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Game-theory Models of Interactions Between Tumour Cells

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The population of cells that comprises a tumour may consist of genetically different individuals. Often, such polymorphisms result from the expansion of a new, advantageous clone. The hypothesis is presented that sometimes tumour cells may adopt genetically-determined strategies to boost their own replication at the expense of other cells in the tumour. Simple game-theory models have been used to study this hypothesis, taking as an example the hypothetical advantage gained by tumour cells which produce a cytotoxin to harm other tumour cells. The models show that genotypes which cause cells to produce cytotoxic substances can spread through the tumour cell population, as can genotypes for resistance to the cytotoxin; in other circumstances, stable polymorphisms between these strategies can occur. The path of the tumour cell population to internal or external equilibrium is often complex, with large fluctuations in genotype frequencies. Flexible strategies are usually superior to fixed strategies. As in populations of whole organisms, 'social' interactions between tumour cells can act in favour of the individual cell at the expense of the tumour as a whole: strategies that retard the growth of the tumour can be selected and tumour regression is theoretically possible. Many mutations in tumours, especially in large or late-stage lesions, may play a role in relations between tumour cells rather than providing those cells with a simple replicative advantage. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

INDIVIDUAL TUMOURS may be comprised of a population of cells that is genetically polymorphic. There are many possible reasons for this. Perhaps the most commonly recognised form of polymorphism is the expansion within the tumour of a new clone with an added selective advantage [1]. In effect, this polymorphism is transient. However, there are also situations in which stable polymorphisms may be envisaged [2]. Some of these polymorphisms might benefit the tumour as a whole: some tumour cells might produce growth factors to boost cell replication, for example. Other polymorphisms may result in slower tumour growth: tumour cells may benefit from the deaths of their neighbours, for example, and the production of substances toxic to other tumour cells may be favoured, as may resistance to these substances.

Most models of tumour growth have assumed cell autonomous action [1, 3–10]. Previous models of non-autonomous interactions between tumour cells analysed simple situations of angiogenesis factor production, prevention of programmed cell death and avoidance of the immune response [2]. They have shown that stable polymorphisms could occur within tumours, but that 'altruistic' actions were not selected, even though tumour growth as a whole would have been faster. In these models, a cell's actions only influenced other cells as an incidental effect. The models did not consider the plausible situation in which the main or sole purpose of cells' actions is to affect other cells.

This study presents the hypothesis that, as a result of mutations, some tumour cells attempt to gain an advantage by actively harming neighbouring tumour cells. The hypothesis is tested using mathematical models which are based on simple game theory [11]. This method assumes that individuals (organisms, cells, etc.) play fixed or variable, genetically-determined strategies against the environment and against each other. Perhaps the 'hawk–dove' and 'prisoner's dilemma' contests are the best known. An individual's genotype leads inevitably to the adoption of a particular strategy

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(although in other circumstances, different strategies may be achieved by changes in gene expression, without any difference in genotype). It is possible to determine which strategy (and hence, genotype) is of maximum overall benefit, which strategies lead to equilibria and which strategies can be invaded by alternative strategies. The game-theory models below consider a number of biologically-plausible situations and possible fixed and flexible strategies that tumour cells can adopt to overcome these situations. The models suggest which strategies are likely to be the most successful and which are likely to lead to genetic polymorphisms within tumours.

It is sometimes assumed that game theory requires the contestants to possess some sort of intelligent or plastic behaviour. Whilst the more complex game-theory models of behaviour do have this underlying assumption, the more simple models do not. Game theory can be applied just as well to fixed strategies, or strategies which incorporate a small degree of flexibility. The interactions between tumour cells represent simple strategies that may be modelled by game theory. Each strategy has an associated pay-off depending on the two cell genotypes that interact. Pay-offs are represented in a matrix of interactions. The mean pay-off for each strategy is calculated by summing the products of pay-offs and interaction frequencies for that strategy. Genotype frequencies are changed in successive cell generations according to the normalised fitnesses of the strategy corresponding to that genotype.

The models make a number of assumptions. The population of tumour cells is large and reproduces asexually (a feature which is especially suited to game-theory analysis). Population size is not necessarily constant, but genotypes are generally considered in terms of their frequencies rather than absolute cell numbers. At the level of the cell, different strategies are genetically dominant. It is assumed that genotypes are distributed homogeneously throughout the tumour and cells interact with their neighbours with probabilities dependent solely on the genotype frequency in the population.

In the models, it is assumed that harm to tumour cells is caused by some cytotoxic substance which is produced by cells of the appropriate genotype; the cytotoxin diffuses away from the cell and does not affect the cell itself. Cells can acquire genetic resistance to the cytotoxic substance, for example via a membrane transport protein; the resistance strategy has no effect on other cells. Production of the cytotoxic substance and the resistance protein are costly. Non-resistant cells subjected to the cytotoxic substance suffer a disadvantage (usually short of death) and cells that produce the cytotoxin gain an advantage if they affect a non-resistant cell (for example, through decreased competition for resources).

The primary aim of the models is to show that under some circumstances, all the cells within a tumour can acquire genotypes that cause them to harm other tumour cells and to gain a benefit as a result. In different circumstances, all tumour cells can develop resistance to the harmful effects of other tumour cells. Polymorphisms between different strategies can also result. In some of the models, detailed presentation of the analysis has been sacrificed for brevity, although the general conclusions of the models are presented. This is not a severe limitation, since there are few data on which to base the parameters of the model and all conclusions must therefore be qualitative rather than quantitative.

METHODS AND RESULTS

Basic model

It is assumed that a cell can produce a substance substantially to harm other tumour cells and gain a benefit itself from doing so. In the tumour, three strategies/genotypes are considered initially:

1. Cell produces a cytotoxic substance against adjacent cells;
2. Cell is resistant to the cytotoxic substance;
3. Cell neither produces the cytotoxic substance nor is resistant (baseline).

For simplicity's sake, the genotype of "both producing the cytotoxin and being resistant" is not considered yet. It is compared against other situations below, since it is unlikely to arise in the population before strategies (1) and (2) have arisen. It is assumed that:

(a) Baseline fitness is z;
(b) Cost of producing cytotoxin is e ($e>0$);
(c) Disadvantage of being affected by cytotoxin is f ($0<f<z$);
(d) Advantage conferred after having subjected another cell to the cytotoxin is g ($g>0$);
(e) Cost of resistance to cytotoxin is h ($h>0$).

The frequency of cell type (1) is p, that of type (2) is q and that of type (3) is r.

The cell–cell interaction matrix is then

		Pay-off to (1)	(2)	(3)
Encounter with	(1)	$z-e-f+g$	$z-h$	$z-f$
	(2)	$z-e$	$z-h$	z
	(3)	$z-e+g$	$z-h$	z

The expected pay-offs are then

$$\begin{aligned} E(1) &= p(z-e-f+g)+q(z-e)+r(z-e+g) \\ &= z-e+p(g-f)+rg \\ E(2) &= z-h \\ E(3) &= z-pf \end{aligned}$$

At any triple equilibrium,

$$\begin{aligned} E(2) &= E(3) \Rightarrow \\ p &= h/f \\ E(1) &= E(3) \Rightarrow \\ pf &= e-p(g-f)-rg \Rightarrow \\ r &= e/g-h/f \\ q &= 1-p-r \Rightarrow \\ q &= 1-h/f-e/g+h/f \Rightarrow \\ q &= 1-e/g \end{aligned}$$

Therefore, for a polymorphism between all three strategies,

Table 1. Dependence of equilibrium values of p, q and r on initial values and parameters of selection under the basic model

e	f	g	h	p_i	q_i	r_i	p_{eq}	q_{eq}	r_{eq}
0.1	0.4	0.01	0.25	0.333	0.333	0.333	0.396	0.000	0.604
0.3	0.4	0.1	0.25	0.333	0.333	0.333	0.000	0.000	1.000
0.1	0.7	0.1	0.25	0.333	0.333	0.333	0.263	0.000	0.737
0.1	0.4	0.2	0.25	0.333	0.333	0.333	0.750	0.250	0.000
0.1	0.4	0.1	0.4	0.333	0.333	0.333	0.458	0.000	0.542
0.05	0.4	0.1	0.25	0.333	0.333	0.333	0.667	0.333	0.000
0.01	0.8	0.3	0.8	0.333	0.333	0.333	1.000	0.000	0.000
0.25	0.9	0.01	0.02	0.333	0.333	0.333	0.000	0.000	1.000
0.1	0.4	0.15	0.25	0.333	0.333	0.333	0.625	0.333	0.042
0.12	0.2	0.24	0.05	0.333	0.333	0.333	0.000	1.000	0.000
0.1	0.4	0.2	0.25	0.333	0.333	0.333	0.750	0.250	0.000
				0.500	0.500	0.000	0.750	0.250	0.000
0.05	0.4	0.1	0.25	0.333	0.333	0.333	0.666	0.333	0.000
				0.500	0.500	0.000	0.666	0.333	0.000
0.05	0.4	0.1	0.3	0.333	0.333	0.333	0.833	0.167	0.000
				0.500	0.500	0.000	0.833	0.167	0.000
0.15	0.25	0.2	0.1	0.333	0.333	0.333	0.400	0.250	0.350
	0.24			0.333	0.333	0.333	0.417	0.250	0.333
	0.23			0.333	0.333	0.333	0.435	0.250	0.315
	0.22			0.333	0.333	0.333	0.457	0.250	0.293
	0.212			0.333	0.333	0.333	1.000	0.000	0.000
	0.21			0.333	0.333	0.333	1.000	0.000	0.000
0.4	0.8	0.75	0.3	0.333	0.333	0.333	0.000	1.000	0.000
		0.7		0.333	0.333	0.333	0.000	1.000	0.000
		0.65		0.333	0.333	0.333	0.000	1.000	0.000
		0.62		0.333	0.333	0.333	0.000	1.000	0.000
		0.6		0.333	0.333	0.333	0.325	0.350	0.325
		0.5		0.333	0.333	0.333	0.375	0.200	0.425

p, q and r and e, f, g and h are as given in the text. The subscripts i and eq denote initial and equilibrium values, respectively. The table shows: triple polymorphic (internal) equilibrium; double equilibria (except between q and r which does not occur); fixation of p, q and r; dependence and independence of equilibrium values of p, q and r on initial values; and the threshold change from stable to unstable internal equilibrium that can occur as parameters of selection vary. Empty cells carry the same parameter value as the cell immediately above

$$0<h/f<1$$
$$0<e/g-h/f<1$$
$$1>e/g>0$$

that is, the cost of being affected by cytotoxin (f) is greater than the cost of resistance (h) and the advantage after subjecting another cell to the cytotoxin (g) must exceed the cost of making the cytotoxic substance (e). Both are plausible inequalities. Initial genotype frequencies and baseline fitnesses do not determine equilibrium frequencies.

Owing to the complexity of this model, it is most convenient to simulate changes in genotype frequency. Table 1 shows typical results from various initial values of p, q and r and different values of e, f, g and h. The following conclusions can be drawn:

(i) Triple polymorphisms may occur independent of initial values of p, q and r; but some equilibria are unstable; stability exists when the above in qualities hold and when (if, say, q is displaced by d from equilibrium) the following complex inequality also holds

$$|d| > |((z-h)(1-e/g+d)/$$
$$(z+(g-f)(p^2+pr)-ep-q))-1+e/g|$$

(ii) Two-strategy polymorphisms between p and r and between p and q may occur (investigated further below);

(iii) No two-strategy polymorphism between q and r occurs, because E(3) > E(2) if $p = 0$;

(iv) p, q or r may become fixed in the population; *ceteris paribus*, fixation of p is favoured by small e, large g, small f and large g; fixation of q is favoured by small h; fixation of r is favoured by small f;

(v) Initial genotype frequencies may influence the subsequent changes in genotype frequency (for example, r is always favoured by low initial p and p is favoured by low p if $f > g$, but favoured by high p if $g > f$) and determine whether genotypes are lost from the population (although the genotype frequencies if triple polymorphisms actually exist are independent of initial frequencies, as above);

(vi) Before reaching equilibrium (whether internal (polymorphic) or boundary), genotype frequencies tend to oscillate wildly, hunting around the internal equilibrium values with decreasing amplitude when internal equilibrium is stable, or hunting around those same values with increasing amplitude when internal equilibrium is unstable; this behaviour results from the frequency-dependent pay-offs in the models which often favour strategies when rare, but not when they are common; internal equilibrium is reached if cycling occurs with decreasing amplitude, but boundary equilibrium occurs otherwise;

(vii) Maximal population fitness is given by maximising

$$z - p(e+f+g) + pq(f+g) - qh$$

over p and q; clearly, however, equilibrium values are sub-optimal in many cases;

(viii) All strategies can be fixed in the population and stable to invasion by other strategies depending on the values of e, f, g and h;

(ix) Replication rates at equilibrium may fall below the baseline (for example, if $q = 1$); and

(x) Equilibrium values do not depend on z and if z is small, tumour regression is theoretically possible.

Now, the cases are investigated in which there is a polymorphism between p and q, or there is a polymorphism between p and r. It is easiest to do this by eliminating the strategy that is lost from the population from the analysis. This enables the equilibrium genotype frequencies to be predicted, but only after it has been established using the three-genotype model that one genotype is lost from the cell population.

Considering p and r first, at equilibrium

$$\begin{aligned} \mathrm{E}(3) &= \mathrm{E}(1) \Rightarrow \\ fp &= e - pg + fp - rg \Rightarrow \\ r &= e/g - p \quad \text{but} \quad r = 1 - p. \end{aligned}$$

Equilibrium only occurs, therefore, when $e = g$. Otherwise, strategy (3) becomes fixed with large e and lost with small e relative to g. When $e = g$, initial values of p and r (and q) determine equilibrium values, but there is always internal (polymorphic) equilibrium once q is lost from the population. If $q = 0$ initially, then p and r remain at their initial frequencies. If $q>0$ initially, q declines to zero and p and r rise by equal amounts.

For p and q, at equilibrium

$$\begin{aligned} \mathrm{E}(2) &= \mathrm{E}(1) \\ h &= e - pg + fp - rg \Rightarrow \\ p &= (h-e)/(f-g) \text{ and equilibrium occurs when} \\ 0 &< (h-e)/(f-g) < 1 \end{aligned}$$

Strategy (1) is fixed if $(h-e)/(f-g)>1$ and lost if $(h-e)/(f-g) < 0$. Equilibrium genotype frequencies appear not to depend on initial frequencies once r has been lost. However, not all equilibria between p and q are stable. Generally, extreme initial p values and $e>h$, $g>f$ favour unstable equilibrium. Examples of how final genotype frequencies depend on initial p, q and r and on e, f, g and h are shown in Table 1.

Clearly, the equilibrium values when one genotype is lost are different from those that apply to the same two strategies when all three genotypes are retained in the population of cells.

Cytotoxin-producing/resistant cell

Here, a situation is considered in which a cell has the strategy/genotype (4) of both producing the cytotoxin and being resistant. It has not yet been compared against other situations, since it is unlikely to arise in the population before evolution of other strategies has occurred. Since strategies (2) and (3) do not occur in the population together at equilibrium, the comparison will be made (for simplicity's sake) between strategies (1) (cytotoxin producer), (3) (baseline) and (4). The frequency of cell type (4) is s. The cell–cell interaction matrix is then

		Pay-off to (1)	Pay-off to (3)	Pay-off to (4)
Encounter with	(1)	$z-e-f+g$	$z-f$	$z-e+g-h$
	(3)	$z-e+g$	z	$z-e+g-h$
	(4)	$z-e-f+g$	$z-f$	$z-e-h$

The expected pay-offs are then

$$\begin{aligned} \mathrm{E}(1) &= p(z-e-f+g) + r(z-e+g) + s(z-e-f+g) \\ &= (p+r+s)(z-e+g) - f(p+s) \\ &= z - e + g - f(p+s) \\ &= z - e + g - f(1-r) \\ \mathrm{E}(3) &= z - f(p+s) \\ &= z - f(1-r) \\ \mathrm{E}(4) &= z - e - h + g(p+r) \\ &= z - e - h + g(1-s) \end{aligned}$$

At triple equilibrium,

$$\mathrm{E}(1) = \mathrm{E}(3) \Rightarrow g = e$$

and from setting $\mathrm{E}(1) = \mathrm{E}(4)$ and $\mathrm{E}(3) = \mathrm{E}(4)$,

$$p = 1/f(h + s(e-f)), \quad r = 1 - ((h+se)/f), = 1 - p - r$$

with restrictions such that $p, r, s>0$ and $p + r + s = 1$

Clearly, this is not a general equilibrium because g and e are very unlikely to be equal, but it is stable. Simulations show that, in general, if $e>g$, r is fixed, but if $e < g$, p or s can be fixed, or there may be a polymorphism between p and s. Any strategy can be fixed in the population. Generally, fixation of p is favoured by large g, small f, small e and large h; fixation of r is favoured by small f and fixation of s is favoured by small e, small h and large g. Initial genotype frequencies can influence which strategy becomes fixed.

The only realistic polymorphisms that occur in this model do so between p and s when r is absent or becomes lost from the population (see below). Perhaps the most plausible scenario is for genotype (4) to arise at a low frequency in a population in which (1) and/or (3) are both present already. The pay-off to strategy (4) is greatest at low s and this genotype can increase in frequency (often to fixation) under values of e, f, g and h that favour it. With appropriate values of e, f, g and h, any of the three genotypes can be fixed and resistant to invasion by other strategies in this model.

Of the potential two-strategy polymorphisms in this model, that between p and r has been studied above and that between r and s appears to be unstable (details not shown). Consider, however, the possible polymorphism between p and s when r is absent or lost from the population. At equilibrium,

$$\mathrm{E}(1) = \mathrm{E}(4) \Rightarrow s = (f-h)/g$$

This equilibrium exists as long as $0 < (f\text{-}h)/g < 1$. It is stable and independent of the initial frequencies of p and s (given $r = 0$).

Flexible resistance and cytotoxin-producing strategies

This model considers responses that can be modified according to a cell's encounter. Here, genotype (5) (frequency x) adopts the following complex strategy:

(i) To produce cytotoxin substance only when encountering a non-resistant cell;

(ii) To produce resistance only when encountering cytotoxin-producing cells;

(iii) To do nothing when encountering a cell with the potential to produce both cytotoxic substance and resistance (that is, a cell like itself).

Clearly, such a complex strategy is unlikely to occur in reality, although some cruder version may well be possible and can be represented by this model. The pay-off matrix is then

		Pay-off to			
		(1)	(2)	(3)	(5)
Encounter with	(1)	$z-e-f+g$	$z-h$	$z-f$	$z-e+g-h$
	(2)	$z-e$	$z-h$	z	z
	(3)	$z-e+g$	$z-h$	z	$z-e+g$
	(5)	$z-e-f$	$z-h$	$z-f$	z

The expected pay-offs are

$$E(1) = z - e - f(p+x) + g(p+r)$$
$$E(2) = z - h$$
$$E(3) = z - f(p+x)$$
$$E(5) = z - e(p+r+g(p+r) - hp$$

In some cases where r became fixed when strategies (1), (2) and (3) were present r may still be fixed, especially if x is initially small. In all other cases, x spreads to unity. The advantage of flexible strategies is illustrated, although this advantage would have been diminished had any cost of flexibility been assumed.

Incorporating a replicative advantage into the models

Here, one or more genotypes possess a replicative advantage unrelated to the strategy used in interactions with other cells. This model simulates situations in which either a new, advantageous mutation occurs (which leads to a higher rate of cell-autonomous proliferation), or new strategy mutations arise in disequilibrium with cells' underlying replicative advantages. These advantages are denoted $a1$, $a2$ and $a3$, for genotypes (1), (2) and (3), respectively. In this model, the selective coefficients $a1$, $a2$, $a3$, e, f, g and h can be assumed to represent absolute effects on genotype numbers, not just relative effects.

The cell–cell interaction matrix is then

		Pay-off to		
		(1)	(2)	(3)
Encounter with	(1)	$z-e-f+g+a1$	$z-h+a2z-f+a3$	
	(2)	$z-e+a1$	$z-h+a2z+a3$	
	(3)	$z-e+g+a1$	$z-h+a2z+a3$	

$\{a1 > 0$ and/or $a2 > 0$ and/or $a3 > 0\}$

The expected pay-offs are then

$$E(1) = z - e + p(g-f) + rg + a1$$
$$E(2) = z - h + a2$$
$$E(3) = z - pf + a3$$

If $a3>0$ ($a1$, $a2 = 0$), at equilibrium

$$p = (h + a3)/f$$
$$q = 1 - (a3 + e)/g$$
$$r = 1 - p - q = (a3 + e)/g - (h + a3)/f$$
$$0<p,\ q,\ r<1,\ p+q+r = 1$$

By comparison with the basic situation with $a1$, $a2$, $a3 = 0$ (with $p = h/f$, $q = 1\text{-}e/g$, $r = e/g\text{-}h/f$ at equilibrium), r is more likely to be fixed. However, internal equilibrium is not abolished: triple equilibrium may be retained, be converted to a double equilibrium or boundary equilibrium as the value of $a3$ increases. Indeed, internal equilibrium is not necessarily made less likely and may even be made more likely (depending on the values of $a1$, $a2$, $a3$, e, f, g, h).

For the situation $a1>0$ ($a2$, $a3 = 0$), at equilibrium

$$p = h/f$$
$$q = 1 - (e - a1)/g$$
$$r = 1 - p - q = (e = a1)/g - h/f$$
$$0<p,\ q,\ r<1,\ p+q+r = 1$$

For the situation $a2>0$ ($a1$, $a3 = 0$), at equilibrium

$$p = (h - a2)/f$$
$$q = 1 - e/g$$
$$r = 1 - p - q + e/g - (h - a2)/f$$
$$0<p,\ q,\ r<1,\ p+q+r = 1$$

The same general conclusions apply to $a1$ and $a2$ as apply to $a3$, except that p and q are more likely to be fixed, respectively.

It is possible to incorporate different growth advantages $a1$, $a2$ and $a3$ simultaneously into the models, to take into account the possibility that the mutations for the cytotoxic substance and resistance arise in cells with different underlying replicative advantages. The pay-off matrix is as above, and at equilibrium

$$p = (h - a2 + a3)/f$$
$$r = (a3 - a1 + e)/g - (h - a2 + a3)/f = (a3 - a1 + e)/g - p$$
$$q = 1 - p - r = 1 - (h - a2 + a3)/f$$
$$0<p,\ q,\ r<1,\ p+q+r = 1$$

Without presenting detailed analyses, it is apparent from the above that internal equilibria are generally possible when different replicative advantages are associated with different strategies for interacting with other tumour cells. The qualitative conclusions of all the models are therefore robust to changes in underlying replicative rates in different cells.

DISCUSSION

The models have analysed the hypothesis that tumour cells can adopt genetically-determined survival strategies to harm other tumour cells and gain a benefit for themselves. They have also considered cases in which cells additionally have different replicative rates, in addition to their interactive strategies. Each strategy is a form of social interaction between cells. Interactions have been assumed, for simplicity, to occur between individual cells: the results from the more complex interactions found in reality can be inferred from the individual interactions.

There are several general conclusions from the game-theory models. First, the production of cytotoxic substances against other tumour cells can evolve within the tumour cell population. Resistance to cytotoxic substances can also evolve as a consequence. Second, different strategies may be present in the tumour cell population at stable internal points of equilibrium (although the approach to equilibrium is often slow and the population may, in reality, track successive points of equilibrium rather than reaching them). It is also possible for several different strategies to become fixed in the population, depending on selective parameters and initial genotype frequencies. Third, flexible strategies are generally superior to fixed strategies (unless flexibility carries significant costs). Fourth, tumour growth may be retarded by the action of tumour cells against one another, even though individual cells may benefit. It is theoretically possible for tumour regression to occur, but baseline replication rates (relative to normal tissue) must previously have fallen to a low level.

Above all, the models emphasise the complexity of tumorigenesis. Not all mutations found in tumours necessarily promote tumour growth. In this way, the process of somatic evolution that is tumorigenesis mimics some forms of evolution in whole organisms, in which individuals adapt to social pressures from within their species, rather than selection resulting from the physical environment or other species: apparently maladaptive characters such as stags' antlers and the peacock's tail are examples of traits which are detrimental to the species as a whole, although advantageous to the individual. In the same way, selection acts on the individual tumour cell, rather than the tumour as a whole. Many mutations in tumours, especially in large or late-stage lesions, may therefore play a role in relations between tumour cells. Paradoxically, therapies directed against these mutations might actually result in faster tumour growth. There is little or no experimental evidence for mutations that cause tumour cells to harm their neighbours and such evidence will be difficult to obtain. Nevertheless, this possibility should always be borne in mind when analysing mutations in tumours.

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