MULTIPLE SCALE AGENT-BASED MODEL PREDICTS CANCEROUS FIELD SPREAD IN THE COLON

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ABSTRACT

Colorectal cancer (CRC) is a major cause of cancer mortality world-wide. One of the earliest stages in the disease process is the mutation of the APC gene, causing a number of phenotypic changes in affected cells, including increased stiffness, shorter quiescent phase and resistance to anoikis (adhesion-mediated cell death). After colonising an individual colon crypt, the field of mutated tissue then spreads beyond the original crypt into the wider colon, but the mechanisms behind this expansion are poorly understood.

We have developed a dual-scale agent-based model in order to explore potential mechanisms of field expansion. Following previous models (1) , in the lower scale model individual biological cells are represented as interacting particles (2, 3), whereas in our entirely novel upper scale model, the same representation is applied to colon crypts, including a surrounding ring of mucosal tissue. This representation allows both cell and crypt agents to move according to repulsive forces exerted due to growth and movement. Our cellular scale agents are programmed with behaviour for division, adhesion and anoikis resistance that corresponds either to that of normal colon cells, or those affected by an APC mutation. The rate of field spread generated by this model is then used to parameterise our upper scale model, where crypt agents can undergo flat mucosal invasion according to the state of their neighbours, or execute previously hypothesised behaviours such as fission or death.

At the cellular scale, our model predicts that mutated cells spread through the flat mucosa of the simulated tissue without invading neighbouring crypts - a process not previously hypothesised. The predictions of field sizes generated by the crypt-scale model correspond to those estimated from in vivo studies. Our dual-scale modelling approach renders the spatial and temporal scales at which field cancerisation processes occur in vivo accessible to exploration by simulation for the first time.

REFERENCES

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