Agent based modeling of the natural history of normal human mammary epithelial cells in cell culture

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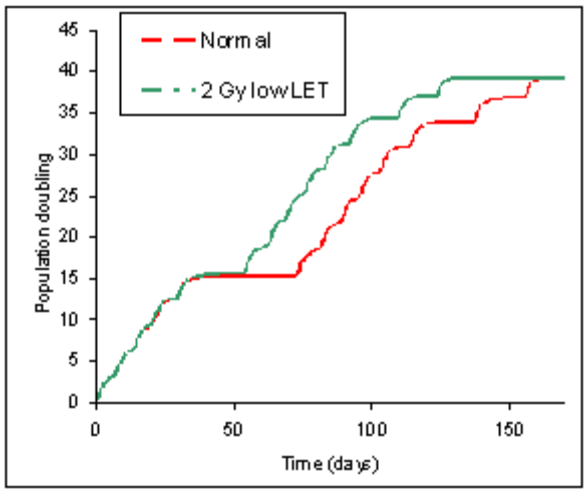
There is a clear need in the field of radiation biology for integrated models of radiation response based on systems biology principles (1). Network interconnectivity and spatial organization of cellular phenotypes within the higher order of multi-cellular structure should be key features in such model. In our approach, "agents" were used to describe cultured human mammary epithelial epithelial cells (HMEC) and their interactions with each other and their environment. The use of agent-based system (2), or cellular automata (3) have considerable potential to model the complex and non-linear behavior of populations. Agent-based programs are a platform to predict phenomena emerging from large population of cells interacting with each other. Agents are objects that have attributes based on rules that mimic individual behavior in a contextual and stochastic manner (non-deterministic). The attributes of one agent can be modified by interactions with other agents or as a result of external stress (e.g. radiation) over iterative steps in time (e.g. cell-cycle status, phenotype).

We developed an agent-based model of the growth of primary HMEC cultured in monolayers. Under serum-free growth conditions, most p16+ HMEC undergo senescence but some cells in which the p16 negative (p16-) promoter is methylated grow out as described by our colleagues (4, 5). Primary HMEC undergo about 15 cell population doubling before reaching the first senescence barrier (i.e. stasis), which is evidenced by a growth plateau. Cells escaping stasis typically divide for another 50 cell population doubling before reaching a barrier called agonescence. One explanation is that p16- cells are induced; alternatively, a very small number of p16- cells could be present in primary cell culture and overtake the post-stasis culture. We modeled this proecess using agents that were given the following attributes: age (number of divisions), cycle status, clone (track ID of original mother cell), individual ID, and cell type. The cell type was an important property of these agents, since different contextual rules were set for different types.

We thus created two cell types: p16+ type 1 and p16- type 2. Type 1 cells were set to divide no more than 15 times and type 2 no more than 65 times. Both were assumed to have both a 24 hour cell cycle. Cells were assumed to be contact-inhibited when they had more than 6 non-senescent neighbors. By assuming that 3% of the population was initially type 2, the outgrowth of type 2 cells was reproduced after 14 simulated passages. The population doubling curves obtained were similar to the one measured in the lab, validating the feasibility of the model.

More recently our colleagues (unpublished work) have shown that exposure of HMEC to -radiation (1 Gy) leads to more rapid escape from stasis. We considered three hypotheses: that radiation induced premature senescence; that radiation induced differential cell kill of type 1 vs type 2 cells, or that both occurred. We tested which hypothesis was most likely by altering the rules of the agent-based simulation. Our preliminary data (Figure) shows that the model in which radiation preferentially kills type 1 cells led to more rapid escape from stasis of type 2 cells, reproducing what has been measured experimentally.



The use of agent-based programming to model the fate of epithelial cells dictated by a very simple set of contextual rules describing proliferation, growth arrest, death or motility can accurately replicate the biological behavior over time. The plan for this model is to refine agent properties, adding cell motility and extend to three-dimensional growth for multicellular behavior. Such a system would then used to simulate the responses to radiation under specific microenvironmental conditions.

References

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