Tumour growth and drug resistance: an evolutionary view with perspectives in therapeutics
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Tumour growth and drug resistance: an evolutionary view with perspectives in therapeutics

Jean Clairambault

1. Introduction

Motivations

• Accounting for drug resistance in cancer requires considering the level of cancer cell populations
• Phenotype heterogeneity in cancer cell populations is likely the main cause of drug resistance
• Heterogeneity in cancer cell populations may be due to fast backward evolution (atavistic theory)
• We can assess it by biological and mathematical models of evolving heterogeneous cell populations
• Therapeutic strategies should rely on optimal control algorithms in such models of heterogeneity

Executive summary

BACKGROUND Drug-induced drug resistance in cancer has been attributed to diverse biological mechanisms at the individual cell or cell population scale, relying on stochastically or epigenetically varying expression of phenotypes at the single cell level, and on the adaptability of tumours at the cell population level.

SCOPE OF THIS REVIEW We focus on intra-tumour heterogeneity, namely between-cell variability within cancer cell populations, to account for drug resistance. To shed light on such heterogeneity, we review evolutionary mechanisms that encompass the great evolution that has designed multicellular organisms, as well as smaller windows of evolution on the time scale of human disease. We also present mathematical models used to predict drug resistance in cancer and optimal control methods that can circumvent it and combined therapeutic strategies.

MAJOR CONCLUSIONS Plasticity in cancer cells, i.e., parietal reversal to a stem-like status in individual cells and resulting adaptability of cancer cell populations, may be viewed as backward evolution making cancer cell populations resistant to drug inadequacy. This reversible plasticity is determined by mathematical models that incorporate between-cell heterogeneity through continuously varying expression of phenotypes at the single cell level. Such models have the benefit of being compatible with optimal control methods for the design of optimised therapeutic protocols involving combinations of cytostatic and cytoclastic treatments with epigenetic drugs and immunotherapies.

GENERAL SIGNIFICANCE Gathering knowledge from cancer and evolutionary biology with physiologically based mathematical models of cell population dynamics should provide oncologists with a rationale to design optimised therapeutic strategies to circumvent drug resistance, but still remain a major pitfall of cancer therapeutics.

2. An evolutionary perspective

“Nothing in biology makes sense except in the light of evolution” (Theodosius Dobzhansky).

... But what evolution? Have a look at the evolution of life on Earth:

Figure 1: Tentative reconstruction of the evolution of life on Earth (Ref. [1]).

• The genes that have appeared in the process of development to multicellularity are precisely those that are altered in cancer.
• In what order in evolution, from 1) proliferation-apoptosis to 2) cell differentiation—division of work, and to 3) epigenetic control of differentiation and proliferation?
• Reconstituting the phylogeny of this ‘multicellularity toolkit’ should shed light on the robustness or fragility of genes that have been altered in cancer.
• Attack cancer on proliferation is precisely attacking its robustness. It would be better to attack its weaknesses (e.g. absence of adaptive immune response).

Heterogeneity in cancer cell populations

• Conditions of oxygenation and intercellular communications are quite poor in cancer cell populations, sending back tumours to very primitive forms of multicellularity (e.g., stochastic distribution of cellular functions without coordination)

Figure 2: Epigenetic cell differentiation in a given genome.

Epigenetic drugs to target bifurcations in a plastic landscape?

The Waddington landscape revisited

The classical ‘metaphoric’ Waddington landscape (1957)

Figure 3: A Waddington landscape revisited (Sui Huang, 2013).

“Nothing in evolution makes sense except in the light of systems biology” (S. Huang, 2012)

Figure 4: Healthy cells: preserved (Ref. [2]).

Figure 5: Cancer cells: eventually extinct (Ref. [2]).

3. Assessing drug resistance

Adaptive dynamics called to predict evolution of cell populations in the presence of drug pressure:

\[
\frac{d\rho}{dt}(x,t) = -\frac{m(x,t)}{\mu(x,t)}\rho(x,t) + \frac{n(x,t)\beta(x,t)}{\mu(x,t)}\rho(x,t)
\]

Figure 6: Environment variables (logistic terms):

\[
\rho(x,t) = \frac{m(x,t)\beta(x,t)}{\mu(x,t)}(1 - \rho(x,t))
\]

\(\beta(x,t)\) cytotoxic, \(\gamma(x,t)\) cytostatic drugs.

Figure 7: Environment variables (logistic terms):

\[
\rho(x,t) = \frac{m(x,t)\beta(x,t)}{\mu(x,t)}(1 - \rho(x,t))
\]

\(\beta(x,t)\) cytotoxic, \(\gamma(x,t)\) cytostatic drugs.

4. Perspectives in therapeutics

• Systematically relating the phylogeny of multicellularity to the phylogeny of cancers (an evo-devo-cancer viewpoint, cf. Ref. [1]) should shed light on the responsible genes of cancer emergence and progression as possible druggable targets.
• Models of adaptive dynamics models for cell populations are relevant to represent their evolution under drug pressure, cf. Ref. [2].
• Taking limitations in space and diffusion of drugs and nutrients is an option when some geometry of the tumour population is known, cf. Ref. [3].
• Epigenetic control genes might offer such targets to stop the emergence of drug resistance (blocking the rise of DTPs, cf. Ref. [4]).
• Optimal control algorithms for anticancer drug infusion are being designed as proof of concept, aiming to block the emergence of drug resistance, cf. Ref. [5]. These should be developed in close collaboration with oncologists in the clinic in the forthcoming years.

5. References