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Backstory

Interdisciplinary research in cancer and immunity employing biophysical approaches

Fabrizio Mattei[1,*] and Mohit Kumar Jolly[2]

Three leading scientists Fabrizio Mattei, Kandice Tanner, and Mohit Kumar Jolly working in different continents and in different areas of cancer and immunology came together for an iScience Special Issue focused on the biophysical aspect of the tumor-immune dynamics. In this backstory, the iScience editor discusses with Mattei and Jolly their thoughts about this topic, the current state of the field, the collection of articles in this Special Issue, and the future of the research in this area in the coming years, and personal advice to aspiring young minds.

What recent advances in cancer and immune response involving immunophysical approaches have gotten you excited and why?

Mattei: The crescent and constant curiosity of the scientific community is boosting and influencing the technologies to study the cells, including those belonging to the immune system and cancer. Efforts have been made to elucidate the way immune cells can physically and spatially interact with neoplastic ones. Together with the innovation and constant renovation of technologies, this allowed onco-immunologists to recruit a new kind of next-generation researchers (i.e., the bioinformaticians, biology-oriented mathematicians, etc.) and complex methodological platforms, with the exciting possibility to study these cells on their biophysical context. Omics platforms, including metabolomics, proteomics, and epigenomics, allowed studying the immune-tumor axis on so far unthinkable levels and higher spatial and temporal resolution. The advent of organ-on-a-chip platforms and machine-learning-based protein-protein binding simulations[1] further boosted the biophysical approaches to the immune system and cancer, being these systems devoted to the recapitulation of the tumor microenvironment (TME) by using several types of gel matrices. On-chip characterization of the biophysical factors behind the binding properties of these matrices to cells will be helpful to acquire novel knowledge in this context, so that the recapitulation of the tumor microenvironment becomes more accurate and trustworthy. Biophysics is an emerging field and it is exciting to observe how this is markedly affecting the cancer research. For example, epithelial-to-mesenchymal transition, a key process for metastatic expansion extensively investigated in cancer, is now repurposed based on its intrinsic biophysical features.[2] This and other reports clearly evidence how the biophysical forces are now on the way to re-evaluate new modalities to approach multiple aspects of cancer research activities. These new innovative scenarios strongly favored multidisciplinary investigations on how molecular interactions are central in establishing the role of immune cells—within the immune microenvironment—on the fate of the TME and the subsequent metastatic expansion. These new platforms represent invaluable and exciting tools to fill the gap between immune system and cancer.

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Jolly: Cancer has been long thought of as a genetic disease. This "organism minus one gene" (or reductionist) approach has been helpful undoubtedly in identifying some key molecules that can accelerate or retard disease progression. Importantly, some of these molecules have even been targets of most successful therapies we have so far in the clinic, but one cannot continue to take the forest for the trees forever. Thus, a systems-level approach where we look at various physiological levels at which the disease manifests should be adopted in parallel to the reductionist strand. When one talks about such emergent multi-scale

Dr Fabrizio Mattei and Prof. Mohit Kumar Jolly during their collaborative meeting in 26 July 2022 at Istituto Superiore di Sanità (Rome, Italy).

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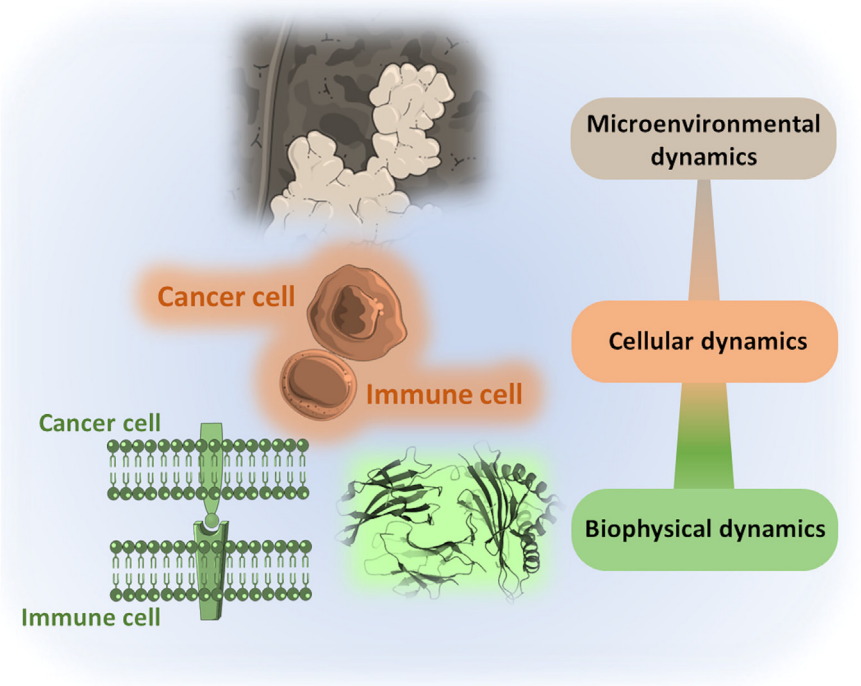
https://doi.org/10.1016/j.isci.2023.106507



The dynamic cues of the tumor microenvironment: from microenvironmental and cellular views to biophysical approaches

Experimental data derived by the multifaceted tumor microenvironmental aspects will represent unvaluable information to define the cell-cell dynamics. In turn, cell-cell dynamics knowledge can be integrated with key experimental and in silico (i.e., advanced protein docking analysis) data.

dynamics, the concepts of physics inherently are bound to appear in a major way. For instance, clusters of circulating tumor cells have been shown to be the major drivers of metastasis; so questions such as how are these clusters formed and maintained during circulation, how do they traverse capillaries etc. pique my interest immediately. There have been exciting studies investigating these questions.[3] Similarly, questions trying to understand why is clustered migration likely to be more efficient are intriguing: a) is it due to some "division of labor" among various subpopulations? b) how do cells "divide their labor" and communicate among one another? c) is there evidence of quorum sensing ongoing that drives behavior of a cell population?

Why do you think there is a need for greater understanding of the physical basis of the immune response mechanism against cancer and knowledge about how cancer cells acquire immune-evasive features? How will the advances in this area move the field forward?

Mattei: Physics is at the basis of all things we can see around. Physical forces and dynamics spontaneously shaped our planet. This is then true also for the cellular units, being them living organisms with intrinsic biophysical interactions. As all cells, immune cells exert their mechanisms thanks to the ability to express surface proteins interacting with specific ligands on the cancer cells. The deep knowledge of the precise modality of interaction of the couple receptor-ligand constitutes a biophysical view allowing to extrapolate the stability of receptor-ligand interactions and the functional activation of the specific axes inside the immune cell and the interacting cancer cell. Therefore, the biophysical knowledge of a specific protein-protein interaction finely reflects the functional activation of a cell. The biophysics of immune-tumor dynamics not only reflects the exact molecular mechanisms by which an immune cell interacts with cancer cells but also leads to a deep knowledge of unexpected novel parameters of a

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protein known to be involved in such dynamics. My opinion is that these technologies will move forward toward the real time and high-resolution imaging of a cell interacting with another cell, including its relating proteins/co-factors. Stimulated emission depletion and super-resolution microscopy represent clear example of these innovative approaches, allowing to see biophysics in action.[4]

Jolly: Physical forces are fundamental at all scales of organization that we are aware of; human anatomy is no exception. For instance, tumors are stiffer than normal tissue, and this stiffness plays a key role in aggravating the disease. Biochemically, multiple pathways can converge on to influence stiffness, and the degree of contribution coming from each pathway may depend on the patient or the tumor, but stiffness stays as a fundamental property. Similarly, tumor-immune interactions depend on physical forces acting at various length and time scales. Understanding the fundamental concepts of these forces such that one can consider perturbing them to achieve desired outcome would be exciting.

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What is your take from the recent studies focused on the biophysical aspect of tumor-immune dynamics, and how has our understanding advanced toward achieving the goal of better control of immune system in patients with cancer and for developing better and safer therapeutics?

Mattei: Many therapeutics approaches have been successfully applied in the cure of cancer patients, such as the strategies based on the discovery of immune checkpoints. However, not all the patients benefit from this therapy. This is a clear example demonstrating that the deep knowledge of the exact interaction dynamics between two factors (i.e., PD-1 and PD-L1) could potentially be helpful to repurpose the role of immune checkpoint inhibition on a biophysical point of view.[5] This will also facilitate the development of safer and optimal therapies against cancer. In addition, the design of new drug agents or druggable factors to be recruited for anticancer therapies can potentially take advantage on the deep knowledge of its biophysical profiling. With this in mind, these agents can be better optimized for cancer therapies in the near-middle future.

Jolly: Recent efforts toward identifying spatial distribution signatures of immune cells in tumors and its connection with patient outcomes is an exciting proposition.[6] Such signatures may be possibly used for stratifying patients for different therapy regimes, especially in integration with techniques such as spatial transcriptomics and non-invasive imaging.

What do you think are the challenges that need to be encountered?

Mattei: Biophysics of immunity and cancer must intrinsically be considered a challenge. A big challenge to be dealing with is represented by economic difficulties to overcome. Indeed, the complex instrumentation systems and platforms to be employed to study the multifaceted biophysical aspects of immune-tumor dynamics need great costs as they are very expensive. This could be overcome, at least in part, by applying to important funding agencies, which can in part support the amounts of these systems. Keeping advantage of complex computational methods is another important challenge. Multidisciplinarity is central for these research activities, but can also constitute a challenge, due to the fact that the scientific dialog among biophysicist, physicists, mathematicians, biologists, and clinicians is not always so easy to maintain to. Another big deal is to use biophysical context to be applied in machine learning algorithms to aid oncologists in the recognition of optimal drugs and therapies. The generation of a personalized bioavatar containing all the individual -omics profiles could constitute an ambitious final goal to be reached by the next-generation researchers. Another example of bioavatar is based on the generation of personalized body-on-a-chip, which will allow to recapitulate in real time our physiology—in health and disease—in a dynamically complex microfluidic multi-platform.[1] In this view, the use of animal research can be an invaluable help due to less stringent ethical issues compared to human studies. Opening our envision of science, so entering in visionary science, is the final destination of science.

Jolly: Addressing the inherent multi-scale nature of tumor-immune interaction is the most challenging question, in my opinion. The scientific community has been investigating these interactions at various levels—molecular (e.g. PD-1/PD-L1 signaling), cellular (e.g. crosstalk among tumor and stromal cells at

paracrine levels), and tissue level (e.g. ability of T cell to infiltrate a tumor) using the latest technological advances, such as spatial transcriptomics and single-cell RNA-seq. We have a deluge of data now at different time and length scales, but how do these scales influence each other remains largely unclear. Thus, if we can aim for a "digital twin" kind of model that can recapitulate emergent behavior of tumor-immune interaction by integrating experimental data with relevant computational frameworks, that is where the maximal predictive ability (of these models) is most likely to lie.

What is your experience has been working in this interdisciplinary research and your participation/collaboration as Guest Editors of this special issue?

Mattei: I am a tumor immunologist working on several aspects of the tumor microenvironment, especially those associated with the translational research. With a number of other independent laboratories, we attempted to repurpose the tumor microenvironment by using the organs-on-chip platforms.[1,7] This new point of view is a valid help to better investigate on how tumor cells interact with immune system components. I firmly believe that behind the complex dynamics of the tumor microenvironment there are strict interactions between proteins and ligands cells express in their surface. Then, deep knowledge of biophysics of these dynamics is central to move forward on the exact behavior of immune and cancer cells in their environments. This is why, based on my immune-oncology point of view, I wanted to create this Special Issue with Dr. Kandice Tanner and Prof. Mohit Kumar Jolly, two excellent investigators leaders in the field of cell morphodynamics, cancer metastasis, and mathematical modeling to decode heterogeneity and plasticity of tumor microenvironment.

Jolly: I am a computational systems biologist focused on developing predictive mechanism-based mathematical models to decode the emergent dynamics of cellular networks driving phenotypic plasticity and heterogeneity during metastasis and therapy resistance. Working in close collaborations with experimental cancer biologists and clinicians, we ask these questions: A) Which regulatory networks drive phenotypic plasticity/heterogeneity? B) Why are these regulatory networks designed the way they are? C) What implications this plasticity and heterogeneity have at multiple length and time scales during the course of disease progression? A shared excitement about some of these themes is what motivated me to join for this special issue with Dr. Kandice Tanner (expert on cancer cell mechanics/biophysics) and Dr. Fabrizio Mattei (expert on tumor immunology & microenvironment)

What is your opinion about the collection of articles in this special issue?

Mattei: The papers published in this special issue shed light on specific opened question on the interactions between cancer and immune systems in the context of biophysical dynamics. Much efforts have been dedicated to cancer stem cells (CSCs), an heterogeneous cell population residing into the tumor microenvironment and playing a key role in cancer resistance. An interesting computational study from Vipparthi and co-workers has elucidated that, irrespective of their genetic nature, CSCs originating in oral cancer are able to re-adapt their phenotype profiles in order to acquire resistance to cisplatin. These CSCs are also able to maintain stemness and higher intratumor heterogeneity during differentiation, by expressing a distinct gene signature, which presumably is of key relevance for cisplatin resistance. These findings can have important clinical implications in the optimization of therapeutic strategies for oral cancer.[8] Wang and co-workers reviewed a set of key biophysical processes which display certain relevance for the formation of contacts between immune and cancer cells. For example, stiffness is an important feature of the cancer cell and is strictly associated with the F-actin moiety and control of polymerization/depolymerization processes behind. Another representative scenario comes from the contact between an immune cell and a cancer cell. This feature strictly depends on the binding affinity of a receptor on the immune cell and its specific ligand on the cancer cell, and this in turn relies on the singular biophysical peculiarities of such a binding moiety.[9] Jenner and co-workers proposed a standardized computational model for the evaluation of diffusion, localization, and clearance of oncolytic viruses in immunohistochemistry images from glioblastoma tissues. This model easily allows oncologists to translate the images into interpretable and quantifiable categorized datasets, which can represent an adjunct value to the clinical correlates currently employed for the diagnosis of glioblastoma.[10] Immune cells and cancer cells can also be considered important players in the developmental control of the nervous system disorders. In an interesting review, Nussinov and co-workers clarify how dysregulated signaling can accumulate germline or embryonic mutations, which in turn can promote changes in chromatin architecture, and thus expression levels of essential genes in neurodevelopment.[11] Finally, a report from Mattei and co-workers illustrates how eosinophils and other innate immune cells engage in trogocytosis with cancer cells via complex molecular pathways reorganizing the F-actin

architecture, as a mechanism of regulation of immune response to tumor.[12] These and other reports included in this Special Issue evidence the important but often hidden role of biophysical dynamics as indispensable for the occurrence of the complex interactions between cancer and immune system.

What personal advice would you give to the young and aspiring investigators working in this area?

Mattei: Young scientists acquire creativity when constantly mentored by enthusiastic, curious, and visionary senior scientists. Mentors get fundamental responsibilities on the career formation of young investigators. They should always transmit to young researchers these messages, with enthusiasm and constructive criticism. This will allow young investigators to be always ambitious and motivated, especially when lab things or experimental plans do not go as well as they should.

Jolly: These are exciting times for the field of onco-immunology aspects with cross-fertilization of ideas coming from various disciplines (oncology, immunology, engineering, physics, mathematics etc.). My request to young investigators would be to be as cross-disciplinary as possible in their approach and being continually enthused about possible collaborations with experts who seem to be speaking a different language but are interested in similar questions. I tell my group members that "Identity crisis (in terms of which discipline they belong to) is your identity" and that they should accept it. When cancer cells use all tools available at their disposal (genetic/non-genetic, different hallmarks, even coaxing their microenvironment), why should we remain restricted by self-constructed silos?

These are exciting times for the field of onco-immunology aspects with cross-fertilization of ideas coming from various disciplines (oncology, immunology, engineering, physics, mathematics etc.).

DECLARATION OF INTERESTS

We, the authors (Dr. Fabrizio Mattei & Prof. Mohit Kumar Jolly), declare to be Guest Editors of the Science Special Issue entitled "Biophysics of tumor-immune dynamics".

REFERENCES

1. Mattei, F., Andreone, S., Mencattini, A., De Ninno, A., Businaro, L., Martinelli, E., and Schiavoni, G. (2021). Oncoimmunology meets organs-on-chip. Front. Mol. Biosci. *8*, 627454. https://doi.org/10.3389/fmolb.2021.627454.

2. Tripathi, S., Levine, H., and Jolly, M.K. (2020). The physics of cellular decision making during epithelial-mesenchymal transition. Annu. Rev. Biophys. *49*, 1–18. https://doi.org/10.1146/annurev-biophys-121219-081557.

3. Au, S.H., Storey, B.D., Moore, J.C., Tang, Q., Chen, Y.L., Javaid, S., Sarioglu, A.F., Sullivan, R., Madden, M.W., O'Keefe, R., et al. (2016). Clusters of circulating tumor cells traverse capillary-sized vessels. Proc. Natl. Acad. Sci. USA *113*, 4947–4952. https://doi.org/10.1073/pnas.1524448113.

4. Xu, X., Wang, Y., Choi, W.S., Sun, X., and Godbout, R. (2021). Super resolution microscopy reveals DHA-dependent alterations in glioblastoma membrane remodelling and cell migration. Nanoscale *13*, 9706–9722. https://doi.org/10.1039/d1nr02128a.

5. Yin, H., Zhou, X., Huang, Y.H., King, G.J., Collins, B.M., Gao, Y., Craik, D.J., and Wang, C.K. (2021). Rational design of potent peptide Inhibitors of the PD-1:PD-L1 interaction for cancer immunotherapy. J. Am. Chem. Soc. *143*, 18536–18547. https://doi.org/10.1021/jacs.1c08132.

6. Yu, C.C., Wortman, J.C., He, T.F., Solomon, S., Zhang, R.Z., Rosario, A., Wang, R., Tu, T.Y., Schmolze, D., Yuan, Y., et al. (2021). Physics approaches to the spatial distribution of immune cells in tumors. Rep. Prog. Phys. *84*, 022601. https://doi.org/10.1088/1361-6633/abcd7b.

7. Vacchelli, E., Ma, Y., Baracco, E.E., Sistigu, A., Enot, D.P., Pietrocola, F., Yang, H., Adjemian, S., Chaba, K., Semeraro, M., et al. (2015). Chemotherapy-induced antitumor immunity requires formyl peptide receptor 1. Science *350*, 972–978. https://doi.org/10.1126/science.aad0779.

8. Vipparthi, K., Hari, K., Chakraborty, P., Ghosh, S., Patel, A.K., Ghosh, A., Biswas, N.K., Sharan, R., Arun, P., Jolly, M.K., and Singh, S. (2022). Emergence of hybrid states of stem-like cancer cells correlates with poor prognosis in oral cancer. iScience *25*, 104317. https://doi.org/10.1016/j.isci.2022.104317.

9. Wang, M., Jiang, H., Liu, X., and Wang, X. (2022). Biophysics involved in the process of tumor immune escape. iScience *25*, 104124. https://doi.org/10.1016/j.isci.2022.104124.

10. Jenner, A.L., Smalley, M., Goldman, D., Goins, W.F., Cobbs, C.S., Puchalski, R.B., Chiocca, E.A., Lawler, S., Macklin, P., Goldman, A., and Craig, M. (2022). Agent-based computational modeling of glioblastoma predicts that stromal density is central to oncolytic virus efficacy. iScience *25*, 104395. https://doi.org/10.1016/j.isci.2022.104395.

11. Nussinov, R., Tsai, C.J., and Jang, H. (2022). Neurodevelopmental disorders, immunity, and cancer are connected. iScience *25*, 104492. https://doi.org/10.1016/j.isci.2022.104492.

12. Mattei, F., Andreone, S., Spadaro, F., Noto, F., Tinari, A., Falchi, M., Piconese, S., Afferni, C., and Schiavoni, G. (2022). Trogocytosis in innate immunity to cancer is an intimate relationship with unexpected outcomes. iScience *25*, 105110. https://doi.org/10.1016/j.isci.2022.105110.