

In order to set up a realistic model we first reconstructed a schematized liver lobule after determination of (i) the mean number of hepatocytes between the central vein and the periphery of the lobule, (ii) the mean size of the hepatocytes and (iii) the mean number of hepatocyte columns in the inner, midzonal and peripheral ring of the lobule (Fig.1A-B). In a next step we determined the time course of cell death and BrdU incorporation after intoxication of male Sprague Dawley rats with CCl_4 , thereby differentiating between inner, midzonal and peripheral hepatocytes (Gebhardt and Burger, 1987). The information acquired analyzing the experimental data was used to parameterize the modeling.

The basic unit of the model (Drasdo and Hoehme, 2005) is the individual cell. Since freshly isolated hepatocytes in suspension have a spherical shape we assume each model cell to be spherical in the interphase and to deform into a dumb-bell during mitosis. In our analysis, we consider a 2D-section of an “ideal” hexagonal liver lobule composed of approximately 300 model cells with the central vein in the middle (Fig.1C). We assume an average intrinsic cell cycle time τ to be influenced at the level of individual cells by regulatory factors and mechanical stress and model the attractive and repulsive interactions due to the Hertz model (Galle et. al., 2005) that yields an appropriate description of the cell-cell interactions (Mahaffy et. al., 2000). Our model is parameterized by measurable quantities. We systematically analyze the influence of (1) the probability of cell division at defined positions of the lobule at a given time, (2) the ability of the cells to coordinately align during the regeneration process into columns towards the central vein of a liver lobule, (3) the duration of the cell cycle, (4) the migration activity and (5) the polarity of the hepatocytes resulting in polar cell-cell adhesion between them.

Our model shows that CCl_4 initially induced cell death of a pericentral ring of hepatocytes, followed by a wave of proliferation that starts in the surviving hepatocytes next to the inner ring of dead cells and continues to the peripheral hepatocytes, finally restoring the characteristic micro-architecture of the lobule in a seven day process (Fig.1C-E).

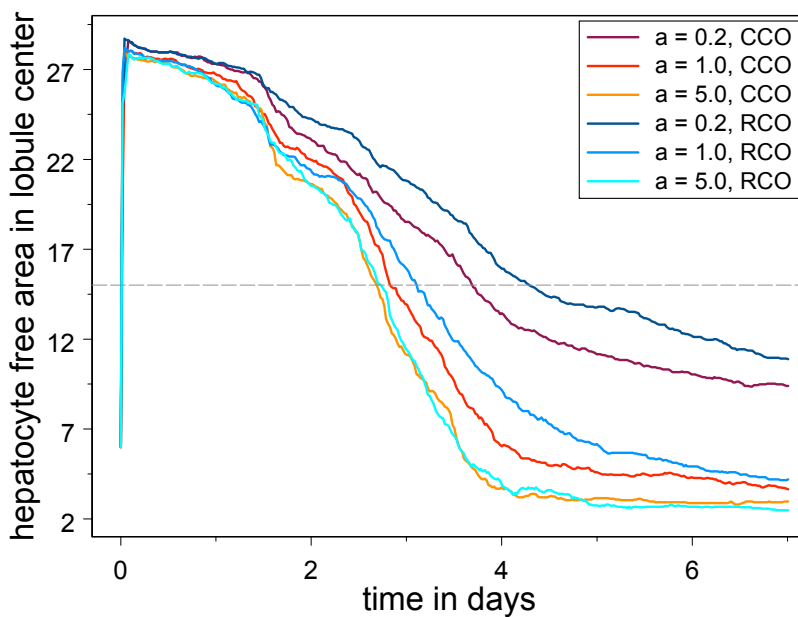


Fig.2: The time until the initial lesion close to the central vein is regenerated decreases with increasing migration activity (a is a multiplicative factor, $a=1.0$: reference migration of hepatocytes) and with increasing ability of the cells to coordinately optimize their alignment (CCO: coordinated cell alignment, RCO: random cell orientation after division and no coordinated cell alignment).

Interestingly, coordinated cell alignment and cell polarity were identified to be the most critical parameters (Fig.2) whose elimination led to destruction of the characteristic micro-architecture of the lobule and to a high degree of disorder characterized by hexagonal cell structures. Our model suggests that the ability of hepatocytes to realign after cell division in combination with cell polarity may be at least as critical as hepatocyte proliferation itself.

References:

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