The Abdus Salam International Centre for Theoretical Physics

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ABDUS SALAM 100 YEARS

ICTP-IISc Workshop on Physics of Cancer | (SMR 4197)

20 Jul 2026 - 31 Jul 2026
Outside, Bengaluru, India

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Cancer cell morphogenesis in 3D soft engineered microenvironments

T01

Abstract for poster: Impact of competition between precursor and mature microRNAs on stochastic gene expression

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In several cancer regulatory networks MicroRNAs (miRNAs) are key post-transcriptional regulators, processed from precursor miRNAs (pre-miRNAs) into mature miRNAs through nuclear and cytoplasmic proteins [1,2]. Recent evidence shows that pre-miRNAs and mature miRNAs can compete for the same target mRNAs [3], yet the impact of this miRNA maturation-driven competition on gene expression noise remains unknown. We address this in widespread feedback motifs [4], where both pre- and mature miRNAs degrade a protein's transcripts, and the protein itself either activates or represses miRNA transcription. Using a mathematical model, we show that miRNA maturation tunes the behavior of positive or negative feedback loops, key building blocks of several cancer regulatory networks, which function as bistable switches or oscillators at the mean-field level, respectively. The relative degradation of mature versus pre-miRNAs and the mRNA-miRNA co-degradation rates can jointly modulate the parameter regions of bistability or oscillations. Moreover, for positive feedback, stochastic simulations reveal that bimodal mRNA distributions emerge near the saddle-node bifurcation boundaries, but not always within the bistable regions. Bimodal mRNA distributions also appear for negative feedback, but outside the region of limit cycles. Importantly, in both feedback types, such noise-induced bimodality emerges in regions where mean-field analysis predicts no bistability or limit cycles. These results demonstrate that noise-induced phenotypic variability cannot necessarily be linked to underlying deterministic bifurcations and elucidate how miRNA maturation shapes phenotypic heterogeneity in stochastic gene expression in regulatory motifs relevant to development and disease.

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T02

Simulating Evolutionary Dynamics: Extending Human Population Models to Predict Cancer Progression

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Our current work applies ABC-DLS [1, 2], a pipeline integrating Approximate Bayesian Computation (ABC), deep learning (TensorFlow/Keras), and Sequential Monte Carlo (SMC), to reconstruct South Asian population demographic history using coalescent simulations (msprime) and site frequency spectrum (SFS) based summary statistics. The pipeline performs both model selection and parameter estimation, recovering divergence times, migration events, and admixture proportions from genomic data.

We present this framework as a candidate approach for tumour chronology inference, where the analogous problem involves recovering, from whole-genome sequencing (WGS) data, the order of driver mutation acquisition, the timing of clonal expansions, and subclone divergence. The conceptual parallels are suggestive: coalescent simulations become tumour growth simulations, the SFS becomes the variant allele frequency (VAF) spectrum, and demographic parameters become somatic evolutionary parameters.

However, the biological and technical challenges of this translation remain open. This poster invites discussion with researchers working at the interface of cancer biology, evolutionary theory, and quantitative modelling, with the goal of identifying the right simulation framework, summary statistics, and data types to make this adaptation tractable.

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T03

Characterization of macrophage phenotypes using mathematical modelling

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Macrophages are innate immune cells with a wide range of functional capacities(Wu et al., 2021). They have been broadly classified into M1 or M2 phenotypes based on environmental signals. Due to variation in such regulatory cues, these macrophages are thought to also show states that are intermediate within a spectrum that has M1 and M2 at its two extremes(Karnevi et al., 2014). However, across all these studies, characterization for hybrid macrophages is not consistent due to overlapping macrophage markers. How hybrid macrophages arise, how stable these states are, how easy is it for them to transition from, or to M0, M1, or M2 states, and how is their stability reinforced or attenuated by the distinct secretory states remains poorly understood. To address these set of problems, we define the hybrid macrophage phenotype based on gene regulatory network (GRN) information at intracellular scale. Our findings reveal a 'teams' structure as an emergent property of the macrophage GRN. Perturbation analysis was done with M1 and M2 as initial states and as two different cases. In one node perturbation, the system is unable to switch its phenotype in either case, but in some two and three-node combinations, the system can switch to hybrid phenotype. Furthermore, overexpression analysis was done, where STAT3 and STAT1 combination was specifically observed to give rise to the most hybrid populations. The phenotypic distribution obtained from the Boolean framework was then validated using RAndom CIrcuit PErturbation (RACIPE). The distribution of steady state in overexpression analysis using RACIPE was consistent with the Boolean framework, making the distribution of steady states a robust dynamical property of the network.

Wu, M.-F., Lin, C.-A., Yuan, T.-H., Yeh, H.-Y., Su, S.-F., Guo, C.-L., Chang, G.-C., Li, K.-C., Ho, C.-C., & Chen, H.-W. (2021). The M1/M2 spectrum and plasticity of malignant pleural effusion-macrophage in advanced lung cancer. *Cancer Immunology, Immunotherapy: CII*, *70*(5), 1435–1450. https://doi.org/10.1007/s00262-020-02781-8

Karnevi, E., Andersson, R., & Rosendahl, A. H. (2014). Tumour-educated macrophages display a mixed polarisation and enhance pancreatic cancer cell invasion. *Immunology & Cell Biology*, *92*(6), 543–552. https://doi.org/10.1038/icb.2014.22

T04

Abstract for ICTP-IISc Workshop on Physics of Cancer

Structural Sensitivity of Drug Response Functions in Tumor-Immune models and its implications for Resistance

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Mathematical models of tumor-immune interactions are widely used to study cancer progression and therapeutic response. However, the reliability of such models depends not only on parameter values but also on the choice of functional forms used to represent processes within the system. Even functions with qualitatively similar properties can produce substantially different model predictions, a phenomenon widely recognized in literature as structural sensitivity. In the context of cancer therapy, drug delivery within the tumor microenvironment is inherently nonlinear, governed by processes such as receptor binding saturation, transport limitations, heterogeneous perfusion, intracellular drug accumulation, diffusion barriers, cellular uptake, and cooperative cell death processes. As a consequence, drug exposure is not limited to tumor cells but also affects healthy and immune cells, leading to incomplete tumor killing and unintended off-target cytotoxicity. In this work, we examine the structural sensitivity of a tumor-immune-healthy cell model to different pharmacodynamic representations of drug delivery within the tumor system. It is of particular interest to investigate whether certain drug-delivery formulations can reduce leakage within the tumor microvasculature while maintaining effective tumor control. In this context, we examine how different delivery functions influence drug penetration, tumor eradication, and off-target toxicity to healthy and immune cells. We aim to examine, using dynamical systems analysis and numerical tools, how different drug-delivery functions influence tumor persistence, control, eradication, and possible partial or transient therapeutic outcomes. Another key question is whether certain delivery mechanisms facilitate the emergence of drug-resistant tumor subpopulations under prolonged treatment. In addition, we are particularly interested in examining whether specific delivery strategies sustain these resistant populations under intermediate dosing, leading to relapse-like dynamics or treatment failures. Since these pharmacodynamic laws can be obtained from standard dose-response measurements, the structural assumptions used here are testable. This motivates further exploration of mathematical models and validation using experimental datasets, which are essential for developing a deeper and more coherent understanding of oncological systems, cancer progression, and for improving patient-specific therapeutics.

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T05

Structural Basis of the Liquid-Solid Transition In An Active Tissue Model

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In various biological processes like cancer cell progression, embryonic development, wound healing etc, the cells shows a solid-to-fluid like transion also called Epithelial-to-Mesenchymal Transition (EMT). We present an active particle-spring model of cell monolayers that undergoes a transition from fluid-like to a solid-like state as cell-cell adhesion increases.This phase transition is marked by a change from diffusive to subdiffusive cell dynamics. During the transition, the tissue can also develop a hexatic order, characterized by rearrangements of dislocation and disclination defects, similar to defect-mediated melting in two-dimensional system according to KTHNY Theory. These preliminary results suggest that tissue monolater may display a hexatic transition, which we aim to explore in detail in future.

T06

Mechanistic modelling of signalling-regulated natural killer cell activity in lung adenocarcinoma

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Cancer remains a major global health concern and a leading cause of death. According to GLOBOCAN, the global burden of cancer is projected to rise by 2050. Lung cancer is one of the most frequently diagnosed cancers and remains the leading cause of mortality, largely due to late-stage detection. Among lung cancers, lung adenocarcinoma (LUAD) is the most common subtype and is often diagnosed at late stages, resulting in high mortality. Therefore, a deeper molecular understanding of advanced-stage LUAD is needed.

Recent systems-level analysis of LUAD *(M Shukla & RR Sarkar, Mol. Gen. Geno., 2024)* has identified a critical LYN–PIK3R1–FYN–FCER1G motif that spans tumor and NK cells and regulates immune signalling. However, despite the identification of this cross-cellular motif, no mechanistic model yet explains the intracellular dynamics underlying its regulatory behavior.

In this study, we developed a dynamic mathematical framework to capture differential regulation of NK cell activation through LYN–FYN–PI3K signaling at Fcε – receptors in advanced-stage LUAD. Our model incorporates the opposing effects of LYN and FYN kinases on PI3K activation and downstream modulation of the phosphatase Shp1, a key mediator of immune response switching. LYN, predominantly expressed in tumor cells, attenuates PI3K signaling, whereas FYN, along with FCER1G and PIK3R1 in NK cells, enhances it.

This mechanistic model provides a quantitative basis to understand how differential kinase engagement governs immune signaling dynamics in LUAD. This framework provides testable hypotheses that link molecular interactions to immune dysfunction, enabling the predictive modelling of tumor–immune modulation and therapeutic targeting strategies.

T07

Abstract for the ICTP-IISc Workshop on Physics of Cancer

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Tumour progression is an emergent phenomenon driven by the interplay between cancer stem cells (CSCs) and the tumour microenvironment (TME). While homeostatic tissues use negative feedback to maintain stability, the regulatory capacity of purely cooperative, positive feedback in spatially constrained systems remains poorly defined. We developed a stochastic spatial agent-based model (ABM) to examine CSC dynamics regulated by juxtacrine (contact-mediated) signalling with stromal cells, utilizing a mean-field ordinary differential equation (ODE) system to isolate the effects of spatial structure. Our analysis reveals that spatial architecture fundamentally alters tumour fate. We identify a paradoxical 'spatial crowding' effect where maximal CSC-stroma cooperation actively self-limits growth by depleting local spatial availability. Furthermore, we show that spatial clustering acts as an evolutionary buffer, rescuing tumours from Allee-type extinction thresholds predicted by well-mixed models. Finally, by simulating cyclic targeted therapies that eradicate CSCs but spare the stroma, we demonstrate that persistent stromal architectures act as a structural memory. This surviving stroma aggressively reprograms differentiated cells, driving a ratchet-like, irreversible enrichment of the CSC compartment. Together, these results establish that spatial microenvironments are not passive backdrops, but primary causal drivers of tumour resilience and therapy resistance.

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T08

Field-Effect Transistor for Breath VOC Cancer Biomarker Detection

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Cancer progression is accompanied by metabolic reprogramming and enhanced oxidative stress, leading to the emission of volatile organic compounds (VOCs) such as acetone, isoprene, and pentane in exhaled breath. These molecules are associated with altered lipid metabolism, cholesterol biosynthesis, and lipid peroxidation pathways in cancer cells, making them promising non-invasive biomarkers for early diagnosis [1]. In this work, we investigate the sensing capability of a plumbene monolayer toward these cancer-related VOC biomarkers using first-principles density functional theory combined with non-equilibrium Green's function (DFT-NEGF) formalism [2,3,4]. Structural optimization confirms the stability of the plumbene monolayer with tunable electronic properties suitable for biomarker sensing. Adsorption studies of acetone, isoprene, and pentane show favorable interaction energies, distinct configurations, and noticeable charge transfer, supported by Bader charge and charge density difference analyses. The adsorption-induced changes in band structure, density of states, and transmission spectra indicate strong modulation of electronic transport, enabling selective detection. Recovery time analysis suggests reversible adsorption under mild conditions. The device concept can be implemented in a field-effect transistor (FET) configuration, where adsorption-driven conductance modulation enables sensitive signal transduction. Overall, plumbene emerges as a promising two-dimensional platform for multi-biomarker breath sensing, offering atomistic insight into VOC detection mechanisms for early, non-invasive cancer diagnostics.

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T09

Quad–Stability, Hybrid Phenotypes, and Spatiotemporal Plasticity Driven by Host–Circuit Coupling

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Phenotypic plasticity and multistability are fundamental features of cancer progression, enabling cells to transition between distinct epithelial, mesenchymal, and hybrid phenotypic states. While mutually inhibitory genetic circuits are widely used to model binary cell-fate decisions [1], the role of growth-mediated resource competition in shaping these dynamics remains less explored [2]. In this work, we investigate how a simple bistable genetic switch behaves under resource-limited conditions coupled with host growth feedback and spatial diffusion [3].

Our analysis demonstrates that strong resource competition can transform a classical bistable system into a multistable one, giving rise to multiple intermediate hybrid phenotypes analogous to hybrid epithelial/mesenchymal (E/M) states observed in cancer systems. Incorporating diffusion further reveals the emergence of diverse spatiotemporal dynamics and spatial heterogeneity. We show that nonlinearity coupled with diffusion and resource competition due to growth collectively regulate transitions among epithelial-like, mesenchymal-like, and hybrid states. Notably, the hybrid states act as dynamic intermediates that facilitate phenotypic switching and enhance overall plasticity. These findings suggest that growth-induced resource limitation alone can generate complex phenotypes without requiring highly intricate regulatory architectures. The study highlights how intracellular host–circuit coupling and intercellular diffusion together contribute to metastasis-associated plasticity, tumor heterogeneity, and adaptive cancer progression. Our framework provides a minimal mechanistic perspective for understanding the emergence of hybrid phenotypes and their role in spatiotemporal organization in cancer systems.

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T10

Modeling ROS Mediated Amyloid Beta Aggregation and the Role of Different Inhibitors

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Alzheimer's disease (AD), the most common form of dementia, is closely related to the overproduction of reactive oxygen species (ROS). A model based on free radical polymerization of amyloid beta (Aβ) utilizing ROS as an initiator is proposed. Model parameters are tuned using the reported experimental data on fibril molecular weight. The tuned model is used to simulate time evolution of fibril length and polydispersity index of Aβ aggregates. A good agreement is observed between the model simulated fibril properties and the reported experimental data supporting the hypothesis of ROS as one of the causes of Aβ aggregation. Sensitivity analyses further establish the reliability of the proposed model.

Seeking therapeutic molecules for Alzheimer's disease that could inhibit or degrade the fibril aggregation effectively has been a major research focus in recent years. The inhibitory molecules can be broadly divided into small molecule and large molecule. The proposed model studying only Aβ aggregation is thus further extended to study the inhibitory and degradative effects of small and large molecules inhibitors.

Chlorogenic acid (CGA), a small molecule inhibitor, is reported to have an inhibition effect on Aβ aggregation, and its effectiveness is reported to be enhanced when loaded with selenium nanoparticles. Therefore, the proposed model based on Aβ aggregation is extended to study the inhibitory effects of CGA and CGA loaded nanoparticles on Aβ aggregation. The model parameter tuning is done using the experimental data to estimate the values of new parameters introduced in the model. The model simulated values are observed to be in good agreement with the experimental data at different doses of both CGA and CGA loaded nanoparticles. Moreover, the sensitivity analyses on model parameters further demonstrate the robustness of the extended model. It is hypothesized that the model may also be used to study the inhibitory effects of other drugs, such as polyphenols, metal chelators, peptides and nanoparticles that show a similar inhibition trend for the inhibition of Aβ fibrillation.

Large molecule inhibitors, such as decapeptide (RYYAAFFARR) and pentapeptide (LPFFD) also exhibit inhibition/degradation effects on amyloid beta fibrils. The proposed model for small molecules is therefore further extended to study the effect of large molecules (peptide-based) inhibitors. The extended model studies Aβ aggregation and inhibitory/degradative action of peptide inhibitors on Aβ fibrillation. Model parameters are tuned by curve fitting the experimental data. The tuned model is used to predict experimental data at different initial dose/fibril concentrations. Model simulated values are observed to be in good agreement with the reported experimental data. It is envisaged that the developed model will be helpful to elucidate ROS-based therapeutic strategies for AD treatment in the near future.

T11

Interconnected axes of phenotypic plasticity drive coordinated cellular behaviour and worse clinical outcomes in cancer

T12

Modelling multiscale cell competitions and cooperations that determine longevity of homoeostasis

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Cell competition is a key mechanism by which tissues regulate cellular fitness and maintain homeostasis. In aging tissues, senescent cells show irreversibly arrested proliferation and yet persist and compete with proliferative non-senescent cells for space. How immune surveillance shapes this competition and regulates health and lifespan of such tissues remains poorly understood especially because of the multiscale nature of interactions.

To address this, we developed a multiscale modelling framework to study **cell competition between senescent and non-senescent epithelial cells** under immune-mediated clearance. At the population level, we formulated a system of **ordinary differential equations (ODEs)** describing competitive interactions among proliferative cells, senescent cells, and immune effectors, incorporating growth, senescence induction, immune recruitment, and senolysis. Analysis reveals regimes of competitive exclusion, coexistence, and senescent dominance driven by nonlinear feedback.

To capture the spatial aspects of such competitions, we constructed an **agent-based Cellular Potts Model (CPM),** in which cells compete locally for space and interact with immune cells. The CPM reveals spatial clustering of senescent cells and stochastic immune clearance absent in mean-field models. By comparing the ODE and CPM models, we aim to shed light on the role of spatial structure, crowding, and cell-niche adhesion, and softness, in immune-regulated competitions during tissue aging.

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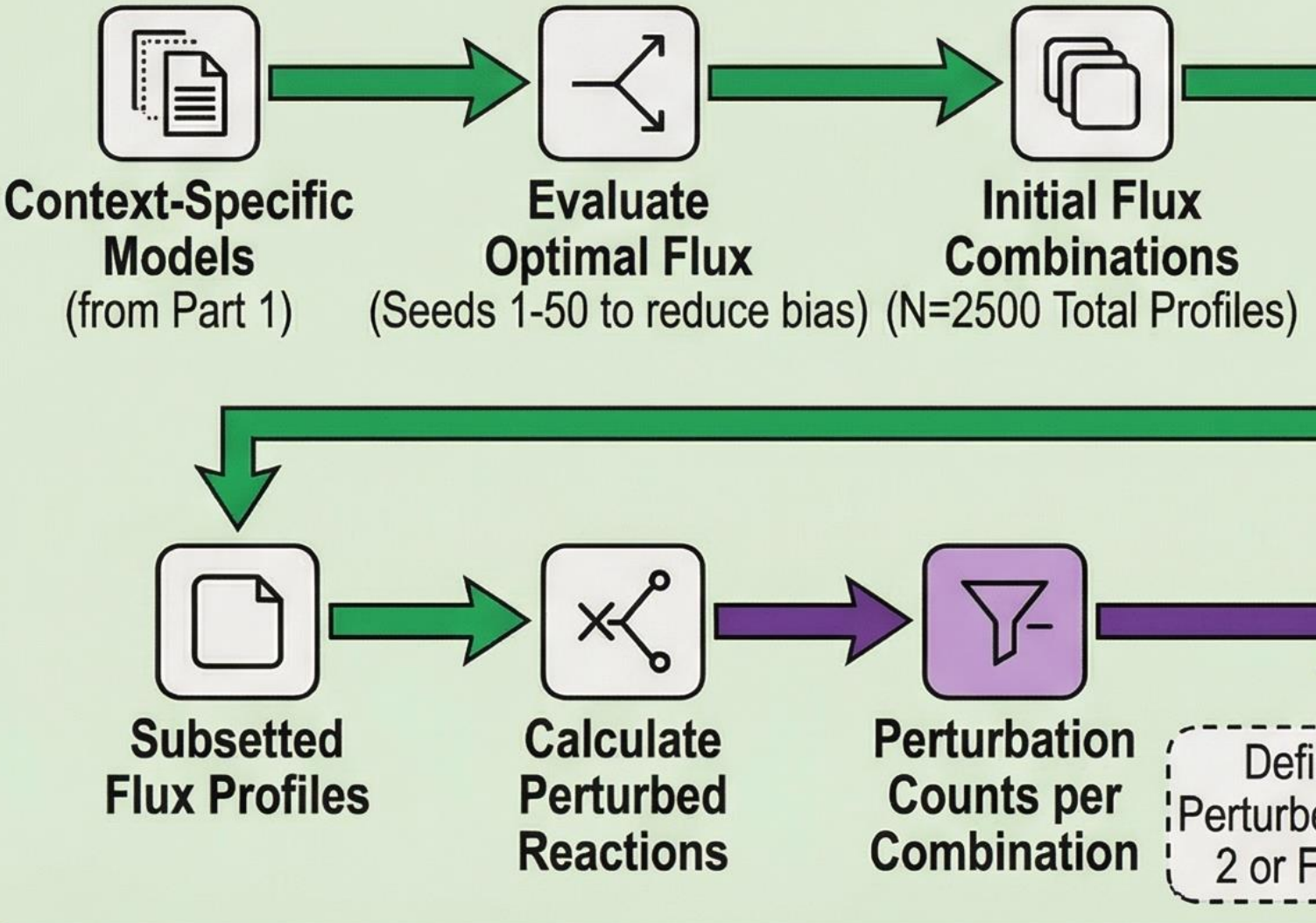
T13

Computational Investigation of Cancer-Associated Single-Point Mutations and Their Impact on Protein Stability and Structural Dynamics Using AlphaFold and Molecular Dynamics Simulations

T14

PART 2: Flux Analysis & Profile Selection Wo



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T15

Cancer cell morphogenesis in 3D soft engineered microenvironments

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In the human body, cells reside in a complex milieu of the tissue microenvironment in conjunction with the extracellular matrix (ECM). The ECM is a major regulator of cellular behavior, fate, and various mechanisms underlying homeostasis, development, and disease (including cancer).[1] Biochemical and biophysical cues in the ECM are exploited by cancer cells enabling them to disseminate, invade, metastasize or lie dormant in various organs, depending on the context. Understanding the cancer cell-ECM interactions is key to unravelling potential mechanisms of tumor progression, chemoresistance, and survival, thereby leading to better effective therapeutic development.[2] In this work,[3] we present soft ECM-mimetic hydrogels composed of fibrinogen conjugated to polyethylene glycol diacrylate (PEGDA), PEG-fibrinogen (PF). These hydrogels can be tuned with varying degrees of polymer content and crosslinking density to obtain a range of matrix adhesivity, porosity, degradability, and stiffness. Breast cancer cells (MCF7, MDA-MB-231) and glioblastoma cells (U87MG, LN229) were encapsulated and maintained in 3D culture within these hydrogels. Their cellular and nuclear morphometric features were tracked over time based on fluorescence imaging of F-actin (phalloidin) and nucleus (Hoechst 33342) and image analysis workflows. These features (cellular protrusivity, spread area, shape index, Feret's diameter, nuclear volume etc.) were correlated to the matrix features (porosity, adhesivity, degradability, and stiffness) to determine the degree/extent of matrix features in governing phenotypic plasticity. Cells in degradable, soft, porous, and adhesive hydrogels displayed higher degree of spreading, higher cell density, longer protrusions, and elongated and larger nuclei compared to those in less degradable, stiffer, less porous, and less adhesive hydrogels. These results highlight the complex interplay between cells and ECM, which could guide the intelligent design of hydrogel biomaterials for various tissue engineering and disease modeling applications.

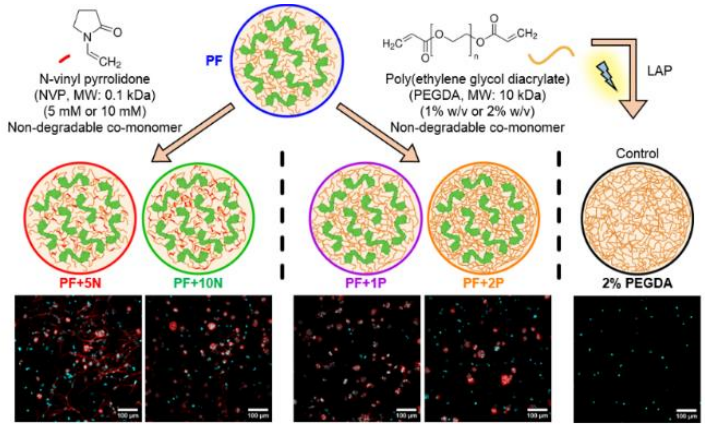

Figure 1: Schematic of six different hydrogel compositions and representative confocal z-stacks of cells with morphological differences in cell spreading, cellular protrusions, and cell shape.
Scale bar: 100 µm.
Red: F-actin, Cyan: nuclei.

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