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Organoid and Primary Epithelial Cell Cultures from Human Prostate Show the Key Role of Epithelial-to-Mesenchymal Transition in the Formation of the Tissue Specific Stromal Cells

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The prostate gland is a small organ in the male reproductive system that is currently under focus of biomedical research due to its leading position in morbidity and mortality from tissue-specific cancer (PC). The epithelium of the prostate gland, which undergoes cancerous transformation, is formed and functions under control of androgens, at the beginning of the disease, prostate epithelium produce the androgen receptor (AR) and is sensitive to androgen-deprivation therapy. However, such therapy inevitably leads to the transition of the disease to the castrate-resistant prostate cancer (CRPC), which is manifested in metastasis and rapid mortality. In CRPC, prostate epithelial cells change their phenotypes, that may be based on mutations of the androgen receptor (AR), and underlies the loss of sensitivity to specific therapy. The mechanism of phenotypic transformation of the prostate epithelium can be hidden in the features of the formation and interaction of stromal and epithelial cells, which are manifested during the formation of primary cultures. In this work, we found that, in contrast to the rapid appearance and formation of a homogeneous population of mesenchymal cells in primary stromal cultures of most tissues, human prostate cell cultures are formed initially from epithelial cells that appear at the 2nd week of cultivation and produce cytokeratins. The formation of a homogeneous population of mesenchymal cells producing vimentin occurs only by the end of 4th week of cultivation and is accompanied by disappearance of epithelial cells. Under epithelial to mesenchymal transition, some epithelial cells simultaneously produce cytokeratins and vimentin. In organoid cultures of the prostate, there is often a concomitant growth on cultural plastic the epithelial but not mesenchymal cells. During pas-

saging of epithelial cells derived from the organoid cultures, they, like the cells of the primary prostate epithelium, show the ability to spontaneous transformation into mesenchymal cells and simultaneously produce cytokeratins and vimentin. Our data suggest, that in primary prostate stromal cultures initially form the epithelial cells. The organoid cultures of prostate can also produce epithelial but not stromal cells. The prostate stromal cells can arise from primary prostate epithelial or organoid cultures, presumably, due to spontaneous epithelial-to-mesenchymal transition (EMT). The tendency to EMT in prostate cells may contribute to the mechanism of high sensitivity of prostate tissue to malignant transformation. Understanding this mechanism will contribute to the development of effective anticancer therapy of PC.

Keywords: organoid, primary stromal and epithelial cultures of human prostate, epithelial-to-mesenchymal transition, prostate cancer