Evolution, Medicine, and Public Health [2018] p. 1 doi:10.1093/emph/eoy003

CLINICAL BRIEFS

Cooperation between cancer cells

Marco Archetti

School of Biological Sciences, University of East Anglia, Norwich, UK

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 not non-producer mutants drive producer cells to extinction?

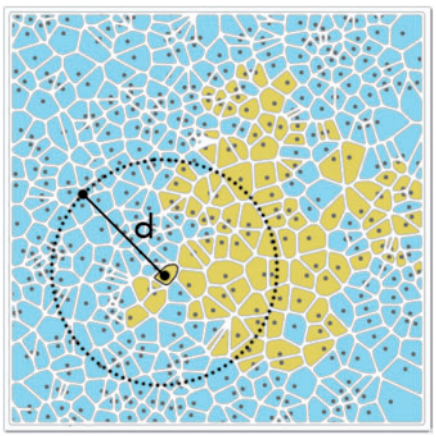

Figure 1. A monolayer of producer (blue) and non-producer (yellow) cells of a growth factor with diffusion range *d*

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].

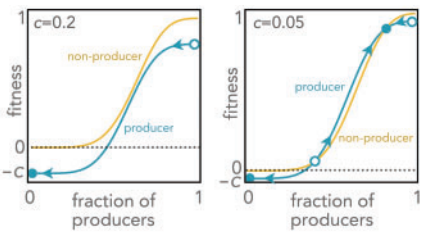

Figure 2. Fitness of producer and non-producer cells as a function of the fraction of producer cells for different costs of growth factor production *c*. Equilibria (full circles: stable; open circles: unstable) and the direction of the dynamics (arrows) are shown

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

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**:646–74.
2. Axelrod R, Axelrod DE, Pienta KJ *et al*. Evolution of cooperation among tumour cells. *Proc Natl Acad Sci USA* 2006; **103**:13474–9.
3. Cleary AS, Leonard TL, Gestl SA *et al*. Tumour cell heterogeneity maintained by cooperating subclones in Wnt-driven mammary cancers. *Nature* 2014; **508**:113–7.
4. Archetti M, Ferraro DA, Christofori G *et al*. Heterogeneity for IGF-II production maintained by public goods dynamics in neuroendocrine pancreatic cancer. *Proc Natl Acad Sci USA* 2015; **112**:1833–8.
5. Pepper JW. Drugs that target pathogen public goods are robust against evolved drug resistance. *Evol Appl* 2012; **5**:757–61.
6. Archetti M. Evolutionarily stable anti-cancer therapies by autologous cell defection. *Evol Med Public Health* 2013; **2013**:161–72.