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Chromatin Remodeling Directs the Fate of Epithelial Cells on Soft Matrix

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Introduction

Cell therapy is an emerging field in the development of regenerative medicine, tissue engineering and cancer immunotherapy. Its efficiency depends on the release of healthy cells to injured sites. These cells can exert therapeutic effects, repair tissue and damaged organs or eliminate malignant tumors. On the other hand, hydrogels, due to their biochemical and physical properties, are materials of choice to mimic the extracellular matrix. Devising strategies to improve cell survival in hydrogels is a major challenge still in progress. To successfully design hydrogels, it is important to known the cellular responses like adhesion, migration, contraction and protrusion to environmental signals. Mechanotransduction events by which cells sense their environment were extensively investigated on mechanosensitive proteins at focal adhesions and inside the cytoskeleton [1-4]. Extra- and intracellular forces are transmitted across the cytoskeleton to the nucleus. These forces can activate integrins at focal adhesions linked to actin filaments, themselves connected to microtubules and to intermediate filaments. The linker of nucleoskeleton and cytoskeleton complex (LINC complex), which enables force transmission across the nuclear envelope, connects cytoskeletal filaments to the nucleus where lamins form an extended part of the LINC complex [5-10]. These forces ultimately propagate to chromatin that represents a site of signal integration and interpretation for activation or gene silencing [11-12].

Interestingly, for the first time, Rabineau et al. [13] focused on how chromatin plasticity is influenced by a change of substrate rigidity. In this context, several works revealed that the nucleus itself acts as a cellular mechanosensor bypassing propagation of mechano-signaling processes through the cytoplasm [8,14]. Rabineau et al. [13] developed a hydrogel based on polyelectrolyte multilayers, made of poly(L-lysine) and hyaluronic acid, $(PLL/HA)_{24}$, capped with a poly(sodium styrene sulfonate)/poly(allylamine hydrochloride), (PSS/PAH)n, multilayer film (Figure 1) as matrix model mimicking the extracellular matrix rigidity of biological tissues [15-17], on which epithelial PtK2 cells were grown. In their model, the rigidity of the hydrogel increases with the number n of PSS/PAH layer pairs [18].

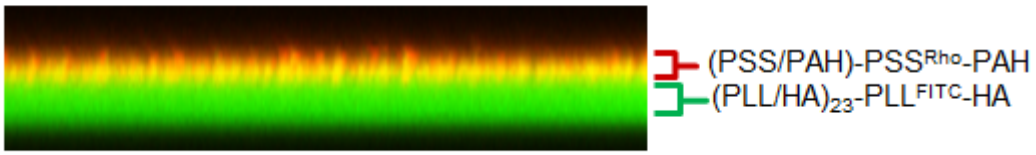

Figure 1: Vertical section image of a (PLL/HA) 23-$_{PLL}$FITC-HA capped with a (PSS/PAH)-$_{PSS}$Rho-PAH multilayer film observed by CLSM.

Two well-defined cytological compartments are structured in the nucleus: the condensed, inactive heterochromatin and the extended, active euchromatin. Heterochromatin is restricted to an irregular rim located at the nuclear periphery and around the nucleolus as well as in patches throughout the nucleoplasm, whereas euchromatin fills up the majority of the nucleus. Rabineau et al. revealed that on stiff matrices, chromatin is in its euchromatin form, whereas a soft matrix partially induces remodeling in its heterochromatin form. On a very soft matrix cells die by necrosis. The original idea of the authors is to influence the cell fate by modifying the organization of the chromatin. The opposing actions of histone acetyl transferases and histone deacetylases (HDACs) dynamically control the acetylation status of chromatin and hence chromatin compaction, by respectively loosening (euchromatin) or condensing (heterochromatin) chromatin structures [19]. More precisely, concerning the formation of heterochromatin, it has been shown that both of H3K9me2/3 and H3K27me3 are associated with this process in mammals [19]. H3K9me2/3 is able to recruit HP1α, which plays a key role in the stability of the higher-order structure of pericentric heterochromatin [20]. Interestingly, as both of the G9a/GLP complex and Suv39h1/2 enzymes interact with DNA methyltansferases and play a role in the maintenance of DNA methylation [21,22], the writers of H3K9me2/3 are also required for the formation of heterochromatin independently of HP1α at specific chromatin loci. The writer for the establishment of H3K27me3 is the PRC2 complex [23]. Recently, it has been shown that PRC2 and H3K27me3 cooperate with H3K9 methylation to maintain HP1α at chromatin [24].

Rabineau et al. [13] use a drug that inhibits histone deacetylases, namely trichostatin A (TSA), to maintain chromatin in euchromatin. On the very soft matrices, they find that PtK2 cells treated by TSA preserve acetylated forms of histones H3, maintain their chromatin in euchromatin and a uniform nuclear distribution of HP1β. These treated cells maintain also their nuclear envelopes intact as well as a residual intermediate filament network around their nuclei. This allows cells to survive in a non-adherent state without undergoing proliferation suggesting that cells might enter in a quiescence state. Importantly, when transferred on a stiff matrix these cells retain their capacity to adhere, to spread and to enter a novel mitotic cycle in a way that depends on their transcriptional competence. These findings might be relevant to maintain cells in the best settings within synthetic scaffolds and in tissue-derived matrices used in tissue regeneration strategies.

The work of Rabineau et al. [13] represent the rational for detailed molecular studies aimed at developing drugs to preserve important nuclear structure, in particular euchromatin and the nuclear envelope, under unfavorable mechanical environment. Chromatin organization has a strong influence on the expression of the genome and chromatin remodeling contributes to many cellular properties as for instance the deformation of the nucleus as well as the cell pluripotency and the cell differentiation [25]. Hydrogels with variable elastic moduli might control the organisation of chromatin and therefore guide the fate of cells of interest for tissue engineering. For example, the behavior of several types of stem cells will be tested according to their level of differentiation. An important aspect is to determine if the elastic modulus durably remodels chromatin after mechanical pre conditioning on a soft substrate. In recent works, the elastic modulus can epigenetically reprogram the cells which maintain a "nuclear mechanical memory" [26-28].

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