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PREVIEWS

Previews highlight research articles published in the current issue of Stem Cells Translational Medicine, putting the results in context for readers.

Stem Cells Translational Medicine

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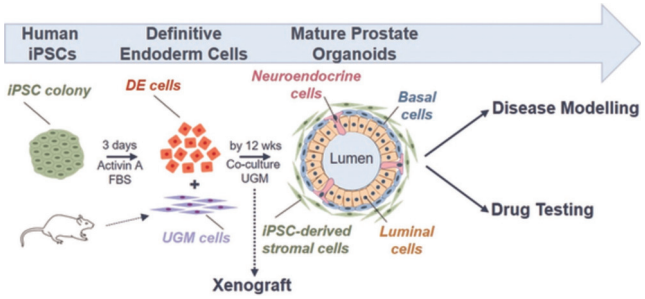
The prostate, an exocrine gland of the male reproductive system, secretes a fluid that enhances sperm motility, prolongs sperm survival, and protects the genetic material contained within. Prostate enlargement due to nonmalignant hyperplasia is a common condition in older men, while prostate cancer represents one of the most common cancers in men in the West, as well as a significant cause of death. The in vitro modeling of the normal and diseased prostate through advanced three-dimensional (3D) culture techniques aims to explore the normal development of the prostate gland, delineate those mechanisms controlling disease onset, and permit the evaluation of novel therapeutics. The generation of 3D prostate organoids had been restricted to cells derived from advanced metastatic tumors[1]; however, recent advances have supported the generation of organoids from more localized cancers.[2] Studies have also reported the generation of prostate tissue in vivo from human embryonic stem cells,[3] although the translation of this approach to in vitro human prostate organoid culture has encountered several obstacles. In our first Featured Article published this month in *Stem Cells Translational Medicine*, Hepburn et al report on the efficient in vitro differentiation of prostate-derived induced pluripotent stem cells (iPSCs) into prostate organoids that fully recapitulate prostate histology and cell type-content.[4] In a Related Article published recently in *Stem Cells*, Yin et al described how the loss of monoamine oxidase (MAO) expression in mice prompted a reduction in stem-like markers in prostate stem cells and the development of smaller atrophied prostates.[5]

The pseudostratified epithelium of the human bronchial airway comprises a luminal layer containing the differentiated mucus-secreting and ciliated cells and a basal layer containing the bronchial stem cells.[6] The mucus-secreting and ciliated cells function to propel trapped pathogens out of the lung as air moves in; however, exposure to chemicals or pathogens can lead to lung injury and the loss of these crucial cell types.[7] In this case, bronchial stem cells differentiate to replace lost cells to return proper function to the lung[8]; therefore, ensuring the appropriate function of bronchial stem cells may represent a crucial aspect governing the recovery of lung function following targeted lung cancer treatments such as radiotherapy. Importantly, progressive lung diseases often present with an imbalance in the proportion of mucus-secreting and ciliated cells, a fact that implicates the dysregulation of bronchial stem cell differentiation in such disorders. Therefore, a deeper understanding of the processes governing bronchial stem cell self-renewal and differentiation may uncover disease-specific mechanisms and help to identify therapeutic targets. In our second Featured Article published this month in *Stem Cells Translational Medicine*, Giuranno et al describe how exposure to small-molecule inhibitors of the Notch pathway can enhance the survival of irradiated bronchial stem cells and may allow normal lung tissue to survive the treatment of lung cancer via radiotherapy.[9] In a Related Article recently published in *Stem Cells*, Malleske et al explored the regulation of mouse bronchial stem cell differentiation by β-catenin and its cofactors in a study with relevance to our understanding of chronic lung disease.[10]

FEATURED ARTICLES

Enhanced Prostate Organoid Formation from Prostate iPSCs may Provide a Therapeutic Boost

Previous research from the laboratory of Rakesh Heer (Freeman Hospital, Newcastle upon Tyne, UK) reported the efficient reprogramming of human prostate cells into iPSCs that displayed a heightened capacity for redifferentiation into cells of the prostate.[11] This research aimed to solve problems related to cell culture from prostate biopsies, such as the limited input from primary biopsies, restrictive ethics, and a lack of access. In their new *Stem Cells Translational Medicine* article,[4] Hepburn et al explore the implementation of prostate iPSCs as part of a more efficient approach to the generation of prostate organoids, which would allow the delineation of developmental and disease mechanisms and the evaluation of novel therapeutic strategies. The authors cocultured definitive endoderm cells differentiated from prostate-derived iPSCs with rat inductive urogenital sinus mesenchyme to induce prostatic differentiation[3] and generate mini 3D prostates that comprehensively recapitulated prostate histology and the full breadth of prostate-specific epithelial differentiation. Importantly, prostate organoids also contained neuroendocrine cells and the stromal compartment. Additionally, this fascinating new study also provided proof-of-concept for the introduction of genetic modifications in their culture approach, thereby laying the foundation for novel preclinical approaches to personalized care for prostate disease sufferers. The authors hope to next apply their protocol to the generation of prostate cancer organoids that would permit research into tumor development, drug screening, and the evaluation of novel therapeutic approaches.



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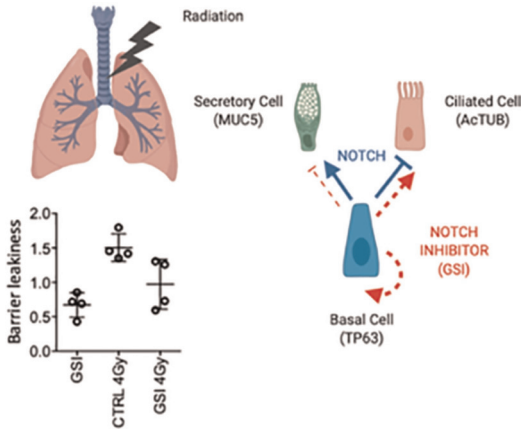
Notch Inhibition Boosts Bronchial Stem Cell Survival during Lung Cancer Radiotherapy

Notch proteins play essential roles during lung development, and evidence also suggests that the Notch signaling pathway controls the self-renewal and differentiation of cells in the lung epithelium. As lung cancers (among others) present with abnormalities that lead to hyperactivate Notch signaling,[12] which promotes tumor growth and radiotherapy resistance,[13] Notch inhibition combined with radiation therapy may represent an efficient antitumorigenic approach. A team of researchers directed by Marc Vooijs (Maastricht University, The Netherlands) sought to explore the relevance of this strategy by evaluating the safety of Notch inhibition combined with irradiation in pseudostratified and polarized bronchial epithelium cultures generated by air-liquid interface culture and a mouse model. In their recent *Stem Cells Translational Medicine* article,[9] Giuranno et al establish that exposure to small-molecule inhibitors of the Notch pathway (GSI) recovered the lost proliferation, differentiation capacity, and viability of human and murine bronchial stem cells treated with irradiation both in vitro and in vivo. Improvements to bronchial stem cell function correlated with a reduced DNA damage response, induced DNA repair levels, and an increased basal cell proliferation level that combined to improve lung epithelial barrier function. The authors hope that their findings represent another step towards the application of Notch inhibition in the reduction of the adverse effects observed in lung cancer patients treated with radiotherapy and the increase in both long-term survival rates and patients' quality of life.

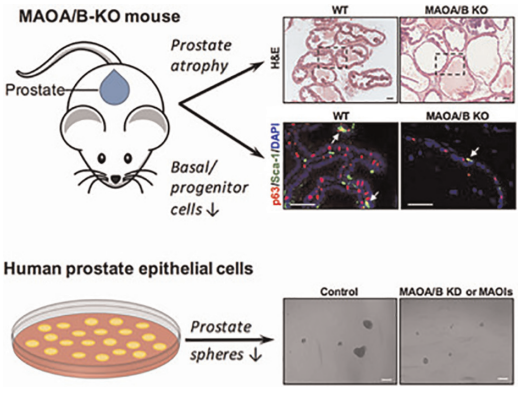


https://doi.org/10.1002/sctm.19-0278

RELATED ARTICLES

MAO Expression Enhances Prostate Stem Cell Activity and Supports Prostate Development

MAOs catalyze the oxidative deamination of biogenic and dietary amines, including monoamine neurotransmitters such as serotonin and dopamine, and have recently been linked to normal prostate physiology and prostate cancer development. Basal epithelial cells of the normal prostate gland express the MAO-A isoform to maintain their undifferentiated state,[14] and a previous study from the laboratory of Boyang Jason Wu (Washington State University) established MAO-A as a therapeutic target in prostate cancer.[15,16] In their subsequent *Stem Cells* article,[5] Yin et al sought to fully explore the influence of the MAO-A and MAO-B isoforms employing in vitro and in vivo prostate model systems. Mice lacking MAO-A and MAO-B expression possessed fewer stem-like cells within the prostate epithelium, displayed decreased epithelial cell proliferation, and presented with smaller prostate masses and an atrophic phenotype in the ventral and dorsolateral prostates. In vitro analysis established that MAO-A and MAO-B loss, by either short hairpin RNA expression or pharmacological inhibition, reduced the sphere-forming ability of prostate stem cells and expression of stem cell markers. Finally, and perhaps most interestingly, the authors discovered the elevated expression of MAO-A and MAO-B in human prostate hyperplasia samples when compared with healthy tissues, thereby suggesting that the pharmacological inhibition of MAOs may hinder the development of prostate cancer. Overall, the authors provide evidence for the importance of adequate MAO regulation to normal prostate stem cell function and prostate maintenance.

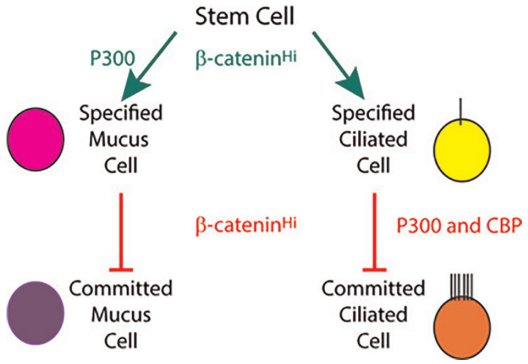


https://doi.org/10.1002/stem.2831

Deciphering the Networks Regulating Human Bronchial Stem Cell Differentiation

A wide range of studies has indicated the overarching importance of activated Wnt/β-catenin signaling and the altered proportions of

mucus-secreting and ciliated cells in chronic lung diseases such as idiopathic pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease.[17] A previous *Stem Cells* article by researchers from the laboratory of Susan D. Reynolds (Ohio State University, Columbus, Ohio) demonstrated that the genetic stabilization of β-catenin in mouse bronchial stem cells hindered differentiation into ciliated cells[18]; however, the role of β-catenin in mucus-secreting cell differentiation remained less well understood. In their subsequent *Stem Cells* article, Malleske et al[10] studied how β-catenin and the P300 (E1A-binding protein, 300 kDa) and cAMP response element-binding (CREB)-binding protein (CBP) cofactors influenced bronchial stem cell differentiation in a modified air-liquid interface culture system. The authors discovered the requirement of β-catenin signaling for bronchial stem cell differentiation, and while a β-catenin/P300 complex promoted mucus-secreting cell specification, the authors also found some evidence that β-catenin interacted with either P300 or CBP to inhibit ciliated cell commitment. The authors hypothesized that chronic lung disease may increase the availability of P300 and active β-catenin to promote mucus-secreting cell hyperplasia; however, the specific roles for β-catenin signaling and P300 and CBP in the inhibition of ciliated cell differentiation remain to be determined. Overall, these findings suggest that β-catenin cofactors can mediate the altered rates of differentiation of bronchial stem cells into mucus-secreting and ciliated cells in response to the elevated levels of β-catenin signaling observed in chronic lung disease.



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