MACROPHAGE ADHESION TO TUMOR CELLS POSITIVELY IMPACTS TUMOR GROWTH

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Background Myeloid cells are major players of the tumor microenvironment contributing to immune evasion mechanisms and providing pro-tumorigenic effects. Here we aim to analyze at the physical and molecular level, how myeloid cells can impact tumor growth and fate.

Methods Combining quantitative cell biology with the derivation of physical modeling of tumor growth, allow us to extract key parameters and make predictions that are testable both, by simulations in silico and by in vitro experiments.

Results We set up an in vitro system to follow the growth of tumor spheroids in 3D by real-time microscopy over long periods of time. Importantly, we replicate in this system the strong positive effect of alveolar macrophages on tumor growth and the poor effect of monocytes. From the quantifications and growth curves obtained, we derived mathematical modeling of spheroid growth in 2 and 3D. The semi-continuous model we developed makes use of a particle-based model which allows the treatment of proliferating cells in physical interactions. This model, tested in simulations, fits well with the data obtained in the absence or presence of macrophages. The model predicted that adhesion forces between tumor cells and macrophages are key in the pro-tumoral effect observed. Among the integrins potentially mediating these forces, CD11c stands out as a key candidate since it is expressed by alveolar macrophages but not by monocytes. Anti-CD11c blocking antibodies indeed diminish cell-to-cell adhesion forces as measured by a rupture force assay, prevent spheroid nucleation, and impair spheroid growth.

Conclusions Our results establish that adhesion of macrophages to tumor cells can have a direct impact on tumor growth by modifying key physical parameters. These findings may lead to the identification of new approaches targeting myeloid cells to counteract their pro-tumoral activity within the tumor microenvironment.

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