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1. Introduction

The bone marrow is home to early and late-stage B cells and long-lived plasma cells. This joint study of experiment and theory investigates the spatial colocalization of different types of cells in the bone marrow by applying an image-based systems biology approach. This approach includes: generating confocal laser scanning microscopy images of histological sections from murine bone marrow, automated and quantitative image analysis and realistic computer simulations of the experimental system for hypothesis testing. In particular, we tested the observed spatial colocalization of cells in the bone marrow against computer simulations based on the hypothesis that cells are uniformly distributed in the bone marrow.

2. Image-based Systems Biology

Workflow diagram of the quantitative image analysis

Microscopy image → Image analysis result → In silico model → Hypothesis testing → Simulation result → Setup of random cell position (RCP) model: numerical experiment

First, the stroma (white) from the input image is reconstructed in the model. This is followed by filling the excluded areas (grey) as determined during the image processing. Afterwards, the same number of B cells (blue), eosinophils (red) and plasma cells (green) as observed in the original image, are simulated as circular cells that are randomly placed in available image areas.

3. Results

Cell contacts with stromal cells. (a) Fractions of cell contact numbers for B cells (B), eosinophils (E) and plasma cells (P) with stromal cells (S) relative to the total number of cells per cell type. (b) Distributions of intercellular spacings between cells and the stroma.

Cell contacts among cells of the same type. (a) Fractions of cell contact numbers for B cells (blue), eosinophils (red) and plasma cells (green) among cells of the same type. (b) Cell exclusion probability $P_{X,X}^e(r)$ for cells of type X as a function of the exclusion radius r . (c) Cell-cell pair distribution $g_{X,X}(r)$ for cells of type X as a function of the radial pair distance. The experimental data are shown in dark colors and the simulation results of the RCP model are shown in light colors.

Cell contacts among cells of different type. (a) Fractions of cell contact numbers for B cells, eosinophils and plasma cells among cells of a different type. (b-d) Cell-cell pair distribution $g_{X,Y}(r)$ for cells of type X and type Y as a function of the radial pair distance.

4. Conclusion

- The image-based systems biology approach represents a comprehensive strategy for identification of spatial correlations in microscopy images of biological systems.
- The spatial organization of the three cell types in the bone marrow is not random.
- B cells and plasma cells have significantly increased contact numbers with stromal cells and also eosinophils reside in close proximity to the stroma.
- B cells and eosinophils form clusters of cells among themselves having significantly increased numbers of contacts.
- Cellular aggregates exist between colocalizing plasma cells and eosinophils in a loose fashion without direct contacts.

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