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Prediction and validation of an order principle to restore tissue architecture in liver regeneration after drug-induced damage: from experiments to modeling and back

Not much is known about how cells coordinately behave to establish functional tissue structure and to restore micro-architecture during regeneration. Research in this field suffers from a lack of techniques that permits quantification of tissue architecture and its development. To bridge this gap we have established a procedure based on confocal laser scans, image processing and three-dimensional tissue reconstruction, as well as on quantitative mathematical modeling. To illustrate our method we studied regeneration after toxic liver damage. We have chosen the example of the regenerating liver, because liver function depends on the complex micro-architecture formed by hepatocytes (the main type of cells in liver) and micro-vessels (sinusoids) that ensures optimal exchange of metabolites between blood and hepatocytes. Our model of regeneration after toxic damage captures hepatocytes and sinusoids of a liver lobule during the regeneration process. Hepatocytes are modeled as individual agents parameterized by measurable biophysical and cell-biological quantities. Cell migration is mimicked by an equation of motion for each cell subject to cell-cell-, cell-extra-cellular matrix-, and cell-sinusoid-forces, as well as the cell micro-motility. We demonstrate how by iterative application of the above procedure of experiments, image processing and modeling a final model emerged that unambiguously predicted a so far unrecognized mechanism, the alignment of daughter hepatocytes along the closest sinusoids as essential for liver regeneration. In absence of this mechanism, the simulated tissue architecture was in dis-agreement with the experimentally obtained data and no other likely mechanism could replace it. To experimentally validate the model prediction, we three-dimensionally analyzed the orientation of daughter hepatocytes in relation to the sinusoids. The results of this analysis clearly confirmed the model prediction.

References

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