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Microenvironment promotes cytoskeleton remodeling and adaptive phenotypic transition

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Abstract: The cytoskeleton includes three main classes of networked filaments behaving as a coherent and complex structure that confers stability to cell shape while serving as sensor of internal/extracellular changes. Microenvironmental stimuli interfere with the non-linear dynamics that govern cytoskeleton architecture, namely by fostering symmetry breakings and transitions across different phenotypic states. Such process induces a whole-coherent adaptive response, involving the reprogramming of biochemical and gene-expression patterns. These characteristics are especially relevant during development, and in those conditions in which a deregulated crosstalk between cells and the stroma is at the core of the pathological process. Therefore, studying how the cytoskeleton can be modified–both pharmacologically and/or through microenvironment-dependent changes–has become a major area of interest in cancer and developmental biology.

The Background

The cytoskeleton (CSK) constitutes a pivotal structure that confers shape and stability to the cell, while serving as a sensor of mechano-biological inputs from the microenvironment (Ramaekers and Bosman, 2004). CSK can be viewed as a sensor of both internal/extracellular changes and a promoter of the adaptive response that follows a wide range of biophysical stimulations. Environmental cues generate mechanical forces that regulate cytoskeletal organization: CSK remodeling is then mechanically transduced to organelles and even into the nucleus (Kim and Wirtz, 2015), ultimately promoting a wide modulation of biochemical pathways through complex rewiring of the nucleoskeleton (NSK) (Stroud, 2018). Namely, F-actin reorganization leads to nuclear lamina deformation that influences heterochromatin localization and core histone protein mobility, which exerts mechanical control on nuclear morphology and chromatin organization. The complex dynamical interplay between CSK and NSK, in the end, results in differential gene expression patterns (Ramdas and Shivashankar, 2015). The mechanical link between CSK and NSK substantiate a dynamic reciprocity between the nucleus and the outside of epithelial cells and tissues.

Namely, the existence of an intermediate filament cage surrounding the nucleus, and occasionally passing into the nuclear space through invaginations or tunnels in the nucleus, suggests a unique mechanical coupling between receptors on the plasma membrane and the nucleus (Jorgens *et al.*, 2017). These bewildering properties of cell scaffolding are especially important in the context of development-when cells are highly sensitive to their environment-during cell differentiation, and in all those conditions in which cells undergo a transition from a phenotypic state to another (Lim and Plachta, 2021). Therefore, studying how the cytoskeleton can be modified–both pharmacologically and/or through microenvironment-dependent changes–has become a major area of interest in cancer and developmental biology.

Despite structural differences between the main components of CSK (actin, microtubules and intermediate filaments), all three classes of filaments share common features: (1) they are composed of monomeric subunits; (2) monomers are assembled and disassembled according to the rules of non-equilibrium thermodynamics (Tabony, 1994), thus making the CSK architecture highly sensitive even to mild fluctuations in the environmental forces; and (3) they are connected both to the cell membrane (forming highly structured adhesion complexes), and to the cell nucleus by anchoring to the nucleoskeleton (Simon and Wilson, 2011) (Fig. 1).

Specifically, remodeling of CSK has been observed in all those conditions in which a phenotypic transition comes into play (Datta *et al.*, 2021). A profound disorganization of CSK

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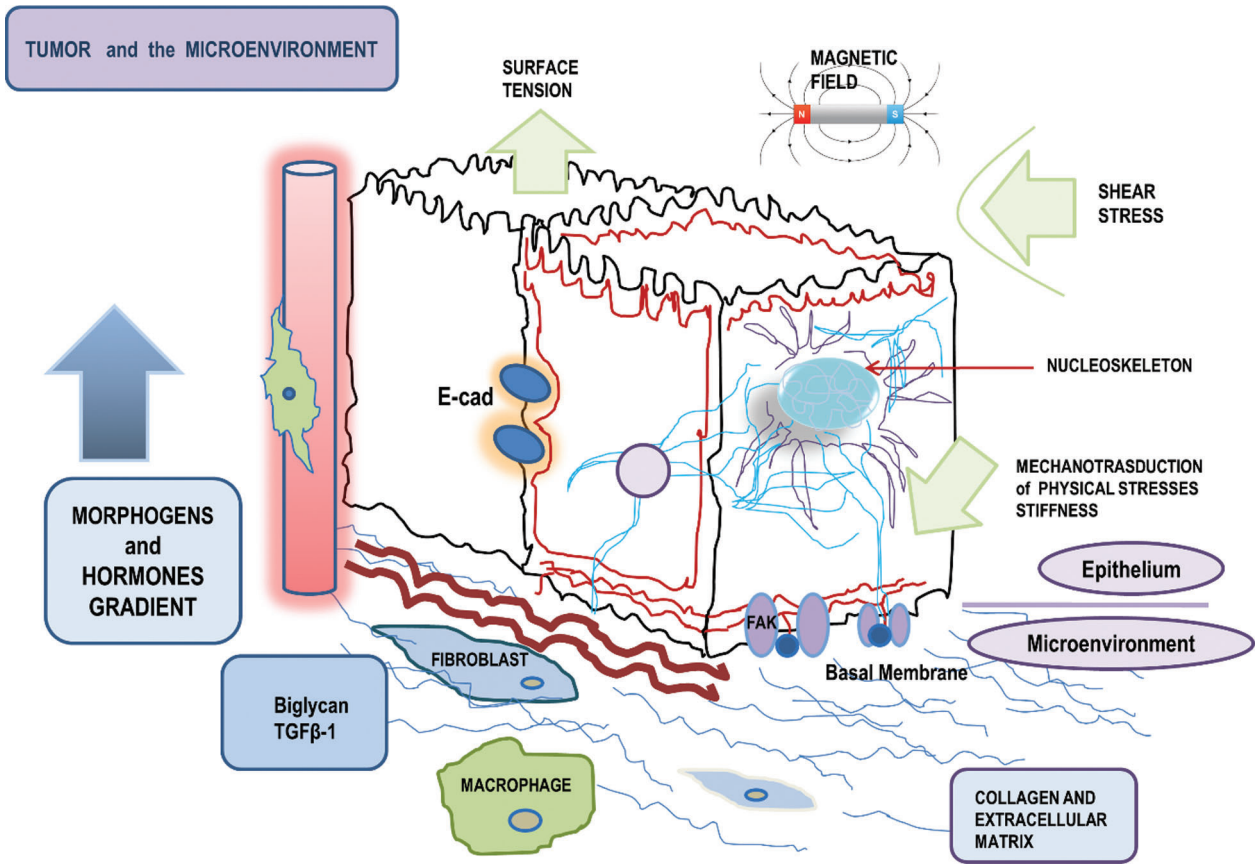

FIGURE 1. The CSK constitutes a key network that confers shape and stability to the cell, while serving as a sensor of mechano-biological inputs from the microenvironment. Environmental cues (emerging from stroma density, collagen architecture, fibroblasts activity, etc.) generate mechanical forces that regulate cytoskeletal organization. Reframing of the CSK is mechanically transduced to organelles, biochemical pathways (some of which are physically linked to the CSK), and to the nucleus. Conclusively, transmission of environmental forces through the mechanobiology apparatus results in significant modification of enzymatic, protein and gene expression patterns. Focal Adhesion Kinases, FAK; E-Cad, E-cadherin.

has been recorded in cancerous cells, in which actin and microtubules remodeling is instrumental in promoting an invasive/migrating phenotype (Hall, 2009). Even neoplastic invasion is initiated and maintained by microenvironmental cues that control cytoskeletal dynamics in tumor cells and the turnover of cell-matrix and cell-cell junctions, followed by cell migration into the adjacent tissue (Friedl and Alexander, 2011). Moreover, the reciprocal reprogramming of both the tumor cells and the surrounding tissue structures not only guides invasion, but also generates diverse modes of dissemination. Similarly, profound CSK changes coupled to epithelial-mesenchymal transitions are observed during normal developmental processes (Li *et al.*, 2017). However, it is still a matter of investigation if CSK changes happen as secondary events or if they are true causative factor in promoting critical transitions. This is a key issue because several conditions may affect the composition and the biophysical properties of the microenvironment, which can consequently foster CSK remodeling and thus adaptive change in gene expression and cell phenotype. Focusing on the microenvironment would implies we should switch from a cell-centered perspective toward a wide, systems-based view given that the complex crosstalk in between cells and stroma is ultimately responsible for those processes that involve tissue morphogenesis and its pathological outcomes, like cancer (Sonnenschein and Soto, 2020).

The Perspective

An exemplary model of how mere physical changes in the microenvironment can dramatically interfere with CSK architecture and promote cell phenotype differentiation–without the need of any "instructive", molecular "signal"–has recently been provided by studies performed on microgravity. Living cells cultured in microgravity are subjected to relevant morphological changes associated with the emergence of two phenotypes-an 'adherent' and a 'floating cell clumps' one–in which the native population is almost equally partitioned within the same culture (Bizzarri *et al.*, 2018). This phenomenon is reversible, as both clusters collapse into the original phenotype when cells are seeded again into a 1 g gravity field. This simple experiment demonstrated that the "removal" of a biophysical constraint (the gravity) can spontaneously promote a cell fate commitment. Noticeably, this process is primarily triggered by the remodeling of CSK (Po *et al.*, 2019). Subtle modifications in gene and protein expression are secondary, adaptive arrangements that stabilize the configuration assumed by each cell cluster. In fact, CSK is under a continuous stochastic fluctuation and this activity is highly sensitive to modifications in the non-equilibrium dynamics. In absence of gravity, CSK cannot find a proper equilibrium stabilization, losing its native orientation. Impairment of

CSK architecture, in turn, favors the spontaneous emergence of novel phenotypes. Thus, changes in CSK architecture are instrumental in shaping cell morphological rearrangement, and in mechano-sensing physical perturbations that, in turn, are transduced to influence cell growth, metabolism and differentiation. In absence of gravity, CSK remodeling is an everlasting phenomenon (due to non-equilibrium dynamics), which will lead to an endless rearrangement, while cells are oscillating in between different morphological configurations. These findings highlight the relevance of the biophysical properties of the microenvironment and the concomitant adaptive changes that, by involving the CSK, can successfully promote the emergence of novel phenotypes. These results further vindicate the assumption for which the genotype does not determine by itself the phenotype but requires additional, environmental cues to proper finalize cell commitment (Prasun *et al.*, 2007).

Conversely, pharmacologically induced modifications in CSK architecture have been demonstrated to favor the reversion of (apparently) firmly established phenotypes. Myo-inositol (myo-Ins) administered at pharmacological doses in breast cancer cells promotes bewildering rearrangements of CSK, which in turn almost completely inhibit cell motility and invasiveness (Dinicola *et al.*, 2016). Indeed, myo-Ins significantly reduces vimentin and cofilin expression, stabilizes cortical F-actin and suppress the emergence of lamellipodia and filopodia. Those changes are subsequently followed by reversal of the epithelial-mesenchymal transition, as witnessed by several inhibition of correlated pathways and gene-expression. Those results have been replicated *in vivo*, where inositol administration has proven to suppress the metastatic process in more than 90% of treated animals (Minini *et al.*, 2021). Furthermore, experimental data have shown that chemical/physical manipulation of microenvironment can enhance cancer regression/reversion, mostly by inducing a remodeling of the CSK (Kenny and Bissell, 2003). Current evidence suggests that the stroma stiffness (principally dependent on collagen density and architecture) and the crosstalk between E-cadherin, integrins and CSK components are prominent, key factors in triggering cell fate commitment (Koenig *et al.*, 2006), cell reprogramming, and even reversion of cancerous features (Rubtsova *et al.*, 2021; Perl *et al.*, 1998). Moreover, as inhibition of cancer motility and invasiveness represents a crucial end point in cancer management (Proietti *et al.*, 2018; Gandalovičová *et al.*, 2017), the search for specific treatments able in targeting the metastatic capability of cancer is urgently warranted. Critical assessment of these novel antimetastatic agents to achieve "stable reversion" (Powers and Pollack, 2016) is gaining momentum, and hopefully can establish new and improved options for the treatment of solid cancer, as supported by preliminary, randomized clinical studies (Livraghi *et al.*, 2005).

The Impact of the Novel Paradigm

Biochemical/biophysical changes occurring within the stroma can affect tissue organization and cell fate adaptive function mostly by interfering with CSK architecture and dynamics that, in turn, modulate gene expression and biochemical pathways (Khan *et al.*, 2020). These findings substantiate a paradigm shift, as the "causative" level moves from genes to those factors that can influence the overall system's behavior. The genetic paradigm has largely privileged a specific level of observation, while reducing the complexity of a living system only to its molecular components given that the gene paradigm has been "illegitimately extended as a paradigm of life" (Strohman, 1997). Understanding the logic of organisms implies to perform strict correlations between the 'local' processes and the 'global' structure of the living beings, connecting every level with each other. The existence of levels means that molecules, components and structures belonging to the system are constrained to cooperate in the functionality of the whole. These constraints lie in the boundary and initial conditions, so that the organization becomes cause in the matter. Indeed, CSK can be viewed as the structure in which external and internal stimuli both converge: the crossroads where cell fate decision may either collapse or diverge. It is worth noting that CSK may amplify–or alternatively buffer–strong or mild stimulation, which are in turn transduced to the overall system, thus triggering a collective, sand-pile like, response of all of its components in a coherent fashion (Subramanian and Kapoor, 2012) (Fig. 2).

The CSK-itself a non-equilibrium chemical system-harnesses chemical energy to perform mechanical work that enables cells to migrate, divide, differentiate, and exert forces on their surroundings, principally in response to strong biophysical (thermodynamic) constraints, rather than to single, molecular signals (Hess and Ross, 2017). Briefly, both microtubules and actin filaments display a highly dynamic regimen, involving a continuous disassembly and assembly of their monomer constituents. Under normal conditions, this process displays intrinsic instability, leading tubulin/actin monomers to be preferentially added to one extremity of the filament while being lost from the other, ultimately forming stationary macroscopic patterns. This dynamic equilibrium is highly sensitive to a wide range of biophysical perturbations, including gravity (Papaseit *et al.*, 2000). Microenvironmental cues act by 'canalizing' the higher fluctuations occurring during the remodeling phases that allow CSK to assume a specific configuration. Given that CSK remodeling is a non-equilibrium process–highly sensitive even to weak forces when approaching a tipping point–this interaction causes a 'drift' term, which breaks the symmetry of the transport processes and therefore promotes CSK growth along a specific direction (Portet *et al.*, 2003). Under gravity, striped patterns of microtubules oriented consecutively in an ordered manner, whereas in weightlessness, no pattern formation arises and microtubules self-organize into an isotropic configuration without preferential orientation. In other words, gravity provides a vector of directionality to the self-organizing process (Lim and Plachta, 2021; Sonnenschein and Soto, 2020). Ultimately, the non-equilibrium dynamics modulation of CSK allows cells to display emergent properties, long range correlations and dramatic first-order classes transitions. Indeed, generated stresses and mechanical structures can couple in complex ways such that different dynamic steady states with different structural order can abruptly emerge when applied biophysical

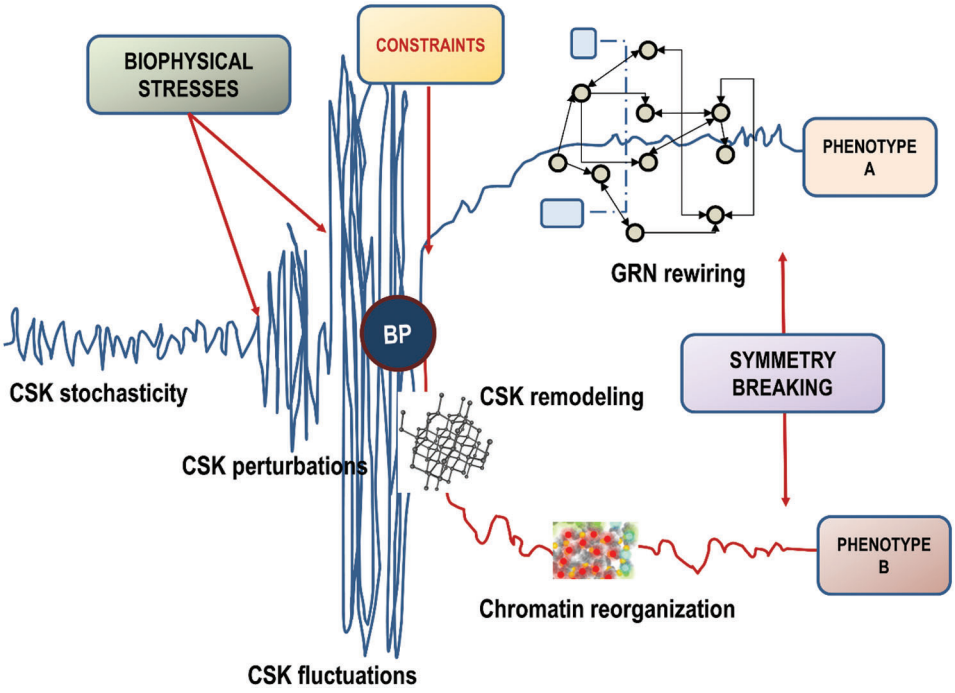

FIGURE 2. Intrinsic CSK dynamics can be described by non-equilibrium thermodynamics, according to self-organized complexity theory. In basal conditions assembly and disassembly of CSK monomers show a stochastic behavior. In response to environmental stresses (physical forces, changes in biochemical gradients, hypoxic conditions, etc.), fluctuation rates within the CSK steadily rise up to a threshold value, at which correlations among its components are maximized. At the bifurcation point (BP) the system displays the highest coherency degree and undergoes a sharp phase transition. Constraints and environmental factors contribute to steering the transition toward a preferred outcome (the attractor), selected among many. Once a new CSK configuration has been achieved, secondary changes intervene to stabilize the novel Gene Regulatory Network (GRN), chromatin organization and consequent gene expression. Overall, the transition ends up providing a new phenotype.

cues interfere with the connectivity of the network by promoting an overall transition according to the self-organized theory (SOC) (Bizzarri *et al.*, 2020). Briefly, symmetry breakings in CSK architecture anticipated and are then instrumental in fostering resultant major structural reorganization (Tan *et al.*, 2018), given that the associated system of CSK-NSK can be viewed as the main driver of critical transitions across the Waddington landscape of living cells (Bizzarri and Pontecorvi, 2021).

This statement has huge consequences at both theoretical and experimental level. First, cell function and behavior cannot longer be studied in isolation, that is, without taking into consideration their three-dimensional microenvironment: two-dimensional cultures can be viewed for many aspects as true "artifacts," which often provide unreliable results (Haycock, 2011). Second, phenotypic commitment should be considered, in principle, a reversible process: both molecular and biophysical cues can efficiently induce phenotypic reversion, as highlighted by cell reprogramming studies (Downing *et al.*, 2013). Third, by shifting our focus from genes to dynamic relationships between the microenvironment and the overall cell structure would imply we have to reframe the dominant paradigm in carcinogenesis (Bizzarri and Cucina, 2016), dismissing the gene-centered approach once deemed the privileged level of causality (Noble, 2012). Therefore, the focus for identifying new therapeutic targets should move from genes to system's parameters as those that control cell shape and CSK performance (Bizzarri and Cucina, 2014). For instance, engineered low-pathogenic microbes have been recently shown to promote mesenchymal stem cells reprogramming into multiple lineages by modulating CSK architecture (Sivasubramaniam and Franks, 2016). Even more intriguing are results provided by Badylak's group (Naranjo *et al.*, 2020), which demonstrated that pre-neoplastic lesions and inflammation in Barrett's esophagus can be mitigated, and the metaplastic changes can be reversed when the microenvironment is "reverted" into a more normal, homeostatic state by coating the esophageal mucosa with a mucoadhesive hydrogel composed of normal porcine esophageal extra cellular matrix components. Recognizing how to modulate the CSK by manipulating/engineering the microenvironment (Ingber, 2008) could help in planning new pharmacological approaches in those diseases arising as a result of disrupted crosstalk between cells and their microenvironment, including developmental-related defects, cancer, and inflammation-based diseases.

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