RESOURCE OVERSUPPLY IN CARCINOGENESIS: MODELLING A COMMON THEME IN DIVERSE RISK FACTORS

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Background

Cancer risk factors, such as obesity, inflammation, and diabetes, have been associated with carcinogenesis by a wide variety of molecular mechanisms; however, ecological, evolutionary and microenvironment-centered mechanisms are under-explored. A common theme underlying these risk factors is the creation of resource oversupply.

We propose normal physiology restricts resource availability to a bare maintenance level, limiting proliferation. Furthermore, we conjecture that lifting this restriction allows for abnormal proliferation and creates a selective pressure for cancer-associated phenotypes, accelerating carcinogenesis. This evolutionary mechanism suggests generalizable treatment and prevention strategies.

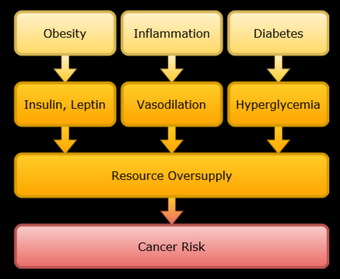
Model Construction

NetLogo 6.0 was used to construct an agent-based model, representing a population of somatic cells with the capacity to mutate, in order to study their evolutionary dynamics.

We consider initially phenotypically identical cells distributed uniformly amongst micro-environments in a tissue, which has a constant resource renewal rate.

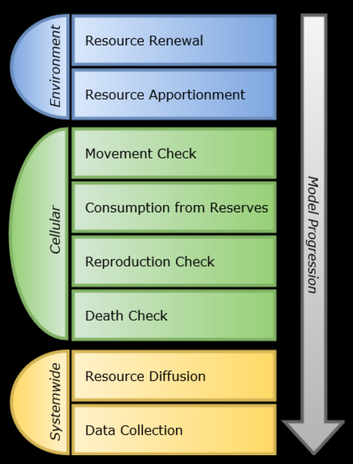
Cells undergo four basic processes: consumption, movement, and reproduction, and death.

Consumption and movement occur according to cell-specific rates, which mutate upon reproduction. Reproduction occurs when cellular energy reserves surpass a reproduction threshold. Death occurs both according to the background mortality rate and when a cell exhausts its reserves.



Causal relations from individual risk factors to cancer risk.

Netlogo 6.0, an agent-based modelling platform.



A depiction of model progression, within each time step.

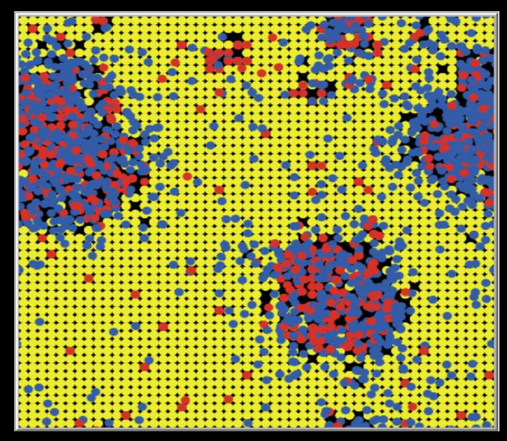
Parameter	Initial Value	Description
Initial Uptake Rate	1	The amount of resources a somatic cell consumes from its microenvironment per time step.
Initial Mobility Rate	0	The initial probability that a cell will move in a time step.
Renewal Rate	**2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8**	The base amount of resources replenished to each microenvironment per time step. A rate of 2 represents a maintenance supply, and is control. **Independent Variable.**
Mutation Rate	0.1	The standard deviation for mutations in motility rate and consumption rate.
Basal Energy Cost	0.5	The energy consumption of each cell per time step.
Reproduction Threshold	50	The amount of stored resources necessary to trigger cell division.
Diffusion Coefficient	0.01	The proportion of each diffusible resource that is diffused in each time step.
Background Mortality	$1.0 * 10^{-6}$	The chance that a given cell will die in a given time step, due to background turnover.
Initial Resources	4	The initial amount of resources in each microenvironment.
Initial Cell Reserves	25	The initial amount of energy in cellular reserves.

Experimentation

We varied the rate of resource delivery to tissue, and assessed its effects on cancer risk. 50 trials were run at each resource renewal rate.

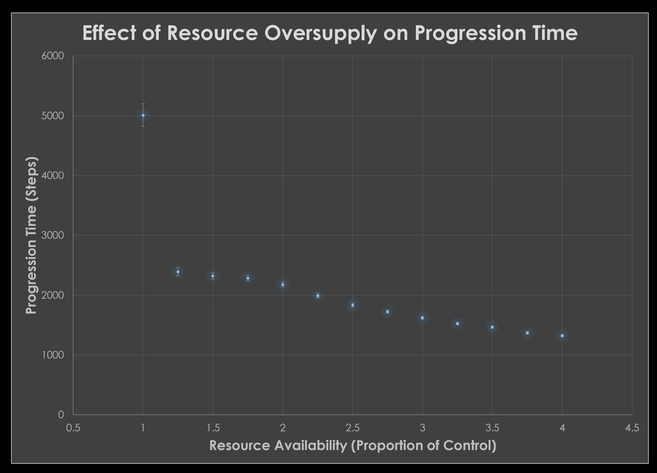
Cancer cells are defined as those with a motility and consumption rate higher than normal, and progression was defined as occurring when cancer cells are the majority subpopulation.

Population and phenotype data was recorded in each time step. Simulations were terminated upon cancer progression, and progression times were recorded.



The model environment, at 4000 time steps, set at control. Unmutated cells are shown in yellow, mutated in red, and cancer in blue.

Results



Graph of progression times over renewal rates (n=50). Error bars are 95% confidence intervals.

Initial departures from a maintenance supply led to a significant shortening of progression times, with further increases in renewal rate causing comparatively lesser decreases in progression times.

Motility, by allowing cells to move from micro-environments they have exhausted, creates a competitive benefit to higher consumption rates. Motility and consumption rates were found to coevolve.

Discussion

Resource oversupply increases cancer risk. Oversupply conditions favor the evolution of neoplastic phenotypes, and provide a selective pressure for such phenotypes. This mechanism is independent of molecular mechanisms, and underlies a wide variety of risk factors.

Only a consistent and prolonged increase in resource availability provides an evolutionary pressure, which expedites carcinogenesis. Resource paucity stymies this effect, suggesting an explanation for the preventative effects of a daily Aspirin regimen.

Further research into non-pharmaceutical "evolutionarily-enlightened" treatment options, such as caloric restriction, intermittent fasting, or variable insulin therapy, may yield alternative intervention and prevention strategies.

Key Points

- Resource paucity restricts proliferation
- Oversupply accelerates carcinogenesis
- Limiting oversupply reduces risk

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