatment is applied. Naturally, it is quite likely that the cost of resistance varies per treatment. Developing evolutionary therapies for treatments with no cost of resistance will certainly be challenging and perhaps even impossible, unless additional therapies having a cost of resistance are included.

The current aim of evolutionary therapies for metastatic cancers is to contain cancer and prolong patient life; in general it is believed that it is not possible to cure very advanced cancers. Containing cancer would be remarkable, but if we understand resistance mechanisms better, we may even be able to cure advanced cancers at some point in the future. Game theory studies closely matched with in vitro and in vivo experiments, along the lines of the Kaznatchev et al. study, may help us to achieve this goal. ❐

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Competing interests

The author declares no competing interests.