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Nuclear actin

A key player in extracellular matrix–nucleus communication

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Decades of research have shown that there is an intimate relationship between the extracellular matrix (ECM) and cellular phenotype. While the existence of this relationship remains inarguably clear, the exact details through which the extracellular matrix controls phenotypic behavior at the gene expression level are, for the most part, elusive. In a recent study on mammary epithelial cells, nuclear actin was identified as a key effector protein through which laminin Type III (LN1) attenuates RNA polymerase activity to promote growth arrest. This finding forms the basis from which one can begin to envision a mechanism through which the ECM can control nuclear function to enact changes in cell behavior. Here I will briefly discuss the current depth of knowledge with regards to the relationship between LN1 and nuclear actin and its implication in mammary epithelial cell growth and function.

Key words: actin, nucleus, mammary, epithelial, extracellular matrix, laminin

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It is well known that the structure of chromatin and the localization of transacting factors with respect to their cognate DNA sequence regulate nuclear metabolic processes such as transcription, DNA repair and DNA synthesis. Nuclear actin plays a direct role in RNA polymerase activity,[1-3] mediates DNA movement,[4,5] maintains the structural integrity of the nucleus,[6] and enhances chromatin remodeling activity.[7] Because nuclear actin is an important regulator of both nuclear structure and function, it is likely that its levels are strictly enforced in vivo through tightly regulated mechanisms that, for the most part, lack definition.

The extracellular environment has a profound influence over cell phenotype. In particular, the extracellular matrix molecule LN1 has been shown to arrest the growth of mammary epithelial cells, and in conjunction with lactogenic hormones, promote the expression of tissue-specific genes (reviewed in ref. 8). Until earlier this year, the mechanism through which LN1 influences nuclear processes to promote mammary epithelial cell growth arrest had been poorly defined. However, recent findings have identified nuclear actin as a key effector of LN1-mediated growth arrest for this cell type.[9] More specifically, the treatment of mammary epithelial cells with LN1 had been shown to cause a dramatic drop in nuclear actin which resulted in attenuation of transcription and DNA synthesis.[9] Overexpression of a NLS-tagged beta-actin construct opposed these responses, indicating that the effect of LN1 on nuclear actin was sufficient to drive these outcomes.[9] Of particular interest to these findings, however, was the speed and intensity of this effect: over half of DNA synthesis, nuclear actin content and transcriptional activity was downmodulated after only 2 h of LN1 treatment and then reduced by an additional 50% after exposure for another 2 h.[9] Such a rapid and dramatic outcome raises the question of exactly how LN1 is affecting the nucleus through nuclear actin to exert its control over transcriptional events which are linked to mammary epithelial cell growth.

To begin to answer to this question, RNA polymerase II and III levels have been measured in mammary epithelial cells and shown to remain constant in

response to LN1 treatment for at least 4 h.[9] However, the levels of both RNA pol II and III molecules associated with the detergent-insoluble, transcription-rich nuclear fractions was significantly affected: RNA pol III then RNA pol II association decreased two-fold during the respective first (2 h) and second (4 h) response of nuclear actin, transcription and DNA synthesis to LN1 treatment.[9] Protein synthesis is essential for cell division[10] and driven through nuclear actin-dependent processes such as tRNA and mRNA production.[1,2,11] The initial effect of LN1 on RNA polymerase III localization suggested that this ECM molecule attenuated growth by reducing protein synthesis and depleting the cell of protein resources which would be required for basic cell functions such as division. This effect likely contributed towards the secondary effect of LN1 on RNA pol II function. However, a direct effect on this enzyme also could have been possible if the population of actin associated with this polymerase was more resistant to the effects of LN1 than the population associated with RNA pol III. Such a possibility has not been explored but can be investigated through characterization of the composition and localization of nuclear actin-containing protein complexes in LN1-treated mammary epithelial cells.

The recently discovered relationship between LN1, nuclear actin, RNA polymerase activity and cell growth provides some insight into how LN1 mediates growth arrest through changes in nuclear structure and function. However, several questions about this relationship remain unanswered. For example, how does LN1 down-modulate nuclear actin levels? Does LN1 mediate growth arrest through other effector proteins, and if so, how? Preliminary data has shown a link between a decline in PI3K signaling activity and reduced nuclear actin levels,[9] but the ability of LN1 to down-modulate nuclear actin levels through PI3K remains to be shown. It is also important to consider that adhesion of a mammary epithelial cell to LN1 influences the activity of signaling pathways involved in different aspects of cellular function, some which influence polymerase activity and some which cross-talk with one another.[12-14] Thus, LN1 likely mediates growth arrest through a host of effector proteins and the identification of these players will require an in-depth characterization of the immediate-early signaling targets for this ECM molecule. Lastly, although the effect of LN1 on nuclear actin and transcription levels is pronounced, it is not absolute. Mammary epithelial cells that were treated with LN1 for two days maintained detectable, but low, transcription and nuclear actin levels.[9] This assessment was made from cells which were treated with LN1 in a background of lactogenic hormones. Under such culturing conditions, the gene expression program of a mammary epithelial cell ultimately transitions from one which promotes cell division to one which favors the expression of tissue-specific genes such as beta- and alpha-casein.[8] Tissue specific genes have been shown to represent less than 15% of the genome[15] and, in mammary epithelial cells, to be expressed through chromatin remodeling activities[16] which are dependent on nuclear actin.[7] Tied together, these observations raise the possibility that a differentiated cell requires low levels of nuclear actin to mediate tissue-specific gene expression.

Although the evidence discussed above relates to nuclear actin, it must be recognized that LN1 also alters the physical properties of cytoplasmic actin in mammary epithelial cells.[17,18] Exactly how this effect influences cell function is unknown. However, it is clear that actin likely serves as a liaison through which the ECM and nucleus communicate with one another. Expanding our understanding of the relationship between the ECM and the nucleus will be vital for elaborating the true complexity of cellular life in a tissue environment.

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