Resistance is ... complex

The evolution of resistance has consequences for both food security and healthcare. To meet this challenge we need large-scale data to distinguish between what is evolutionarily plausible and what actually occurs in the field and the clinic.

Resistance to chemical treatments is an increasing concern in medicine and agriculture. Appreciation that the problem is an evolutionary one has contributed to the use of treatment regimes such as combination therapy and integrated management, in which constant use of a single chemical is avoided. However, a study of herbicide resistance by Hicks et al. highlights the need for large-scale testing of such strategies and reminds us that the evolutionary logic behind them rests on assumptions that may not be correct.

Hicks et al. assembled a dataset of the abundance and herbicide-resistance status of the agricultural weed *Alopecurus myosuroides* (blackgrass) on 71 farms across England. They combine this with data on the herbicide and crop management regimes applied by the farmers over a ten-year period. The results confirm that resistance is driving weed abundance by showing a link between fields with high abundance and high levels of resistance. However, the authors found that the main predictor of resistance was the overall intensity of historical herbicide application, with no obvious effect of herbicide diversity or crop rotations. This is important because combination treatments, in which different herbicides are cycled either temporally or spatially (or both), are an evolutionarily informed way of reducing resistance evolution, often recommended by agricultural agencies. Equivalent strategies have been successfully applied in medicine, with HIV treatment being a notable example[1]. The fact that they do not seem to be effective for blackgrass suggests that there may be shared resistance mechanisms between the different herbicides the authors tested, and that we cannot assume that resistance is conferred by a small number of drug-specific mutations.

Another example from agriculture comes from genetically modified crops that express insecticidal proteins from the bacterium *Bacillus thuringiensis*. 'Bt crops', which include cotton, corn and soybean, have been a global commercial success since they were developed two decades ago. However, unsurprisingly, many insect pests have evolved resistance, with nearly half of Bt crop varieties experiencing resistant pests by 2016[2]. The key to those cases that have not experienced substantial resistance evolution is a combination of management strategy and genetics. Refuges of non-Bt crops or other non-Bt host plants are planted to provide food for insects that are still susceptible to Bt toxins. If the genetic basis of resistance in the insects is recessive, then the presence of a large number of susceptible insects from these refuges can considerably delay the evolution of resistance. A study in China showed that a similar effect could be produced by planting an F2 hybrid crop in which a quarter of plants were non-Bt, providing an inbuilt refuge without the need to persuade farmers to plant whole fields of sacrificial crops[3].

Maintaining susceptible populations is also the basis of adaptive therapy, which has been proposed as an alternative to combination therapy for cancer treatment. In adaptive therapy, the dose of drug is constantly updated with the aim of maintaining tumour size rather than eliminating it. The resultant doses of drug are low enough to maintain a population of sensitive cells that have a growth advantage over resistant cells and therefore stop the resistant population from expanding. However, we need a demonstration that this strategy works in practice, especially in light of the cautionary message from the blackgrass herbicide study that evolutionary informed approaches may not have the desired effect. A recent study that combines mathematical modelling and cell culture results takes the first steps towards providing such evidence[4]. The authors show that low doses of cyclin-dependent kinase inhibitors are better at preventing growth of tumour spheroids than high doses, because they allow susceptible cells to outcompete resistant cells. Importantly, the effect only works when there is spatial structure, and not in monolayer cell cultures.

Adaptive therapy is a promising alternative to more traditional combination therapies for cancer. The potential value of maintaining susceptible populations was not lost on the organizers of the recent International Society for Evolution, Ecology and Cancer (www.iseec.org) conference, who invited several speakers who do not work on cancer. These included Bruce Tabashnik, author of the studies on the evolution of resistance to Bt crops and the role of susceptible refuges[2,3]. However, in light of both the Bt work and the blackgrass herbicide resistance study, we should maintain caution in our optimism about adaptive therapy. Both sets of agricultural results show that there is no substitute for large-scale field or clinical data to test whether the predictions of evolutionary theory and the results of exploratory studies hold true in a real-world situation.

The economic and health costs of evolved resistance are huge, for agriculture, cancer and also the crisis of antibiotic resistance. Hicks et al. also probed the economic cost of blackgrass herbicide resistance. When they considered the combined costs of herbicide and yield loss, they found that the weed had a substantial detrimental effect only at high densities, which are also associated with high levels of resistance. Therefore, minimizing the spread of resistance, rather than eliminating the presence of blackgrass per se, is likely to be a more sustainable, and cost-effective, strategy. The authors also note that the increase in resistance to different herbicides has increased the reliance on the broad-spectrum herbicide glyphosate, to which resistance has already arisen in several countries. Further spread of resistance to glyphosate could have significant economic consequences for food security and thus human health, which must be considered together with further investigation into the controversial question of whether the herbicide is carcinogenic.

All these problems have an evolutionary basis, but we should not be deceived into thinking that they persist simply because evolutionary thinking has not yet been fully applied. Evolutionary logic looks very promising in the case of adaptive therapy for cancer, but in the case of combination strategies for herbicide resistance such logic may so far have been applied too simplistically and too optimistically. ❐

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