MECHANOBIOLOGY FOR CLINICAL CANCER PROGNOSIS: CONTEMPORARY SCIENCE AND FUTURE, APPLICATIVE PROSPECTS

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Background

Cancer is currently the second cause of death worldwide, with 90% of mortality resulting from local or metastatic tumour-cell spreading. A critical step in metastasis formation is forceful invasion of tumour-detached cancer cells through dense tissue-microenvironments. To traverse their surroundings, invading cells must change morphology and apply forces. We and others have shown that invasive, metastatic cells are dynamically softer both internally [1,2] and externally as compared to non-invasive or benign cells, yet can also adapt and apply strong adhesive [3] and invasive [4,5] forces if advantageous. This perspective talk will be used to discuss the unique, highly dynamic and adaptable mechanobiology of cancer cells as well as the mechanostructure and force application mechanisms that facilitate invasiveness. In addition, we will demonstrate how mechanobiology may innovatively be used to rapidly provide a clinically relevant cancer diagnosis and prognosis of metastasis likelihood, potentially also identifying target body-site.

Recent advances

The current, clinical gold-standard for tumour staging and treatment-choice is histopathological examination, which may take several weeks. Over the last decade we have shown that invasiveness of cancer and tumour cells may rapidly (2-3 hours) be evaluated *in vitro* via their forceful interactions [4,6]. Specifically, invasive cancer-cell subsets can forcefully push into and indent elastic, impenetrable, physiological-stiffness, synthetic gels [4,7], while non-invasive or benign cells do not significantly indent gels. The ensuing mechanical invasiveness measure, combining the percent of indenting cells and their attained depths, provided accurate, early prediction of invasiveness in agreement with clinical prognosis [7,8]. Invasive subpopulations include, for example, cancer stem cells [9], associated with grim patient prognosis.

Invasive force application mechanisms require cells to adapt their mechanostructure and interact with their microenvironment (cells & substrate). Cells reorganize their dynamic cytoskeleton [10,11] to facilitate force application. Via finite element models (FEM), we have shown that invasive-indentations must include a normal force element [12], and are not, e.g., a side-effect of strong, adhesive tractions. Solid-tumour cells typically invade via collective migration attached cell-cohorts that typically utilize strong cell-cell bonds. We have shown, however, that closely adjacent cells can indent more deeply than well-spaced cells, even without direct cell-cell interactions [5], likely resulting from substrate-mediated additive and synergistic force-interactions [13]. We have further observed that cell invasiveness is highly dependent on microenvironment/gel mechanics [3,4], yet cell mechanics effects are minimal [13]. Mechanobiology can thereby be used to rapidly predict tumour invasiveness, nevertheless there is more to learn from the mechanical interactions of invasive cells.

Daphne Weihs is an A/Professor at the Department of Biomedical Engineering, Technion-Israel Institute of Technology. She obtained her PhD in Chemical Engineering at the Technion-Israel Institute of Technology in 2004. She was a post-doctoral fellow at University of California at Los Angeles in 2004-2006. Her current research mainly focuses on the mechanobiology of living cells in health and disease, and specifically cancer cell mechanics and their interactions to predict metastases formation. She has authored over 60 articles in international peer-reviewed journals, 15 book chapters and conference papers, and over 140 contributions to International and National Conferences.

Future directions

As organs vary in stiffness and the mechanical invasiveness is affected by gel mechanics, future developments include an approach to predict the likely metastatic body-site, within the same time-frame. We will discuss the ability to rapidly and quantitative predict the likelihood for metastasis and its effects on the clinic.

References

[1] Gal & Weihs, Cell Biochem. Biophys. 63:199-209, 2012.
[2] Goldstein et al.,Soft Matter, 9:7167-7173, 2013.
[3] Massalha & Weihs, BMMB, 16: 961-970, 2017.
[4] Kristal-Muscal et al, New J. Phys. 15:035022, 2013.
[5] Merkher & Weihs, Ann Biomed Eng 45:1399-1406, 2017.
[6] Alvarez-Elizondo & Weihs, Tiss Eng C 23:180-187, 2017.
[7] Merkher et al., ABME 48:2846-2858, 2020.
[8] Kortam et al., BMMB 20:1767-1774, 2021.
[9] Alvarez-Elizondo & Weihs, Cell Mol Life Sci 79:134, 2022.
[10] Alvarez-Elizondo et al., ABME 49:1342-1352, 2021.
[11] Dvir et al., New J. Phys. 17:043010, 2015.
[12] Ben-David & Weihs, BMMB 20:1187-1194, 2021.
[13] Tulchinsky & Weihs, Acta Biomater., 2022.

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