I3PT INSTITUT D'INVESTIGACIÓ I INNOVACIÓ PARC TAULÍ

ciberes Centro de Investigación Biomédica en Red Enfermedades Respiratorias

BRN SEMINARS

Scientific workshops to foster collaborative research

Organized by: Barcelona Respiratory Network Collaborative research

Endogenous Progenitor Cells

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DISCLOSURES

- No relevant disclosures
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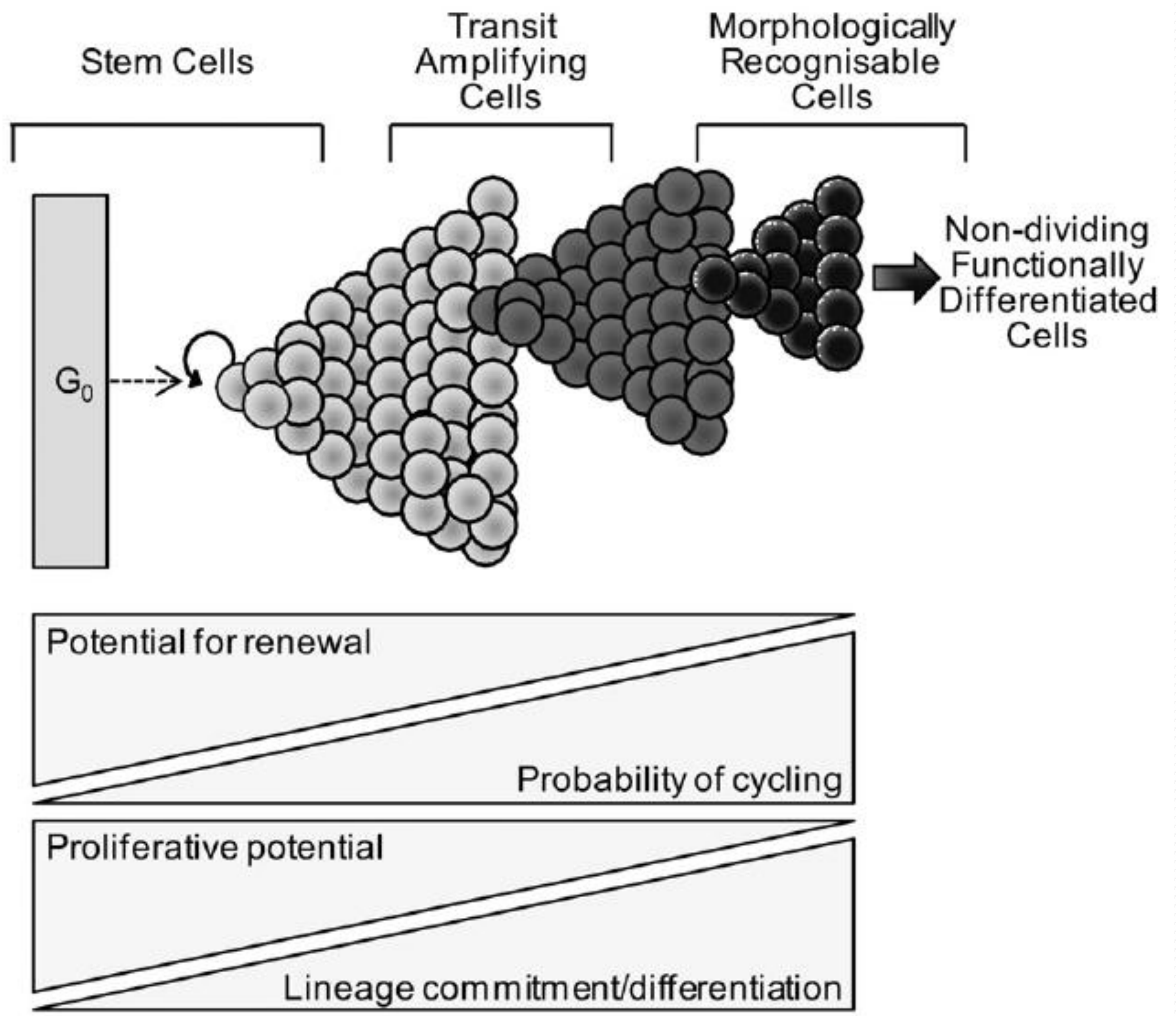
Which is the definition for Stem Cells?

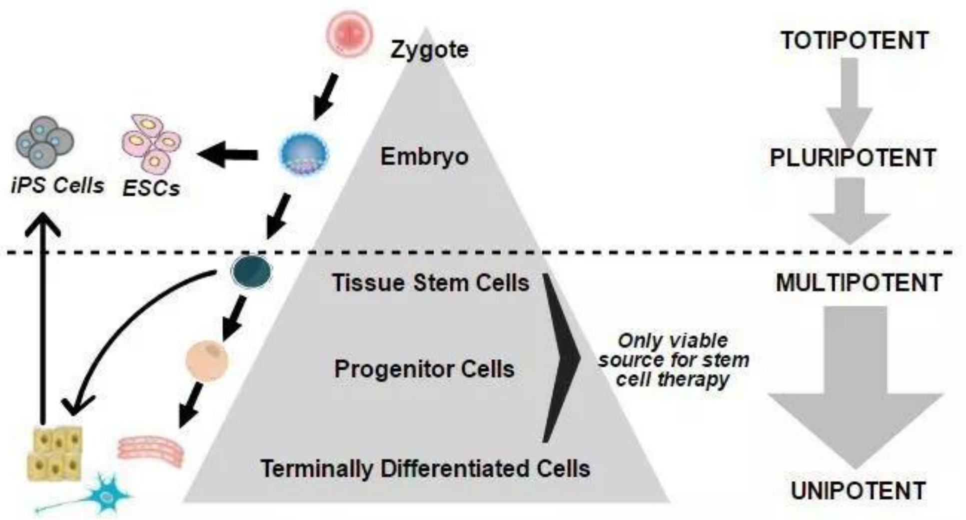
Stem Cell hierarchy

- Self-renewal
- Multipotentiality



Bertoncello I. And McQualter J.L., Respirology 2013

Stem Cell hierarchy



<table>
<tr><th colspan="3">Term</th><th>Definition</th><th>Example</th></tr>
<tr><td rowspan="4">Primitive cell</td><td rowspan="3">Stem cell</td><td>Totipotent</td><td>Capable of division and differentiation to produce a complete organism</td><td>Fertilised oocyte or zygote</td></tr>
<tr><td>Pluripotent</td><td>Ability to differentiate into almost all cells of the three germ layers</td><td>Embryonic stem cells</td></tr>
<tr><td>Multipotent</td><td>Capable of differentiate into a limited range of cell lineages appropriate to the location</td><td>Adult, somatic or tissue-based stem cells</td></tr>
<tr><td colspan="2">Progenitor cell</td><td>Ability to generate one cell type</td><td>Type II pnemocyte</td></tr>
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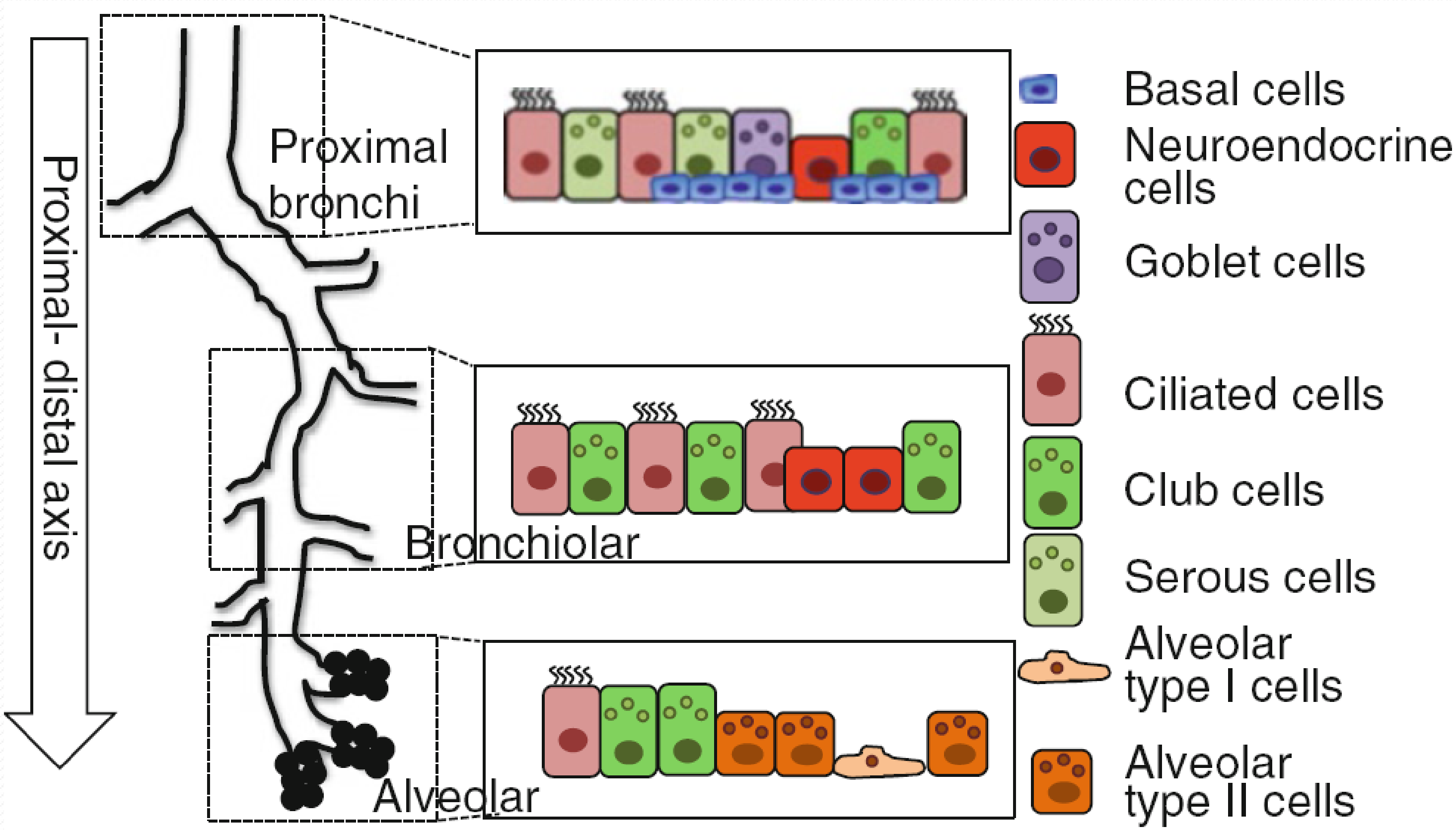
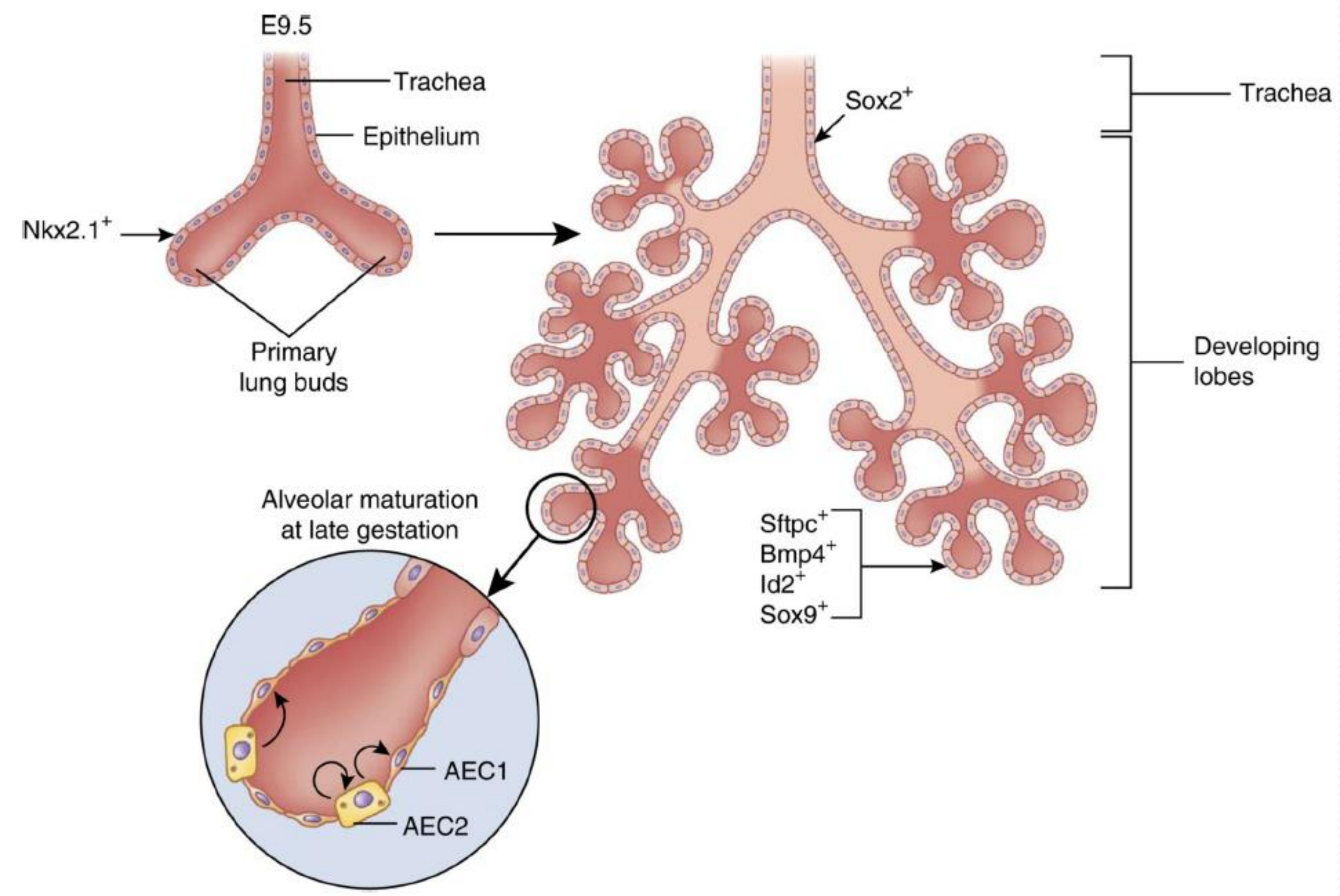
Are there Endogenous Progenitor/Stem Cells in the Lung?

The lung is composed by more than 40 different cell types



Ray S. and Stripp B.R., Does a Lung Stem Cell Exist? 2015

Orchestrated crosstalk between primitive lung endodermal and mesodermal cell lineages



Lung Endogenous Progenitor/Stem Cells

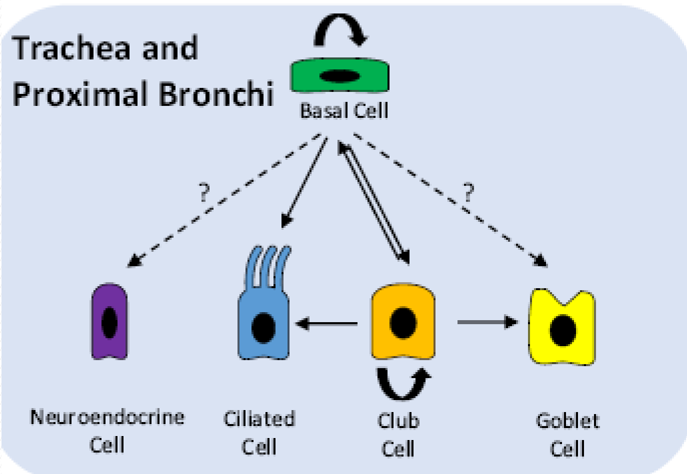
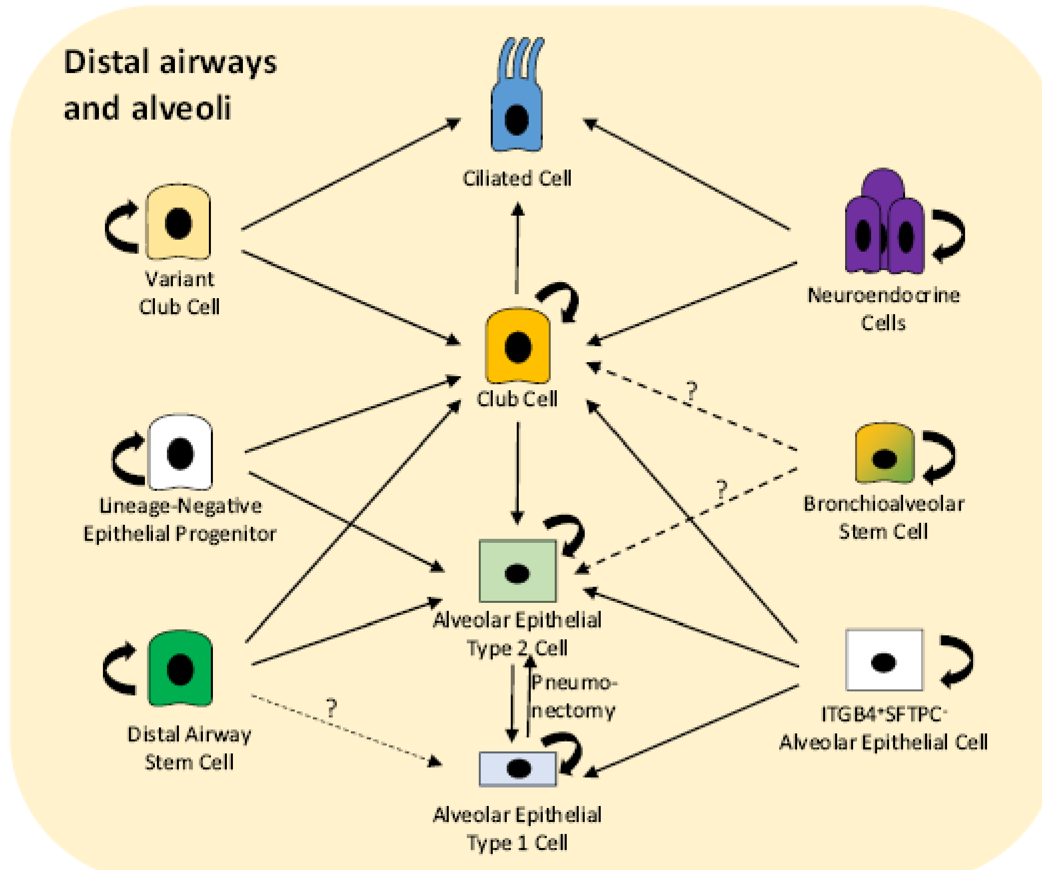


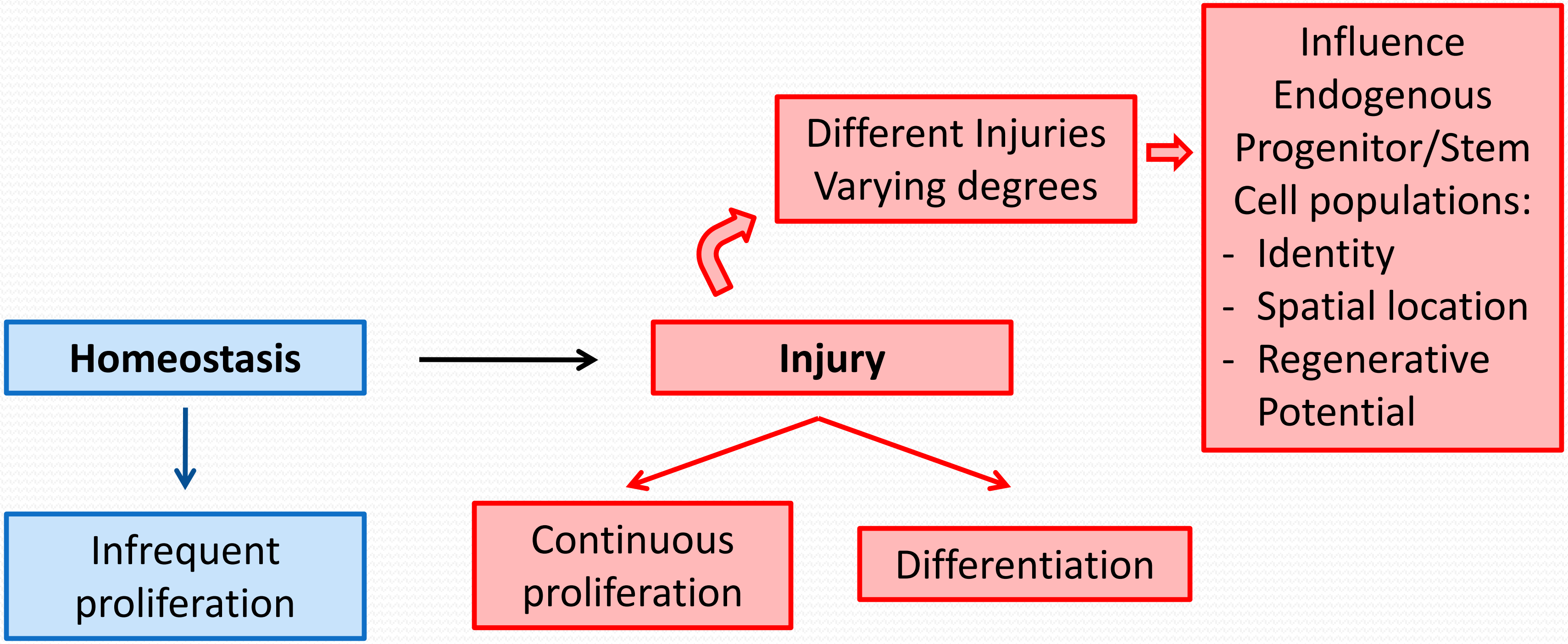
Figure 1 Epithelial stem cells of the mouse lung and their response to injury. **Arrows** indicate cells that have been suggested by lineage-tracing techniques to generate the indicated lineages after injury. **Solid arrows** represent lineages that are generally accepted, whereas **dotted arrows with question marks** are speculative lineages. **Curved arrows** represent self-renewal.



Chen F and Fine A., The American Journal of Pathology 2016

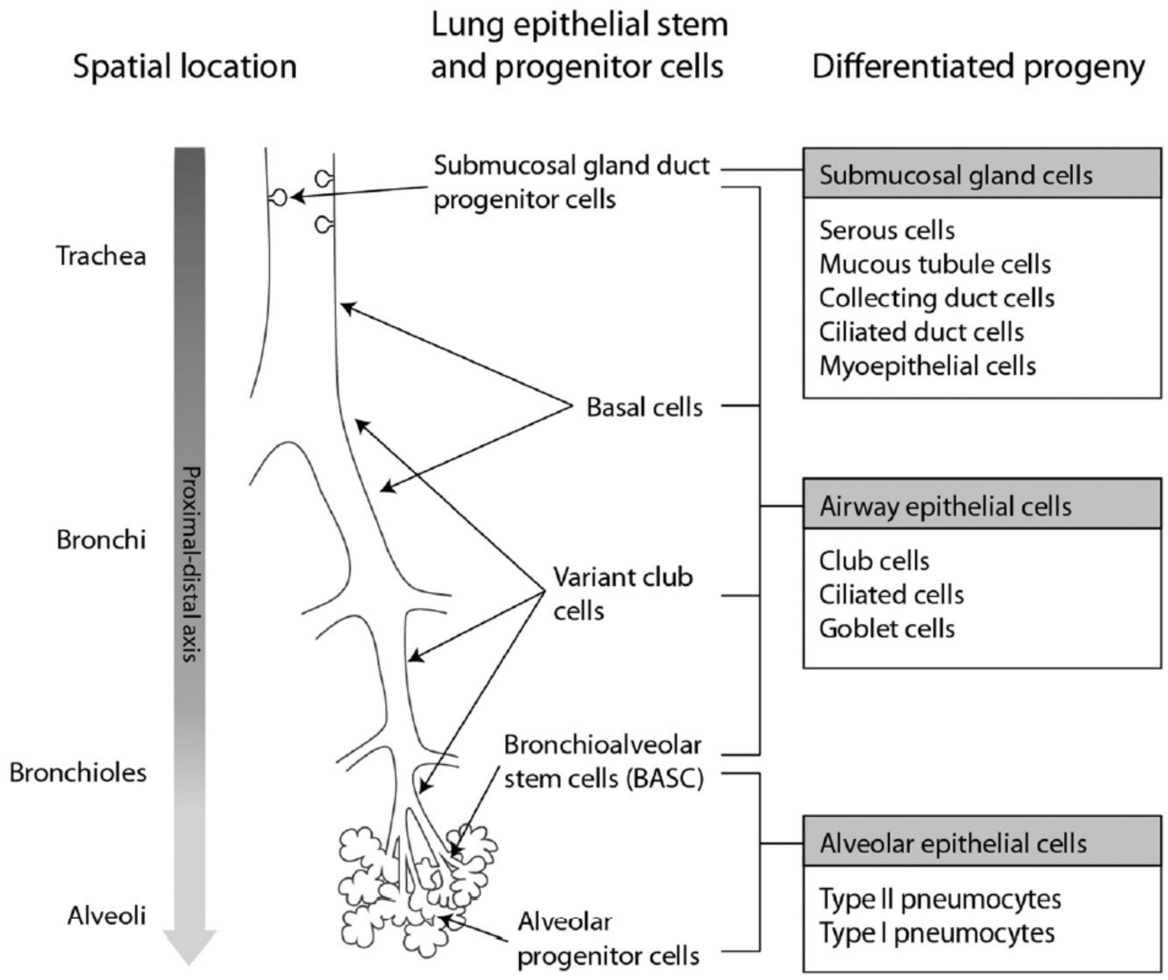
Are Lung Endogenous Progenitor/Stem Cells activated after injury?

Lung Endogenous Progenitor/Stem Cells after injury



The lung has a low rate of cellular turnover during homeostasis that is increased after injury

The role of the niche in Stem Cell differentiation



Bertoncello I. And McQualter J.L., Respirology 2013

The crosstalk between the stem cell and its niche profoundly affects stem cell behaviour and functionality

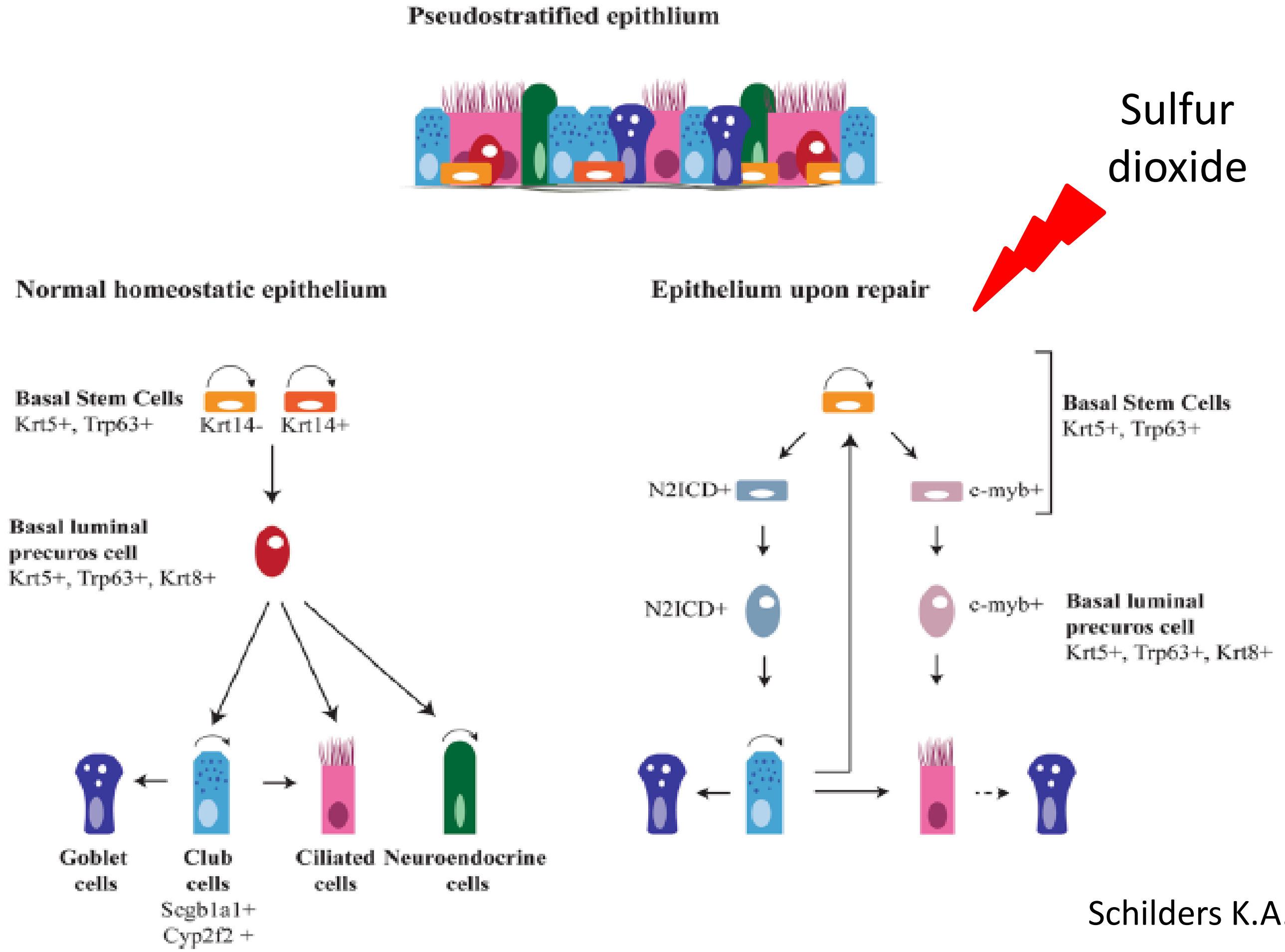
Identity and Location of Stem Cell Populations mediating tissue repair

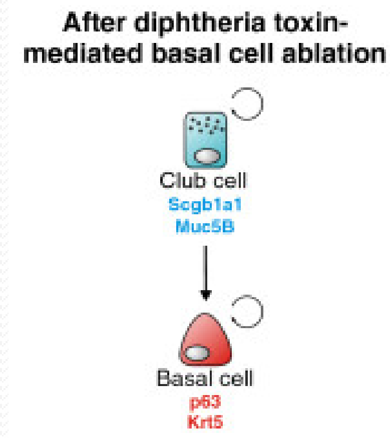
Tissue and region	Stem cell	Marker genes	Daughter cells	Key signals
Trachea and proximal airway	Basal cell	*TRP63*$^+$, *KRT5*$^+$, *NGFR*$^+$, *PDPN*$^+$, *KRT14*$^+$	Ciliated, club, self	NOTCH
	Club cell	*SCGB1A1*$^+$, *CYP2F2*$^+$	Basal, ciliated, goblet, self	NOTCH, SPDEF, HDAC1/2
Distal airway	Variant club cell	*SCGB1A1*$^+$, *CYP2F2*$^-$, *UPK3A*$^+$	Ciliated, club, self	NOTCH, FGF10
	NEC	*ASCL1*$^+$, *CGRP*$^+$, *PROX1*$^+$	Ciliated, club, self	?
	DASC	*TRP63*$^+$, *KRT5*$^+$, *KRT6*$^+$	AEC2, club, self, AEC1?	?
	LNEP	*ITGA6*$^+$, *ITGB4*$^+$, *SFTPC*$^-$, *SCGB1A1*$^-$, *KRT5*$^-$	AEC2, club, self	NOTCH
BADJ	BASC	*SFTPC*$^+$, *SCGB1A1*$^+$	Self, club? AEC2?	WNT
Alveolus	AEC2	*SFTPC*$^+$, *LYZ2*$^+$	AEC1, self	WNT, EGFR-KRAS
	AEC1	*HOPX*$^+$, *AQP5*$^+$, *PDPN*$^+$	AEC2, self	TGFβ
	ITGA6$^+$ITGB4$^+$SFTPC$^-$ AEC	*ITGA6*$^+$, *ITGB4*$^+$, *SFTPC*$^-$, *SCGB1A1*$^-$	AEC1, AEC2, club, self	?

Chen F and Fine A., The American Journal of Pathology 2016

Trachea and proximal airway

Stem cell	Marker genes	Daughter cells	Key signals
Basal cell	*TRP63*+, *KRT5*+, *NGFR*+, *PDPN*+, *KRT14*+	Ciliated, club, self	NOTCH
Club cell	*SCGB1A1*+, *CYP2F2*+	Basal, ciliated, goblet, self	NOTCH, SPDEF, HDAC1/2

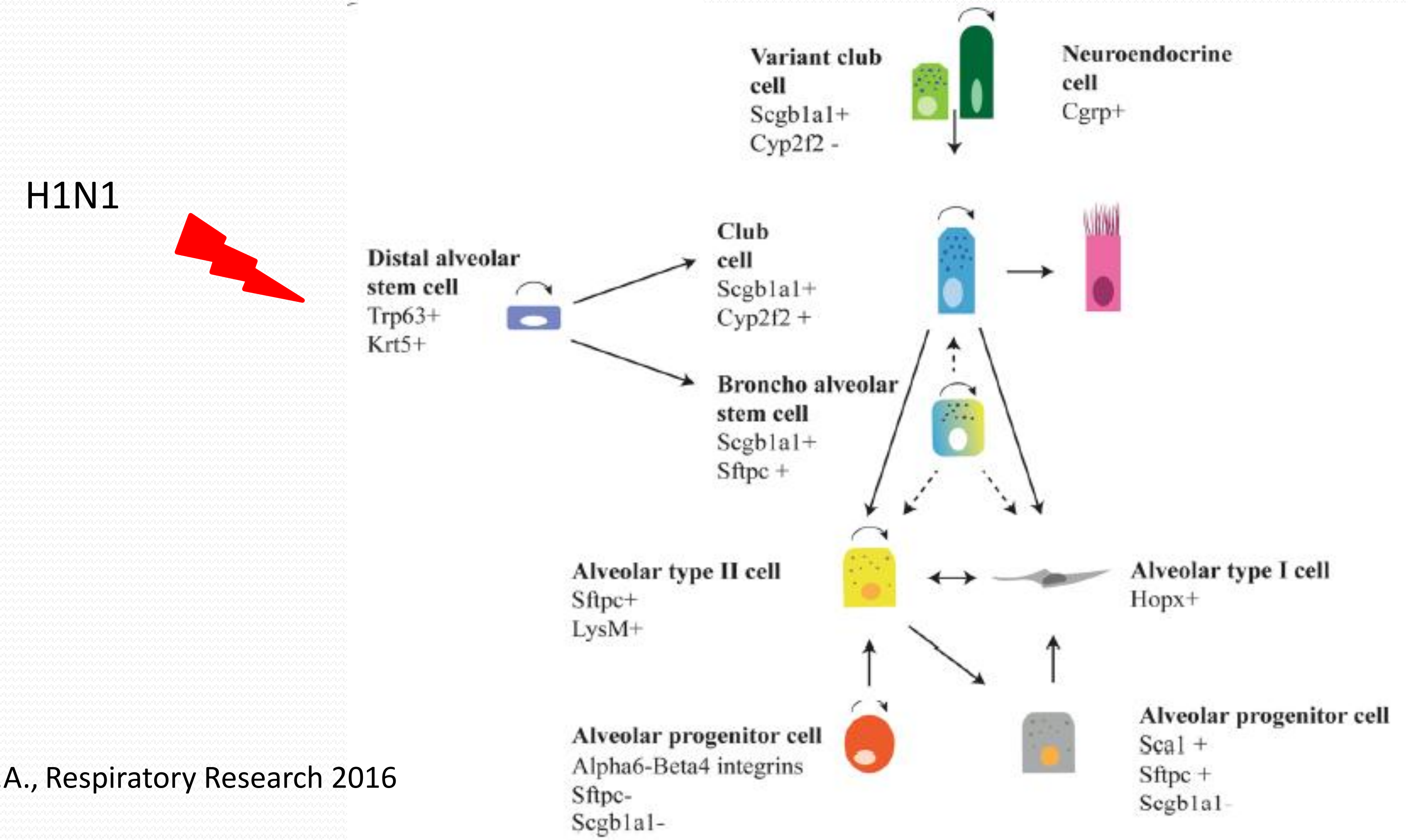




Schilders K.A.A., Respiratory Research 2016

Distal airway and BADJ

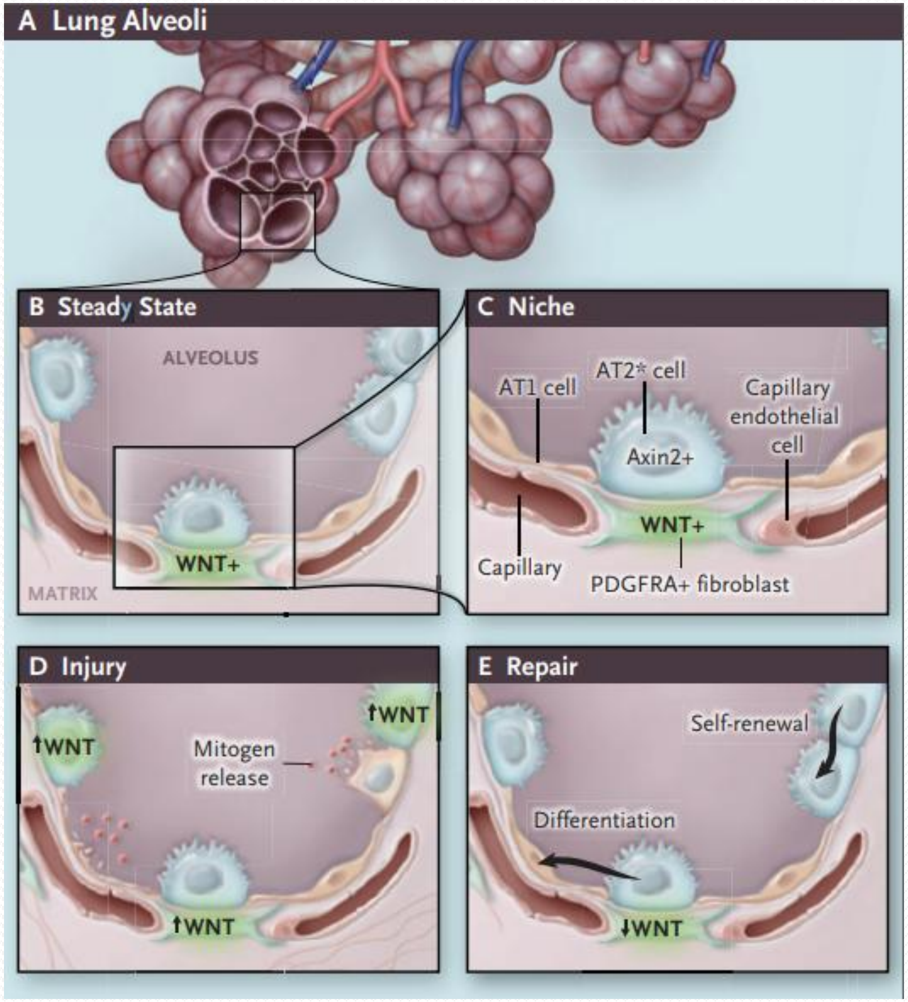
Stem cell	Marker genes	Daughter cells	Key signals
Variant club cell	*SCGB1A1*$^{+}$, *CYP2F2*$^{-}$, *UPK3A*$^{+}$	Ciliated, club, self	NOTCH, FGF10
NEC	*ASCL1*$^{+}$, *CGRP*$^{+}$, *PROX1*$^{+}$	Ciliated, club, self	?
DASC	*TRP63*$^{+}$, *KRT5*$^{+}$, *KRT6*$^{+}$	AEC2, club, self, AEC1?	?
LNEP	*ITGA6*$^{+}$, *ITGB4*$^{+}$, *SFTPC*$^{-}$, *SCGB1A1*$^{-}$, *KRT5*$^{-}$	AEC2, club, self	NOTCH
BASC	*SFTPC*$^{+}$, *SCGB1A1*$^{+}$	Self, club? AEC2?	WNT



Schilders K.A.A., Respiratory Research 2016

Alveoli

Stem cell	Marker genes	Daughter cells	Key signals
AEC2	*SFTPC*$^{+}$, *LYZ2*$^{+}$	AEC1, self	WNT, EGFR-KRAS
AEC1	*HOPX*$^{+}$, *AQP5*$^{+}$, *PDPN*$^{+}$	AEC2, self	TGFβ
ITGA6^{+}ITGB4^{+}SFTPC^{-} AEC	*ITGA6*$^{+}$, *ITGB4*$^{+}$, *SFTPC*$^{-}$, *SCGB1A1*$^{-}$	AEC1, AEC2, club, self	?



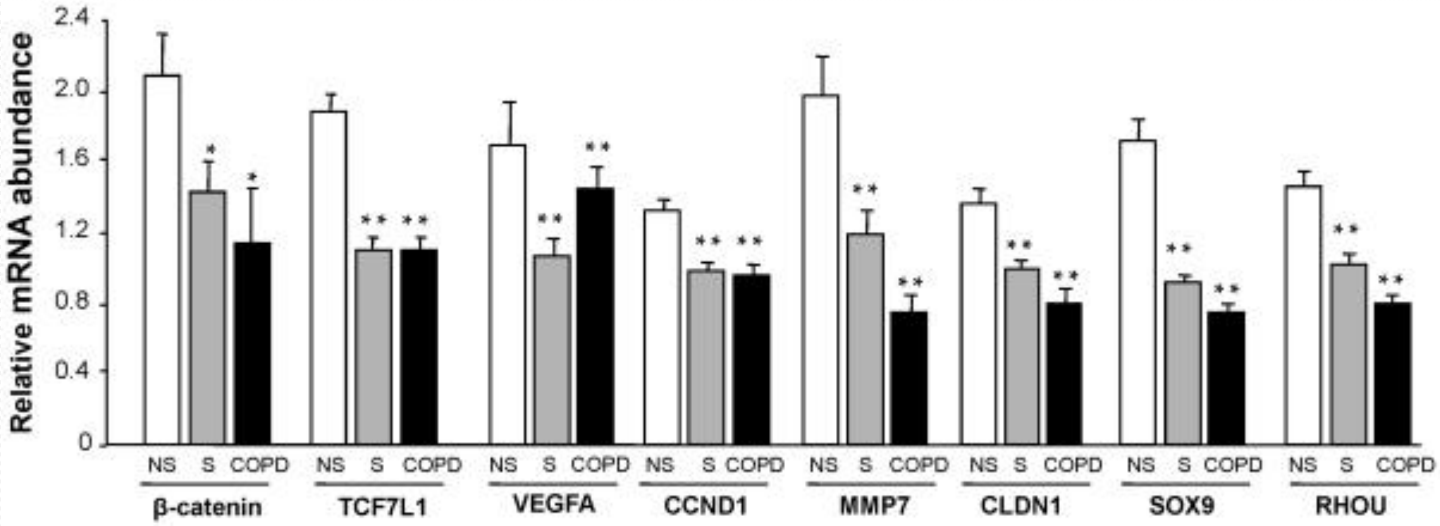
Hogan B., NEJM 2018

Signaling pathways, genes and factors involved in lung development, regeneration and repair

Gene	Molecular function	Lung development	Adult lung regeneration and repair	Pathophysiology
Wnt	Signalling pathway	Regulates early lung endodermal specification	Expansion of the BASC compartment following injury	Chronic activation is associated with increased fibrosis
Notch	Signalling pathway	Differentiation of secretory epithelium from proximal endoderm	Differentiation of basal cells into secretory cells after severe injury	Excess notch signalling promotes mucous metaplasia; loss of notch signalling induces ciliated cell differentiation
TTF-1 (Nkx2.1)	Transcription factor	Required for formation of lung parenchyma and differentiation of lung epithelial lineages	Required for normal differentiation of airway and alveolar epithelial cells	Mutations cause lung diseases of varying severity (e.g. alveolar dysgenesis, interstitial lung disease)
Sox-2	Transcription factor	Normal patterning of proximal airway epithelial lineages	Activated after injury to induce differentiation of ciliated, club, basal and goblet cells	Deletion produces airways devoid of normal epithelial cell types
Gata-6	Transcription factor	Regulates lung epithelial gene transcription during development	Maintains distal airway homeostasis, regulating balance between BASC renewal and differentiation via Wnt signalling pathway	Suppression of Gata-6 is associated with lung adenocarcinoma progression
SPDEF	Transcription factor	Differentiation of goblet cells from basal and non-ciliated columnar epithelial cells	Required for goblet cell differentiation in normal submucosal glands; and following allergen exposure	Deletion blocks goblet cell differentiation in airways and sub-mucosal glands
Myb	Transcription factor	Required for multiciliated cell differentiation	Required for differentiation of ciliated and secretory cells in proximal airways	Myb^{pos} cells are elevated in chronic airway disease; Inactivation leads to failure of proper airway ciliation
HDAC1/2	Histone deacetylases	Regulate Sox2 expression required for proximal airway development	Regulate lung epithelial regeneration by reactivation of cell cycle progression	Deletion of HDAC1/2 results in defective airway repair; inhibition causes emphysema
SHH	Growth factor	Regulates interaction between epithelial and mesenchymal cells during branching morphogenesis	Unclear	Upregulation exacerbates lung fibrosis; associated with bronchopulmonary dysplasia
Fgf10	Growth factor	Branching morphogenesis; saccular lung development; tracheal basal cell maintenance and differentiation	Promotes re-epithelialisation of injured airways by stimulating lung epithelial stem cell proliferation	Reduced FgF10 expression is associated with bronchopulmonary dysplasia
HGF	Growth factor	Required for alveologenesis	Promotes lung repair following injury	Mice lacking HGF receptor (Met) have impaired airspace formation

Bertoncello I., Cellular Physiology 2016

Down-regulation of the canonical Wnt/β-catenin pathway in the airway epithelium of healthy smokers and smokers with COPD

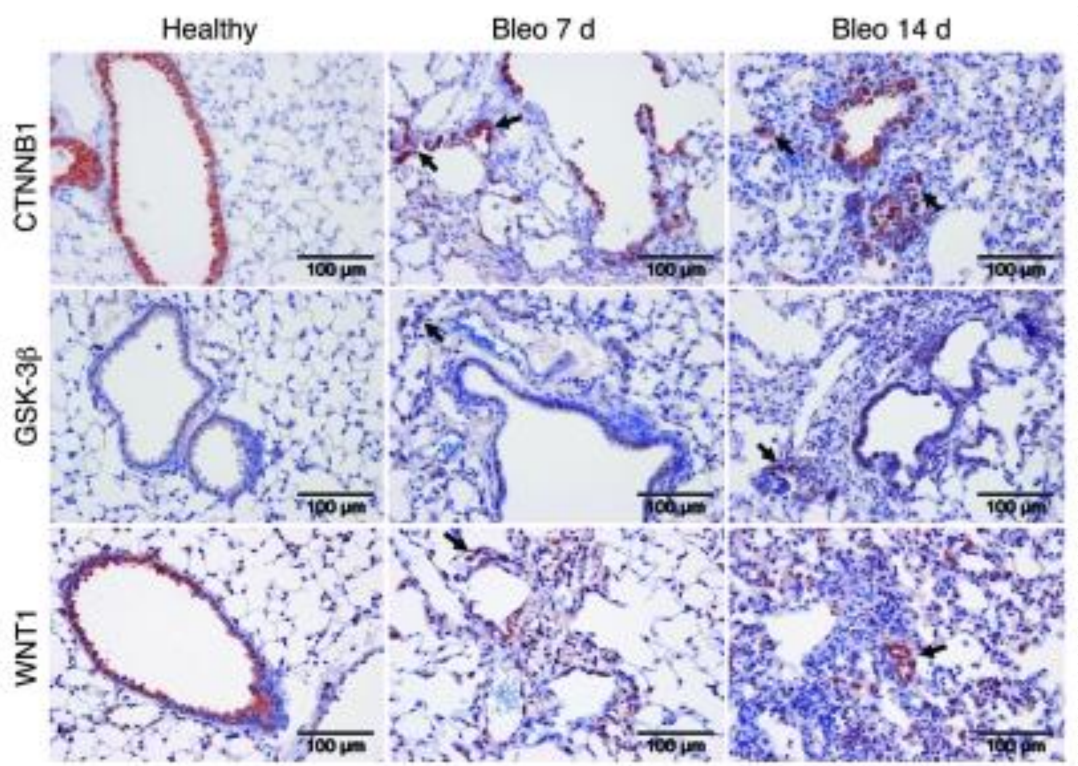


Comparison of the relative expression of the Wnt pathway downstream and target genes in healthy nonsmokers (n = 47), healthy smokers (n = 58), and smokers with COPD (n = 22).

- p<0.05 compared to healthy nonsmokers
- * * p<0.01 compared to healthy nonsmokers

Wang R., Plos One 2011

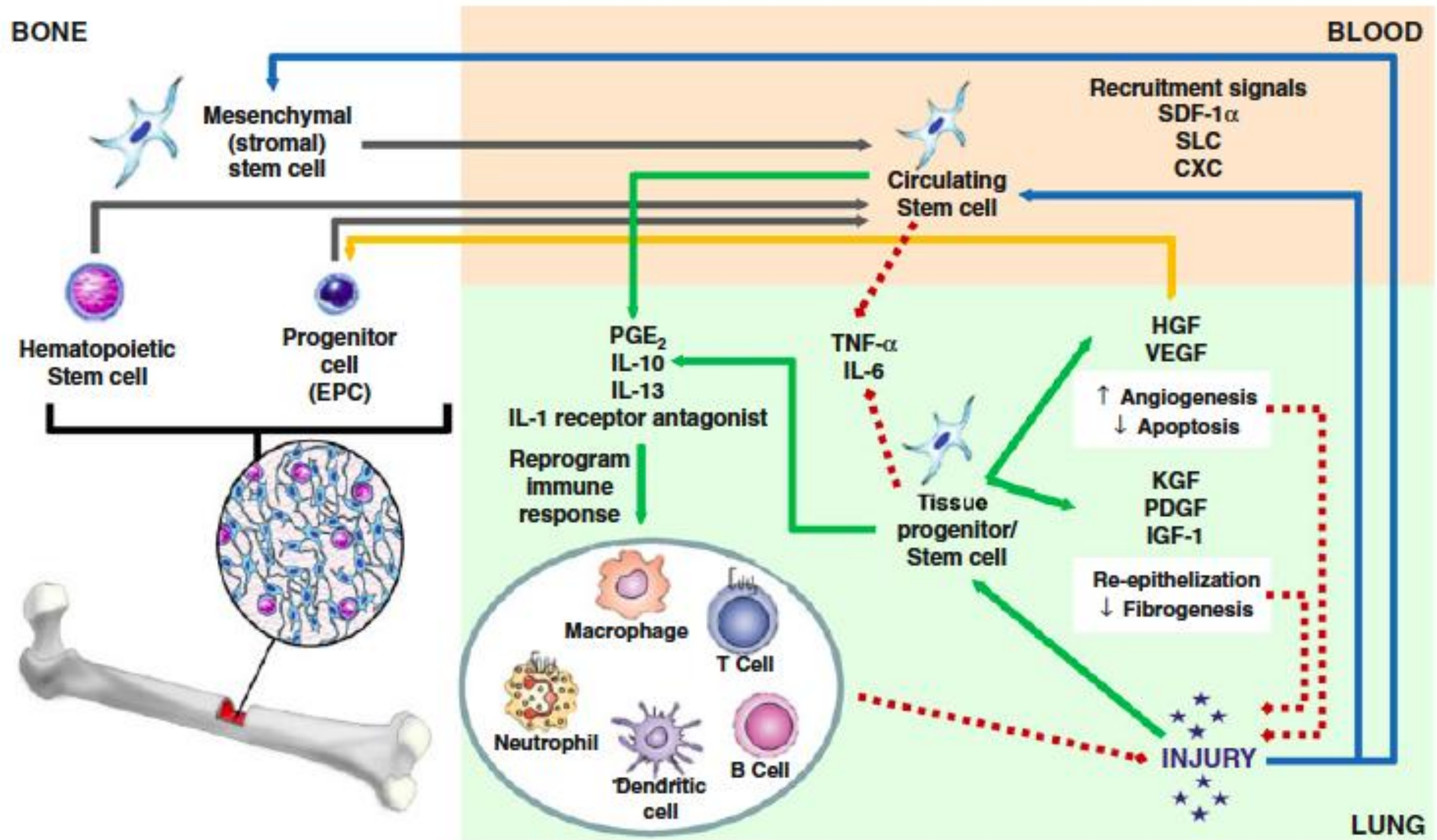
WNT1-inducible signaling protein-1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis



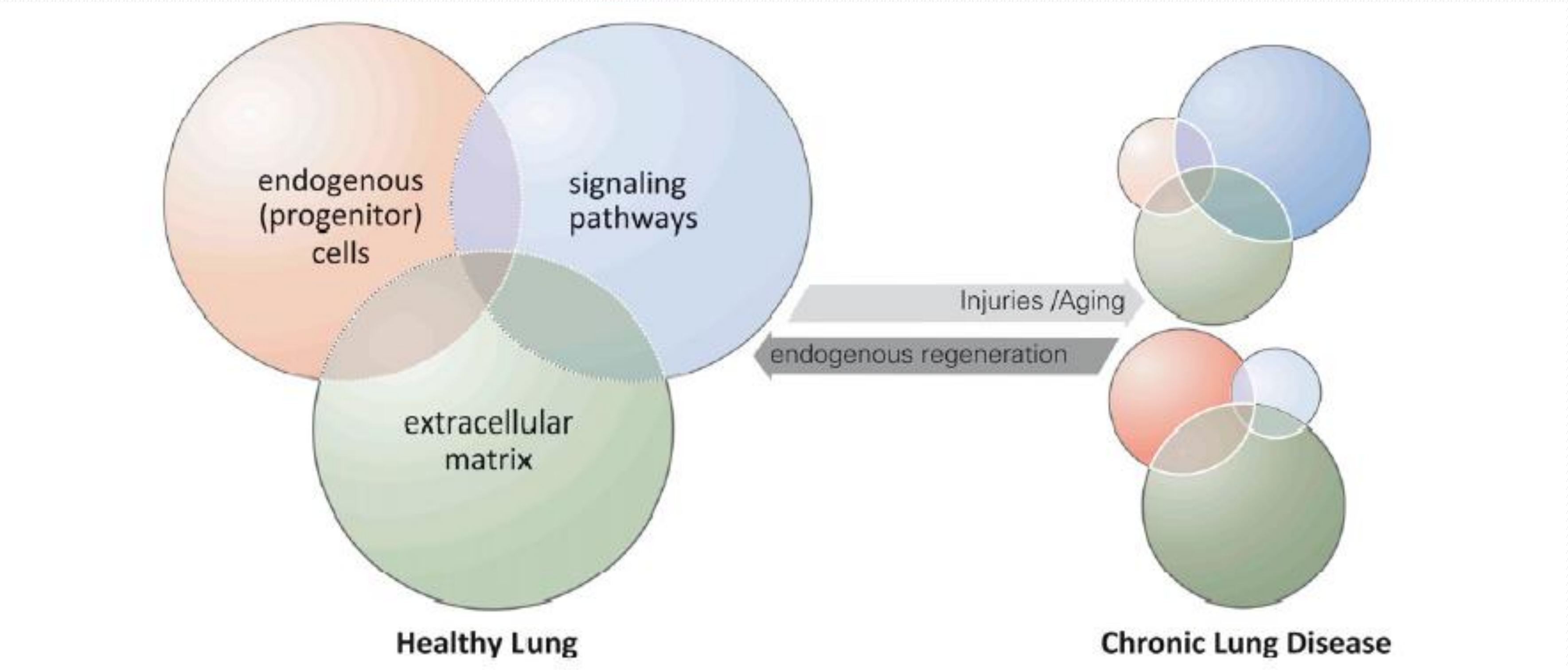
Increased epithelial expression of WNT/β-catenin signaling components in experimental lung fibrosis

Königshoff M., J Clin Invest 2009

Mechanisms of cell therapy in respiratory diseases



Manipulating Endogenous Progenitor/Stem Cells



Restore homeostasis and regeneration of damaged lungs

Rock J. and Königshoff M., Pulmonary Perspective 2012

Take-home message

1. Progenitor cells maintain and repair proximal and distal airway and alveolar epithelial cell lineages
2. Different progenitor cell subpopulations are recruited to repair injury of different type and severity
3. Niche microenvironment dictates regenerative potential
4. Repair invokes critical factors, genes and pathways involved in lung development

New insights into the biology of Lung Endogenous Progenitor/Stem Cells are required

Thank you