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Force Matters in Canalizing Cell Differentiating Paths

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When cells meet an adhesive matrix, they begin to spread and migrate with a speed that depends on the stiffness of the extracellular matrix. On a flat surface, migration speed decreases with matrix stiffness mainly due to an increased stability of focal adhesions. Noticeably, 3-dimensional (3D) cell invasion is enhanced by higher matrix stiffness, opposite to cell behavior in two dimensions, as long as the pore size does not fall below a critical value where it causes excessive steric hindrance (Lang *et al.* 2015). Indeed, non-transformed, premalignant, and transformed cancer cells not only invade in greater numbers but also migrate more persistently within a stiffer 3D type I collagen gel (Haage & Schneider 2014). In this respect, ECM density and composition can impose physical constraints to restrict cell movement by reducing pore size, necessitating a requirement for the cells to degrade the matrix or undergo transdifferentiation (epithelial–mesenchymal transition) to be able to invade and migrate. Conversely, it is of relevance that inhibiting ECM stiffening effectively impairs exogenous and resident cell invasion and migration, eventually promoting the reversion of the inflammatory phenotype and, in some circumstances, even the cancerous transformation (Kenny & Bissell 2003). Overall, this evidence prompted to consider the micro-environment and the mechanotransduction process as new, testable targets in the management of inflammatory-derived diseases, including cancer and age-associated comorbidities. Indeed, amazing examples of the reversion of cancer cells have been obtained by culturing cancer cell in 3D cultures. Those models composed by ECM of stroma cells (myoepithelial and stroma cells) have shown to reproduce the structure as well as the organization of the normal tissue *in vivo* (Speroni *et al.* 2014). Indeed, cells cultured in 3D display several differences regarding those traditionally conditioned in a 2D medium, so much so that the era of 2D studies should now be regarded as definitely waned

(Bissell *et al.* 2017). Overall, these studies allowed for appreciating how critical the interaction among the different components of the micro-environment (collagen fibers, cells, soluble factors, ECM) is in shaping critical biological processes in which a causative role is clearly sustained by biophysical factors and forces (Tracqui, 2009).

Recently, Piccolo and colleagues (Panciera *et al.* 2020) found that a specific receptor tyrosine kinase (RTK)–Ras axis is activated in a process requiring increased force transmission between oncogene-expressing cells and their surrounding extracellular matrix. Noticeably, microenvironments approximating the normal softness of healthy tissues, or blunting cellular mechanotransduction, prevent oncogene-mediated cell reprogramming and tumor emergence. It is worth noting that RTK–Ras pathway empowers a disproportional cellular response to the mechanical properties emerging from the cell/micro-environment cross talk, such that when cells experience even subtle supra-physiological extracellular-matrix rigidity, they are converted into tumor-initiating cells. These regulations rely on YAP/TAZ mechanotransduction, and YAP/TAZ target genes account for a large fraction of the transcriptional responses downstream of oncogenic signaling. Conclusively, these results pave the way to see the mechanobiological machinery as a potential "target", which can be exploited to favor reversion of pre-neoplastic or even neoplastic conditions. Moreover, they vindicate several studies carried out in the last two decades highlighting the biological role sustained by biophysical factors and structural constraints (Bizzarri *et al.*, 2018) originating from bio-electromagnetic fields (Levin *et al.* 2011), or mechanical stresses emerging from the cell-stroma interplay and henceforth transmitted through the cytoskeleton (CSK) (Brock *et al.* 2015) to the nucleoskeleton (NSK) (Poh *et al.* 2012). In turn, mechanical transduction induces adaptive changes in CSK/NSK configuration and in cell shape with subsequent modulation of chromatin structure that constitutes an indispensable premise of any epigenetic reprogramming. These models allow for appreciating significant changes in gene expression patterns (Luo *et al.* 2013) and enzymatic activities which, overall, cooperate in inducing the reversion of the malignant phenotype throughout the physical cue that triggers the entire process (Su *et al.* 2013; Willhauck *et al.* 2007; Paszek *et al.* 2005). Noticeably, even mild "manipulations"—as seen in the report from Piccolo's team—are instrumental in influencing the natural history of cancerous diseases. This is especially true for a few substances that interfere with collagen biosynthesis and ECM composition. Ascorbic acid (Philips *et al.* 2009), hyaluronidase (Benitez *et al.* 2011), and Lysyl-Oxidase (Santhanam *et al.* 2010) inhibitors, as well as polyphenols (extracted from green tea or red wine) (Zlotogorski *et al.* 2013), modify tissue stiffness and collagen structure, contributing to reshaping the micro-environment architecture and exerting a significant clinical activity through this, both in the field of chemoprevention and as treatment (Sagar *et al.* 2006).

Therefore, as aptly asserted in the study, the gathered results "may inform research on potential routes to exploit oncogenic mechanosignalling as a vulnerability at the onset of tumorigenesis, including tumor prevention strategies akin to those used by normal tissues to prevent cancer emergence."

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