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Modelling population dynamics of human epithelial cell lines: the differential expression of c-erbB2 oncogene and breast tumour development

The comprehension of mechanisms underlying cancer development depends on the understanding of processes underlying tissue formation. In physiological condition, the tissues are maintained in a dynamic equilibrium, called homeostasis, where the cell number is kept essentially constant and is regulated based on reproduction, death and half-life rates of cellular population. Molecular alterations that disturb the homeostasis can be potentially dangerous. Mutations that would permit selective advantages, like a faster cell division, could lead to the formation of a clone of continuous growth. Repeated cycles of mutation, competition and natural selection form the basis of cancer development. The c-erbB2 oncogene is a membrane receptor with tyrosine kinase activity that belongs to the epidermal growth factor receptor family. C-erbB2 over-expression is observed in 25-30% of breast tumours and is an adverse prognostic factor. To study the molecular mechanism of c-erbB2, Harris at al. (1999) developed a model of c-erbB2 over-expression in conditionally immortalized mammary luminal epithelial cells. Two new lines, HB4a-C3.6 and HB4a-C5.2, expressing different levels of c-erbB2, were derived from the immortalized cell line HB4a. This work presents a computational model designed to mimic the experimental data obtained from the in vitro culture of HB4a-C3.6 and HB4a-C5.2 lineages. A discrete agent-based model, controlled by a dynamic system that represents c-erbB2 expression, simulates the cell culture dynamics. In order to validate the results, they were compared to experimental data, regarding cell cycle and population dynamics. The model will be applied to evaluate differential expression of 4 transcripts positively regulated by c-erbB2 tumours, evaluated by Real Time PCR in HB4a and HB4a-C5.2 cell lines. Their functional characterization will allow a better understanding of the molecular mechanisms behind c-erbB2 over-expression and breast tumour development.

References

[1] R.A. Harris, T.J. Eichholtz, I.D. Hiles, M.J. Page, M.J. Ohare. New model of erbB-2 overexpression in human mammary luminal epithelial cells. Int. J. Cancer: 80, 477484 (1999).