Mapping the Tumour-Immune Battlefield through Hydrogel Engineering

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The tumour-immune microenvironment (TME) is a dynamic battlefield where cytotoxic T lymphocytes (CTLs) engage in a continuous combat against cancer cells. Central to these interactions, the extracellular matrix (ECM) plays a crucial role in modulating the tumour-immune dynamics. However, the complexity of the TME presents a challenge in unravelling the specific effect of ECM properties on immune cell function and cancer progression. Deciphering these effects is essential for advancing tumour immunology. To deconvolute the impact of ECM properties on TME dynamics, we engineered hydrogels as ECM mimics, independently tuning stiffness while maintaining similar porosity and bioactive cues. With this platform, we found that a stiff microenvironment impairs CTL functions at multiple levels: migration, killing, and synapse formation. CTLs migrate slower in stiff than in soft ECM mimics, but when an enzyme-degradable motif is present, they switch from non-proteolytic to proteolytic migration. Furthermore, CTLs kill target cells less efficiently in stiff ECM mimics, not because of slower migration or a lower probability of encountering target cells, but due to the suppressive effect of stiffness on immunological synapse formation. By mapping the interplay between ECM properties and CTL function, these findings reveal new insights into the mechanobiology of tumour-immune interactions. Our hydrogel system provides a controlled framework to investigate these mechanisms, laying the groundwork for innovative strategies to overcome ECM-driven immune suppression and enhance cancer immunotherapy.