INTRA-TUMOR COOPERATION

Cancer cells secrete growth factors that induce proliferation, protect against apoptosis and the immune system or promote neo-angiogenesis [1]. As they are diffusible (Fig. 1), the growth factors produced by a cell can be used by other neighbouring cells, an example of cooperation among cancer cells [2].

A conceptual problem arises: a non-producer cell can exploit the growth factors secreted by its neighbouring producer cells without paying the cost of production; hence non-producers should have a proliferation advantage and spread in the population. How can intra-tumour cooperation be maintained then? Why do non-producer mutants drive producer cells to extinction?

Figure 1. A monolayer of producer (blue) and non-producer (yellow) cells of a growth factor with diffusion range d

EVOLUTIONARY PERSPECTIVES

In some cases, two clones producing one growth factor each can coexist if both are essential, because the two clones depend on each other [3], similar to mutualism between species. More in general, in cases without such mutual dependence, a clone producing a growth factor can coexist with a clone producing the same growth factor at a lower (or null) rate if its effect is a sigmoid function of its concentration (which is common for growth factors) [4]: in this case, producer cells have a proliferation advantage at intermediate frequencies—leading to a stable mixed equilibrium of the two types (Fig. 2, right panel). Cooperation collapses if the cost/benefit of the growth factor is high enough (Fig. 2, left panel). The dynamics of growth factor production can be studied using evolutionary game theory and experimental evolution [4].

Figure 2. Fitness of producer and non-producer cells as a function of the fraction of producer cells for different costs of growth factor production c. Equilibria (full circles: stable; open circles: unstable) and the direction of the dynamics (arrows) are shown.

FUTURE IMPLICATIONS

Targeted therapies aiming at impairing cooperation by blocking growth factors or their receptors [5] are prone to the evolution of resistance. Understanding intra-tumour cooperation is essential to develop evolutionarily stable therapies. An alternative approach could be to use autologous cancer cells in which genes for growth factors have been knocked out [6].

REFERENCES