Epithelial-Mesenchymal Transition (EMT) in lung fibrosis:
a core determinant of epithelial-mesenchymal crosstalk

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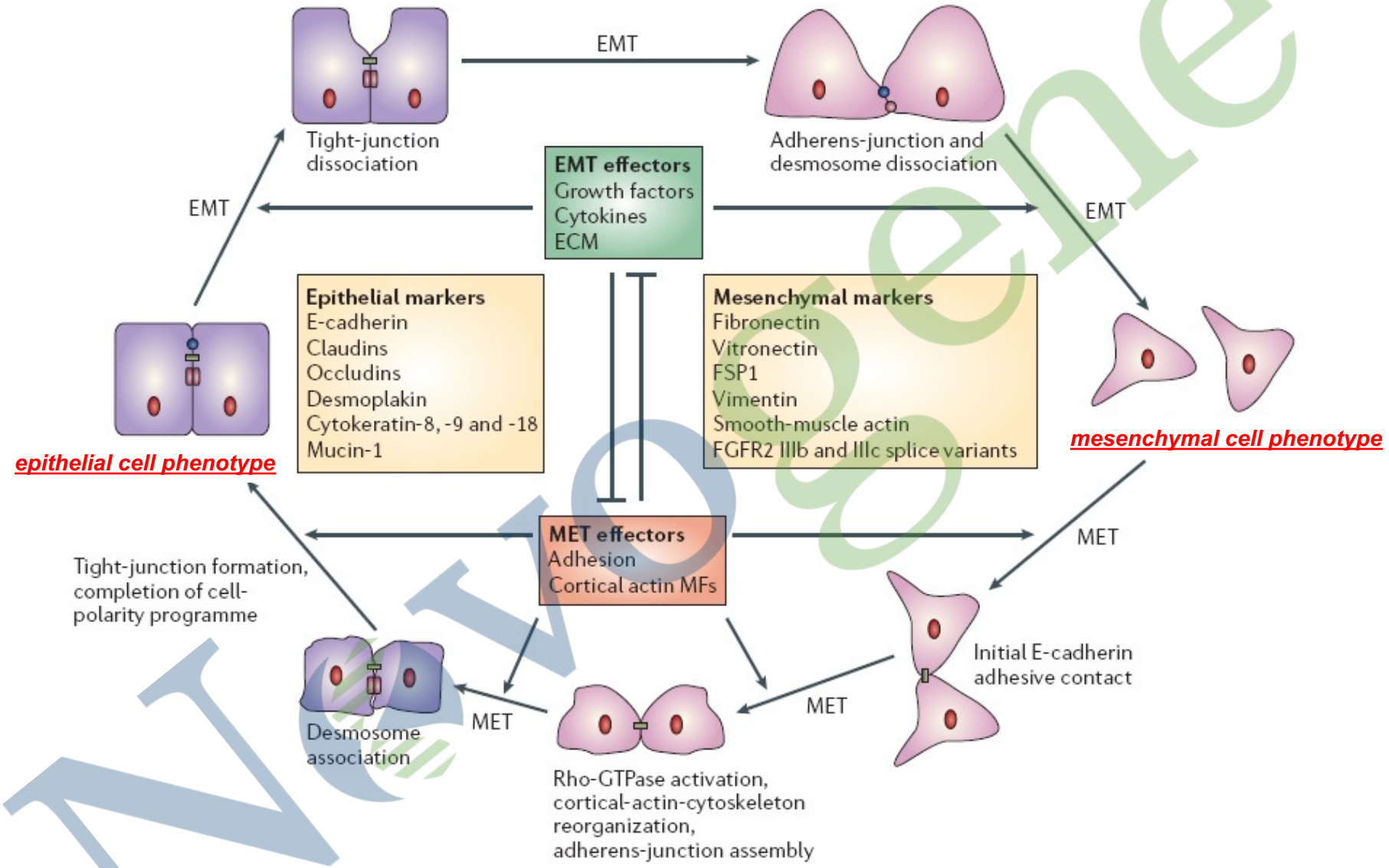
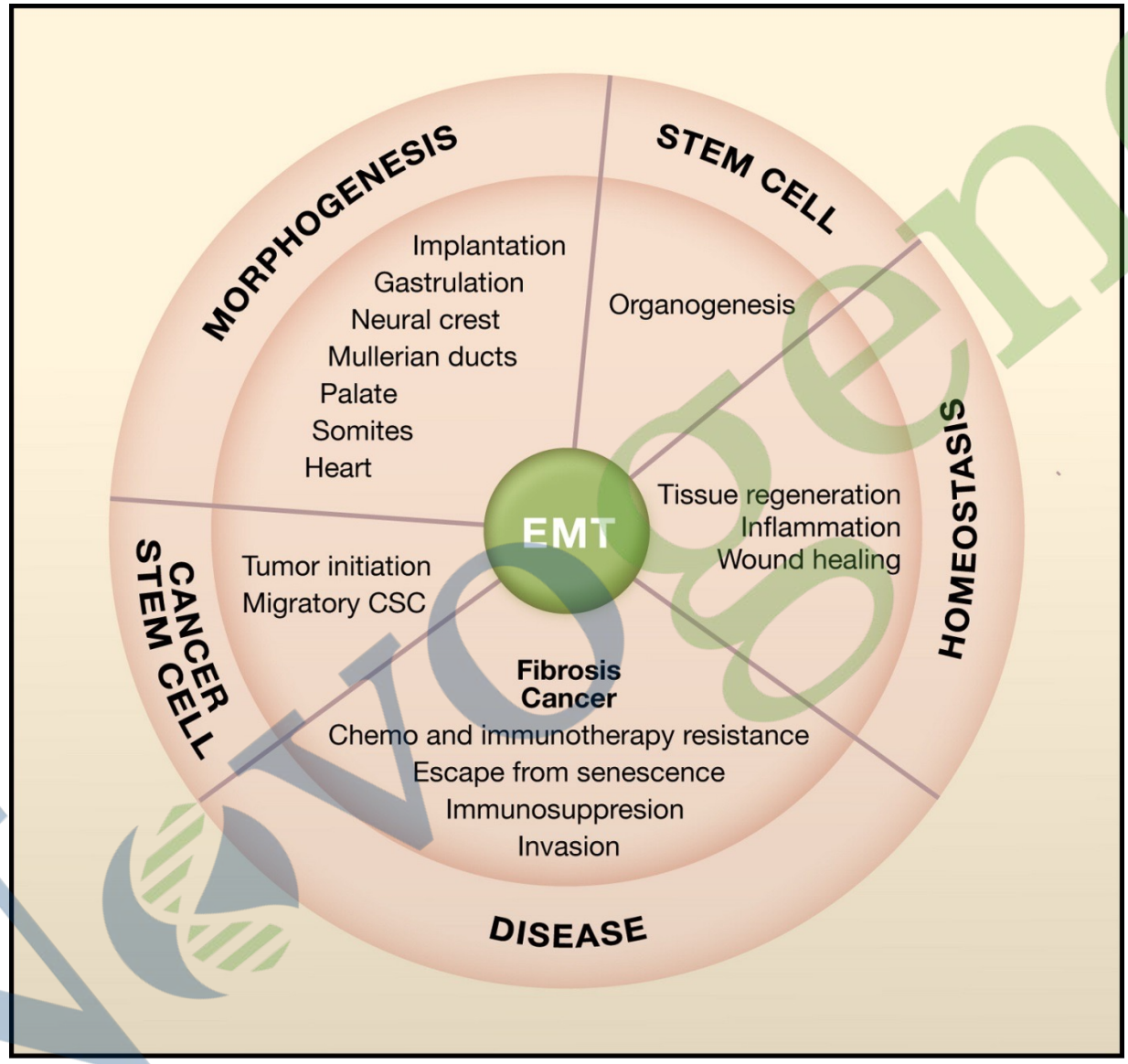


Snail, ZEB and bHLH factors in tumour progression: an alliance against the epithelial phenotype?

Héctor Peinado, David Olmeda and Amparo Cano

Complex networks orchestrate epithelial–mesenchymal transitions

Jean Paul Thiery and Jonathan P. Sleeman†*



Leading Edge
Review

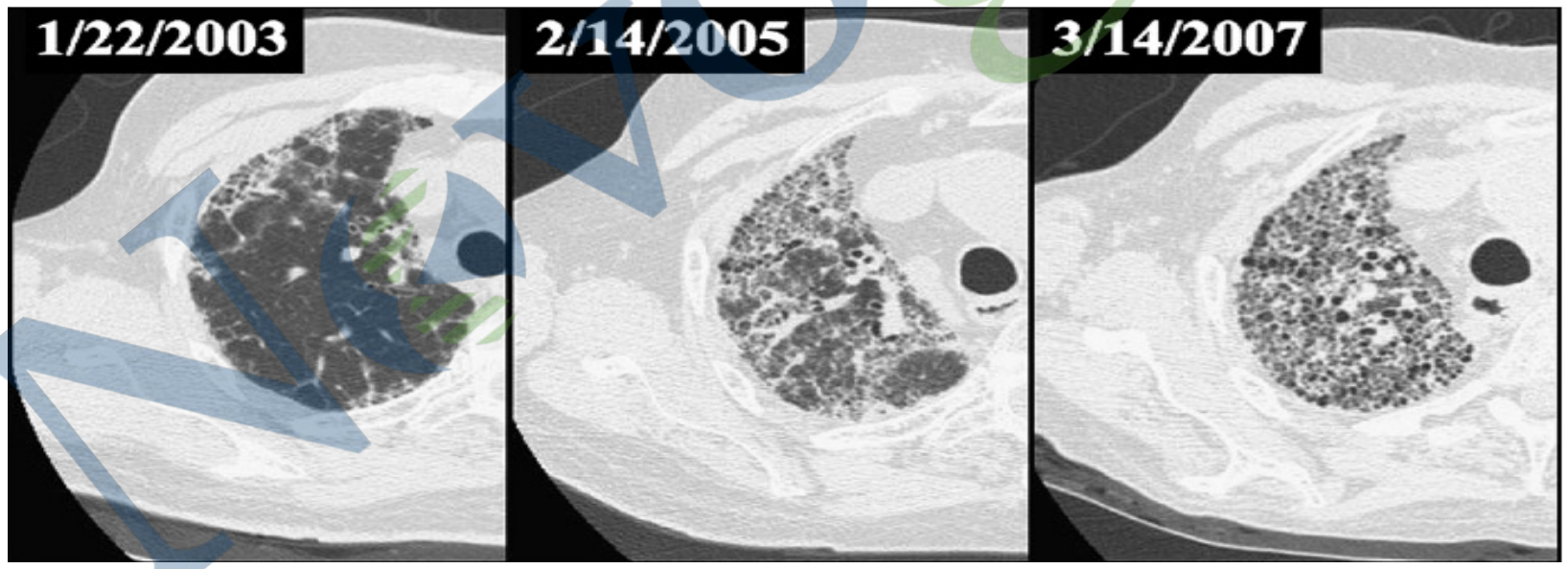
Cell

Epithelial-Mesenchymal Transitions in Development and Disease

Jean Paul Thiery,[1,2,3,*] Hervé Acloque,[4] Ruby Y.-J. Huang,[1,2,5] and M. Angela Nieto[4,*]

Idiopathic pulmonary fibrosis (IPF)

- A progressive fibrotic disease limited to the lungs
- > 5000 cases/year (UK)
- Incidence is increasing
- Median survival from time of diagnosis 3 years



Richeldi et al. *BMC Medicine* 2015; 13:237

Elicker et al. *Resp Med* 2010; 104:426-33

IDIOPATHIC PULMONARY FIBROSIS (IPF)

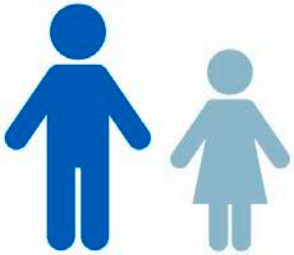
IPF AFFECTS BETWEEN

23

PEOPLE PER

100,000

EUROPE[1]



And is seen **more frequently in men**

Common symptoms:
- ✔ Shortness of breath
- ✔ Chronic dry cough
- ✔ Finger clubbing

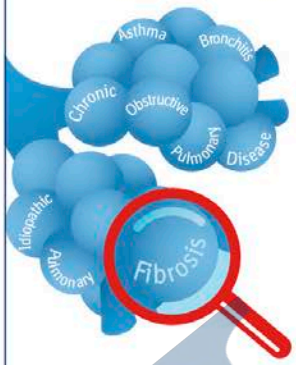
Occasional symptoms:
- ✔ Fatigue
- ✔ Weakness
- ✔ Weight loss

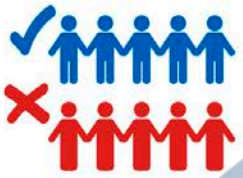
THE CAUSE IS UNKNOWN

but risk factors may include:

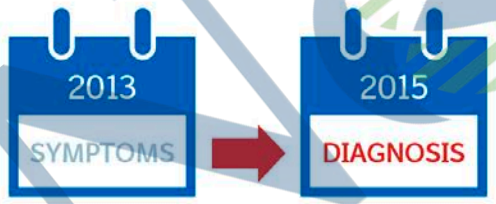
smoking, environmental exposures, chronic viral infections, abnormal acid reflux and family history of the disease

DIFFICULT TO DISTINGUISH





50% are misdiagnosed



Average time to diagnosis is **1-2 years** after onset of symptoms

About **5,000 PEOPLE** are diagnosed in the UK

EVERY YEAR[2]

1 in 3

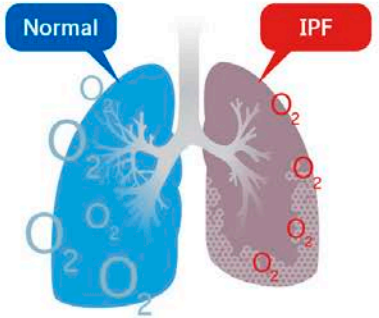
people are expected to die within the next 12 months

average life expectancy after diagnosis is 3 years[3]

50% die within 2 to 3 yrs after diagnosis

Delays in diagnosis are frequent and have a **highly negative impact on patients' quality of life**[4]

Resultant **scarring/honeycombing** in the lung restricts breathing and oxygen exchange



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

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ABSTRACT

BACKGROUND

In two of three phase 3 trials, pirfenidone, an oral antifibrotic therapy, reduced disease progression, as measured by the decline in forced vital capacity (FVC) or vital capacity, in patients with idiopathic pulmonary fibrosis; in the third trial, this end point was not achieved. We sought to confirm the beneficial effect of pirfenidone on disease progression in such patients.

METHODS

In this phase 3 study, we randomly assigned 555 patients with idiopathic pulmonary fibrosis to receive either oral pirfenidone (2403 mg per day) or placebo for 52 weeks. The primary end point was the change in FVC or death at week 52. Secondary end points were the 6-minute walk distance, progression-free survival, dyspnea, and death from any cause or from idiopathic pulmonary fibrosis.

RESULTS

In the pirfenidone group, as compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC (P<0.001). Pirfenidone reduced the decline in the 6-minute walk distance (P=0.04) and improved progression-free survival (P<0.001). There was no significant between-group difference in dyspnea scores (P=0.16) or in rates of death from any cause (P=0.10) or from idiopathic pulmonary fibrosis (P=0.23). However, in a prespecified pooled analysis incorporating results from two previous phase 3 trials, the between-group difference favoring pirfenidone was significant for death from any cause (P=0.01) and from idiopathic pulmonary fibrosis (P=0.006). Gastrointestinal and skin-related adverse events were more common in the pirfenidone group than in the placebo group but rarely led to treatment discontinuation.

CONCLUSIONS

Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis. Treatment was associated with an acceptable adverse effect profile and fewer deaths. (Funded by InterMune; ASCEND ClinicalTrials.gov number, NCT01366209.)

From the University of [illegible] cisco, San Francisco, Brisbane (W.Z.B., E. Cedars–Sinai Medical (P.W.N.) — all in C Clinica San Borja, Alfred Hospital, and Prince Cha QLD (P.M.H.); versity of Miar cine, Miami (N Medical Cent bia Universi (D.J.L.); Inov VA (S.D.N. Federal U (C.A.P.); olina, Ch System, NJ (R. Denv to Dr Univ Par 94

The NEW ENGLAND JOURNAL of MEDICINE

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Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

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ABSTRACT

BACKGROUND

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases. A phase 2 trial suggested that treatment with 150 mg of nintedanib twice daily reduced lung-function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.

METHODS

We conducted two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary end point was the annual rate of decline in forced vital capacity (FVC). Key secondary end points were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period.

RESULTS

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was −114.7 ml with nintedanib versus −239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and −113.6 ml with nintedanib versus −207.3 ml with placebo (difference, 93.7 ml; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with nintedanib, 1.15; 95% CI, 0.54 to 2.42; P=0.67); in INPULSIS-2, there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005). The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively, in INPULSIS-1 and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2.

CONCLUSIONS

In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients. (Funded by Boehringer Ingelheim; INPULSIS-1 and INPULSIS-2 ClinicalTrials.gov numbers, NCT01335464 and NCT01335477.)

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*A complete list of investigators in the INPULSIS trials is provided in the Supplementary Appendix, available at NEJM.org.

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2014

Lung fibrosis: an undervalued finding in COVID-19 pathological series

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With the COVID-19 pandemic having reached tremendous proportions, post-mortem series are under the limelight to explain many of the peculiar clinical findings. Pathological descriptions of disease are fundamental for understanding pathogenetic features and might inform new treatments. Indeed, the widely discussed identification of thrombosis in patients with COVID-19 has garnered much interest, and has resulted in new treatment strategies, with anticoagulants now part of patient management.

See Online for appendix

In their Article, Luca Carsana and colleagues[1] describe the lung findings of 38 patients who died with COVID-19 and show that early-phase or intermediate-phase diffuse alveolar damage is the main pathological finding, as well as fibrin thrombi in small arterial vessels.[1] Other autoptic series, composed of fewer cases, also show thrombotic events to be findings specifically related to COVID-19.[2,3] The fibrotic changes seen in patients who died with COVID-19 who had severe disease of long duration have been, however, only briefly touched upon in published studies, and no complete pathological description of these cases is available.

Between April 16, and May 4, 2020, we collected lung tissue using a cryobiopsy approach from eight patients in our institution who died in intensive care with COVID-19 (unpublished). Patients died after a mean disease duration of 31·3 days (SD 8·3), a much longer duration of illness than reported in the study by Carsana and colleagues, in which the mean time from symptom onset to death was 16 days (SD 6). Tissues obtained by cryobiopsy are comparable to specimens from live patients as the procedure is done within 30 min of death. We observed marked fibrotic lung parenchymal remodelling, characterised by fibroblast proliferation, airspace obliteration, and micro-honeycombing in many of the available cryobiopsies (appendix). This aspect has been described in other series,[1-3] but we feel it has not received as much attention as it should.

Presumably, the fibrotic pathological findings are unlikely to regress in patients with severe COVID-19 who survive, although prospective studies are necessary to identify long-term functional impairment.[4] Whether the cause of fibrotic findings in the lungs is viral infection, the secondary cytokine cascade, related to treatment or ventilation, or a mixture of all these things is unknown; however, tissue collection must be part of, and indeed become the basis for, more in-depth studies.[5]

As more pathological information is being collected from COVID-19 post-mortem series, a clearer picture of the disease, and its possible short-term and long-term complications, will emerge and hopefully aid treatment.

We declare no competing interests.

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FOCUS | REVIEW ARTICLE
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Post-acute COVID-19 syndrome

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for the coronavirus disease 2019 (COVID-19) pandemic, which has resulted in global healthcare crises and strained health resources. As the population of patients recovering from COVID-19 grows, it is paramount to establish an understanding of the healthcare issues surrounding them. COVID-19 is now recognized as a multi-organ disease with a broad spectrum of manifestations. Similarly to post-acute viral syndromes described in survivors of other virulent coronavirus epidemics, there are increasing reports of persistent and prolonged effects after acute COVID-19. Patient advocacy groups, many members of which identify themselves as long haulers, have helped contribute to the recognition of post-acute COVID-19, a syndrome characterized by persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms. Here, we provide a comprehensive review of the current literature on post-acute COVID-19, its pathophysiology and its organ-specific sequelae. Finally, we discuss relevant considerations for the multidisciplinary care of COVID-19 survivors and propose a framework for the identification of those at high risk for post-acute COVID-19 and their coordinated management through dedicated COVID-19 clinics.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen responsible for coronavirus disease 2019 (COVID-19), has caused morbidity and mortality at an unprecedented scale globally[1]. Scientific and clinical evidence is evolving on the subacute and long-term effects of COVID-19, which can affect multiple organ systems[2]. Early reports suggest residual effects of SARS-CoV-2 infection, such as fatigue, dyspnea, chest pain, cognitive disturbances, arthralgia and decline in quality of life[3-5]. Cellular damage, a robust innate immune response with inflammatory cytokine production, and a pro-coagulant state induced by SARS-CoV-2 infection may contribute to these sequelae[6-8]. Survivors of previous coronavirus infections, including the SARS epidemic of 2003 and the Middle East respiratory syndrome (MERS) outbreak of 2012, have demonstrated a similar constellation of persistent symptoms, reinforcing concern for clinically significant sequelae of COVID-19 (refs. [9-11]).

Systematic study of sequelae after recovery from acute COVID-19 is needed to develop an evidence-based multidisciplinary team

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Pulmonary fibrosis 4 months after COVID-19 is associated with severity of illness and blood leucocyte telomere length

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2021-217031).

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ABSTRACT

The risk factors for development of fibrotic-like radiographic abnormalities after severe COVID-19 are incompletely described and the extent to which CT findings correlate with symptoms and physical function after hospitalisation remains unclear. At 4 months after hospitalisation, fibrotic-like patterns were more common in those who underwent mechanical ventilation (72%) than in those who did not (20%). We demonstrate that severity of initial illness, duration of mechanical ventilation, lactate dehydrogenase on admission and leucocyte telomere length are independent risk factors for fibrotic-like radiographic abnormalities. These fibrotic-like changes correlate with lung function, cough and measures of frailty, but not with dyspnoea.

INTRODUCTION

Reports of hospitalised COVID-19 survivors show that there are persistent symptoms, radiographic abnormalities and physiological impairments months after the initial illness.[1 2] Persistent chest imaging abnormalities and histopathological findings of lung fibrosis were also found in a majority of survivors of the SARS-CoV-1 2003 outbreak,[3 4] suggesting that the SARS viruses may lead to a worse fibroproliferative response than other pneumonias.

Cohort studies of COVID-19 survivors report that severity of the initial illness is associated with a greater risk of persistent CT abnormalities,[1 2 5 6] especially for patients requiring supplemental oxygen or mechanical ventilation, but independent clinical, biomarker and genomic risk factors have not been identified. Also, the extent to which CT findings correlate with symptoms and physical function remains unclear. To address knowledge gaps, we conducted a prospective cohort study of survivors hospitalised with severe COVID-19, half of whom were mechanically ventilated, with 4-month and 15 May 2020 who required supplemental oxygen. At 4 months after hospitalisation, participants underwent a non-contrast high-resolution chest CT (HRCT) scan, pulmonary function testing, measurement of 6-minute walk distance (6MWD), assessment of the frailty phenotype and a blood draw for isolation of genomic DNA. Radiographic patterns were categorised and quantitated using a severity scoring system developed by ARDSnet and used in acute respiratory distress syndrome (ARDS) survivors,[7] and classified into two groups (non-fibrotic or fibrotic). Fibrotic-like patterns included those with reticulations, traction bronchiectasis or honeycombing. Telomere length of genomic DNA isolated from blood drawn at the 4-month follow-up visit was measured by a quantitative PCR assay.[8]

We calculated Spearman's rank correlation coefficients between continuous data. We created separate generalised additive logistic models (GAMs) to test adjusted associations between the risk of fibrotic-like patterns on CT scan and independent continuous variables identified in univariable analysis. Due to the moderate cohort size and rate of fibrotic-like radiographic abnormalities, we used generalised covariate balanced propensity scores to adjust for potential confounders. We estimated adjusted ORs using logistic regression models if there was no evidence of non-linearity.

RESULTS

We enrolled 76 patients meeting eligibility criteria (online supplemental figure S1); demographic and clinical features are shown in online supplemental table S1. All participants required supplemental oxygen during hospitalisation, and 32 (42%) required mechanical ventilation.

A median of 4.4 (IQR 4.0–4.8) months after hospitalisation, the most common radiographic abnormality was ground glass opacities (43%)

6-month consequences of COVID-19 in patients discharged from hospital: a cohort study

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Summary

Background The long-term health consequences of COVID-19 remain largely unclear. The aim of this study was to describe the long-term health consequences of patients with COVID-19 who have been discharged from hospital and investigate the associated risk factors, in particular disease severity.

Methods We did an ambidirectional cohort study of patients with confirmed COVID-19 who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7, 2020, and May 29, 2020. Patients who died before follow-up, patients for whom follow-up would be difficult because of psychotic disorders, dementia, or re-admission to hospital, those who were unable to move freely due to concomitant osteoarthropathy or immobile before or after discharge due to diseases such as stroke or pulmonary embolism, those who declined to participate, those who could not be contacted, and those living outside of Wuhan or in nursing or welfare homes were all excluded. All patients were interviewed with a series of questionnaires for evaluation of symptoms and health-related quality of life, underwent physical examinations and a 6-min walking test, and received blood tests. A stratified sampling procedure was used to sample patients according to their highest seven-category scale during their hospital stay as 3, 4, and 5–6, to receive pulmonary function test, high resolution CT of the chest, and ultrasonography. Enrolled patients who had participated in the Lopinavir Trial for Suppression of SARS-CoV-2 in China received severe acute respiratory syndrome coronavirus 2 antibody tests. Multivariable adjusted linear or logistic regression models were used to evaluate the association between disease severity and long-term health consequences.

Findings In total, 1733 of 2469 discharged patients with COVID-19 were enrolled after 736 were excluded. Patients had a median age of 57·0 (IQR 47·0–65·0) years and 897 (52%) were men. The follow-up study was done from June 16, to Sept 3, 2020, and the median follow-up time after symptom onset was 186·0 (175·0–199·0) days. Fatigue or muscle weakness (63%, 1038 of 1655) and sleep difficulties (26%, 437 of 1655) were the most common symptoms. Anxiety or depression was reported among 23% (367 of 1617) of patients. The proportions of median 6-min walking distance less than the lower limit of the normal range were 24% for those at severity scale 3, 22% for severity scale 4, and 29% for severity scale 5–6. The corresponding proportions of patients with diffusion impairment were 22% for severity scale 3, 29% for scale 4, and 56% for scale 5–6, and median CT scores were 3·0 (IQR 2·0–5·0) for severity scale 3, 4·0 (3·0–5·0) for scale 4, and 5·0 (4·0–6·0) for scale 5–6. After multivariable adjustment, patients showed an odds ratio (OR) 1·61 (95% CI 0·80–3·25) for scale 4 versus scale 3 and 4·60 (1·85–11·48) for scale 5–6 versus scale 3 for diffusion impairment; OR 0·88 (0·66–1·17) for scale 4 versus scale 3 and OR 1·77 (1·05–2·97) for scale 5–6 versus scale 3 for anxiety or depression, and OR 0·74 (0·58–0·96) for scale 4 versus scale 3 and 2·69 (1·46–4·96) for scale 5–6 versus scale 3 for fatigue or muscle weakness. Of 94 patients with blood antibodies tested at follow-up, the seropositivity (96·2% vs 58·5%) and median titres (19·0 vs 10·0) of the neutralising antibodies were significantly lower compared with at the acute phase. 107 of 822 participants without acute kidney injury and with estimated glomerular filtration rate (eGFR) 90 mL/min per 1·73 m^2 or more at acute phase had eGFR less than 90 mL/min per 1·73 m^2 at follow-up.

Interpretation At 6 months after acute infection, COVID-19 survivors were mainly troubled with fatigue or muscle weakness, sleep difficulties, and anxiety or depression. Patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations, and are the main target population for intervention of long-term recovery.

Funding National Natural Science Foundation of China, Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences, National Key Research and Development Program of China, Major Projects of National Science and Technology on New Drug Creation and Development of Pulmonary Tuberculosis, and Peking Union Medical College Foundation.

3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study

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For the Chinese translation of the Summary see Online for appendix 1

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Summary

Background The consequences of COVID-19 in those who recover from acute infection requiring hospitalisation have yet to be clearly defined. We aimed to describe the temporal trends in respiratory outcomes over 12 months in patients hospitalised for severe COVID-19 and to investigate the associated risk factors.

Methods In this prospective, longitudinal, cohort study, patients admitted to hospital for severe COVID-19 who did not require mechanical ventilation were prospectively followed up at 3 months, 6 months, 9 months, and 12 months after discharge from Renmin Hospital of Wuhan University, Wuhan, China. Patients with a history of hypertension; diabetes; cardiovascular disease; cancer; and chronic lung disease, including asthma or chronic obstructive pulmonary disease; or a history of smoking documented at time of hospital admission were excluded at time of electronic case-note review. Patients who required intubation and mechanical ventilation were excluded given the potential for the consequences of mechanical ventilation itself to influence the factors under investigation. During the follow-up visits, patients were interviewed and underwent physical examination, routine blood test, pulmonary function tests (ie, diffusing capacity of the lungs for carbon monoxide [DLCO]; forced expiratory flow between 25% and 75% of forced vital capacity [FVC]; functional residual capacity; FVC; FEV_1; residual volume; total lung capacity; and vital capacity), chest high-resolution CT (HRCT), and 6-min walk distance test, as well as assessment using a modified Medical Research Council dyspnoea scale (mMRC).

Findings Between Feb 1, and March 31, 2020, of 135 eligible patients, 83 (61%) patients participated in this study. The median age of participants was 60 years (IQR 52–66). Temporal improvement in pulmonary physiology and exercise capacity was observed in most patients; however, persistent physiological and radiographic abnormalities remained in some patients with COVID-19 at 12 months after discharge. We found a significant reduction in DLCO over the study period, with a median of 77% of predicted (IQR 67–87) at 3 months, 76% of predicted (68–90) at 6 months, and 88% of predicted (78–101) at 12 months after discharge. At 12 months after discharge, radiological changes persisted in 20 (24%) patients. Multivariate logistic regression showed increasing odds of impaired DLCO associated with female sex (odds ratio 8·61 [95% CI 2·83–26·2; p=0·0002) and radiological abnormalities were associated with peak HRCT pneumonia scores during hospitalisation (1·36 [1·13–1·62]; p=0·0009).

Interpretation In most patients who recovered from severe COVID-19, dyspnoea scores and exercise capacity improved over time; however, in a subgroup of patients at 12 months we found evidence of persistent physiological and radiographic change. A unified pathway for the respiratory follow-up of patients with COVID-19 is required.

Funding National Natural Science Foundation of China, UK Medical Research Council, and National Institute for Health Research Southampton Biomedical Research Centre.

1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study

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See Editorial page 775

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Summary

Background The full range of long-term health consequences of COVID-19 in patients who are discharged from hospital is largely unclear. The aim of our study was to comprehensively compare consequences between 6 months and 12 months after symptom onset among hospital survivors with COVID-19.

Methods We undertook an ambidirectional cohort study of COVID-19 survivors who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7 and May 29, 2020. At 6-month and 12-month follow-up visit, survivors were interviewed with questionnaires on symptoms and health-related quality of life (HRQoL), and received a physical examination, a 6-min walking test, and laboratory tests. They were required to report their health-care use after discharge and work status at the 12-month visit. Survivors who had completed pulmonary function tests or had lung radiographic abnormality at 6 months were given the corresponding tests at 12 months. Non-COVID-19 participants (controls) matched for age, sex, and comorbidities were interviewed and completed questionnaires to assess prevalent symptoms and HRQoL. The primary outcomes were symptoms, modified British Medical Research Council (mMRC) score, HRQoL, and distance walked in 6 min (6MWD). Multivariable adjusted logistic regression models were used to evaluate the risk factors of 12-month outcomes.

Findings 1276 COVID-19 survivors completed both visits. The median age of patients was 59·0 years (IQR 49·0–67·0) and 681 (53%) were men. The median follow-up time was 185·0 days (IQR 175·0–198·0) for the 6-month visit and 349·0 days (337·0–361·0) for the 12-month visit after symptom onset. The proportion of patients with at least one sequelae symptom decreased from 68% (831/1227) at 6 months to 49% (620/1272) at 12 months (p<0·0001). The proportion of patients with dyspnoea, characterised by mMRC score of 1 or more, slightly increased from 26% (313/1185) at 6-month visit to 30% (380/1271) at 12-month visit (p=0·014). Additionally, more patients had anxiety or depression at 12-month visit (26% [331/1271] at 12-month visit vs 23% [274/1187] at 6-month visit; p=0·015). No significant difference on 6MWD was observed between 6 months and 12 months. 88% (422/479) of patients who were employed before COVID-19 had returned to their original work at 12 months. Compared with men, women had an odds ratio of 1·43 (95% CI 1·04–1·96) for fatigue or muscle weakness, 2·00 (1·48–2·69) for anxiety or depression, and 2·97 (1·50–5·88) for diffusion impairment. Matched COVID-19 survivors at 12 months had more problems with mobility, pain or discomfort, and anxiety or depression, and had more prevalent symptoms than did controls.

Interpretation Most COVID-19 survivors had a good physical and functional recovery during 1-year follow-up, and had returned to their original work and life. The health status in our cohort of COVID-19 survivors at 12 months was still lower than that in the control population.

Funding Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences, the National Natural Science Foundation of China, the National Key Research and Development Program of China, Major Projects of National Science and Technology on New Drug Creation and Development of Pulmonary Tuberculosis, the China Evergrande Group, Jack Ma Foundation, Sino Biopharmaceutical, Ping An Insurance (Group), and New Sunshine Charity Foundation.

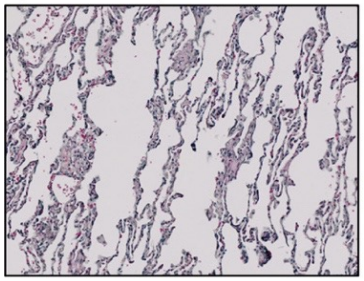
Introduction

The continuing spread of SARS-CoV-2 remains a public health emergency of international concern, resulting in an enormous global disease burden. As of early August, 2021, more than 200 million COVID-19 cases have been confirmed globally, and more than 4·3 million people have died following SARS-CoV-2 infection.[1]

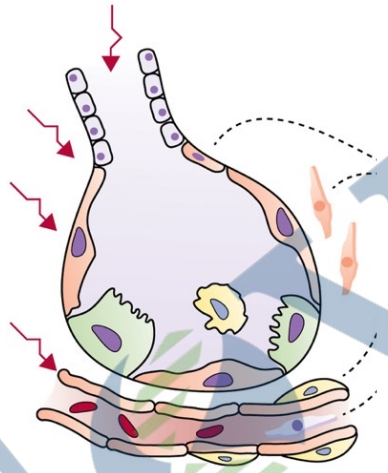
The sequelae after recovery from acute COVID-19 have been widely reported[2-11] and have become an increasing concern. In our previous cohort study with a median follow-up time of 6 months after symptom onset, approximately three-quarters of COVID-19 survivors discharged from hospital still had persisting symptoms, and patients who were critically ill during hospital stay had higher risk of lung diffusion impairment and radiographic abnormality than did those who had lower disease severity.[2] Up to now, only two small studies with no more than 120 COVID-19

IPF pathogenesis remains poorly understood

Dysfunctional epithelium

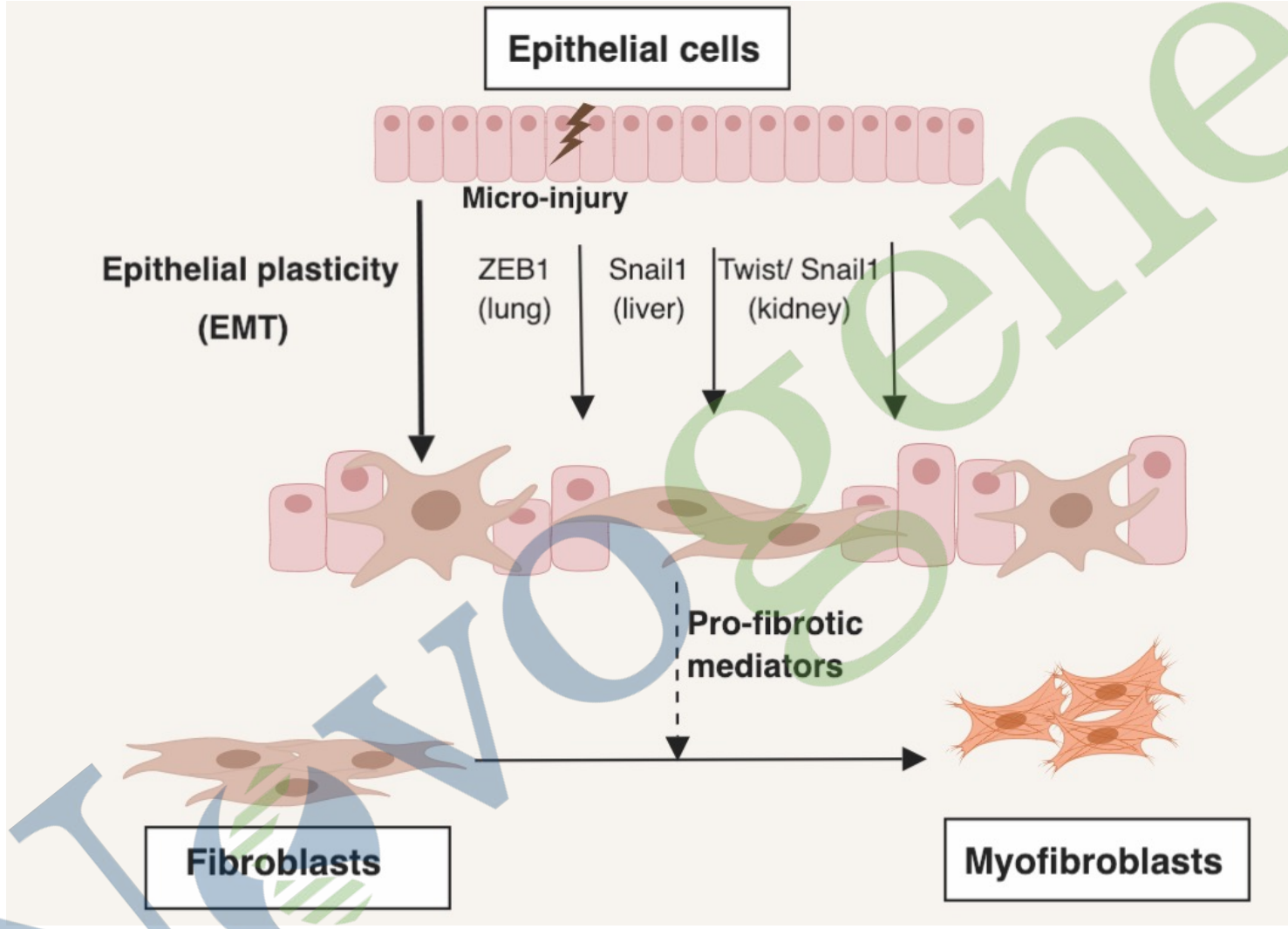


- Genetic susceptibility
- Ageing
- Recurrent microinjury



- Activation of epithelial cells
- Basement membrane disruption
- Dysregulated signalling
- Immune activation

Richeldi, Collard, Jones. *Lancet* 2017;389:1941-52



Hill C, Jones MG, Davies DE, Wang Y. Epithelial-Mesenchymal Transition Contributes to Pulmonary Fibrosis via Aberrant Epithelial/Fibroblastic Cross-Talk. J Lung Health Dis (2019) 3(2): 31-35

Journal of Lung Health and Diseases

Minireview Open Access

Epithelial-Mesenchymal Transition Contributes to Pulmonary Fibrosis via Aberrant Epithelial/Fibroblastic Cross-Talk

Charlotte Hill[1], Mark G. Jones[2,3], Donna E. Davies[2,3,4] and Yihua Wang[1,4*]

Bioinformatics identify EGFR activation in IPF

P value	Q value	Pathway	Source
6.76×10^{-8}	**2.13×10^{-4}**	**EGFR1**	**NetPath**
1.05×10^{-6}	1.62×10^{-3}	FoxO signaling pathway - Homo sapiens	KEGG
1.54×10^{-6}	1.62×10^{-3}	Amoebiasis - Homo sapiens	KEGG
3.11×10^{-6}	2.45×10^{-3}	Interleukin-6 signaling	Reactome
6.73×10^{-6}	3.94×10^{-3}	Hemostasis	Reactome
7.51×10^{-6}	3.94×10^{-3}	Leptin	NetPath
1.93×10^{-5}	8.69×10^{-3}	Extracellular matrix organization	Reactome
2.41×10^{-5}	9.50×10^{-3}	p53 signaling pathway - Homo sapiens	KEGG
4.55×10^{-5}	1.57×10^{-2}	Leptin signaling pathway	Wikipathways
5.00×10^{-5}	**1.57×10^{-2}**	**MAPK1 (ERK2) activation**	**Reactome**
6.00×10^{-5}	1.72×10^{-2}	Thyroid hormone signaling pathway - Homo sapiens	KEGG
7.23×10^{-5}	1.87×10^{-2}	ECM-receptor interaction - Homo sapiens	KEGG
9.32×10^{-5}	1.87×10^{-2}	Platelet activation - Homo sapiens	KEGG
9.60×10^{-5}	1.87×10^{-2}	Retinoblastoma (RB) in Cancer	Wikipathways
1.81×10^{-4}	1.87×10^{-2}	Alpha6Beta4Integrin	NetPath
1.81×10^{-4}	1.87×10^{-2}	Ectoderm Differentiation	Wikipathways
1.83×10^{-4}	**1.87×10^{-2}**	**EGF-EGFR Signaling Pathway**	**Wikipathways**
2.25×10^{-4}	1.87×10^{-2}	Toxoplasmosis	Wikipathways
2.49×10^{-4}	1.87×10^{-2}	Polycystic Kidney Disease Pathway	Wikipathways

SnapShot: Ras Signaling

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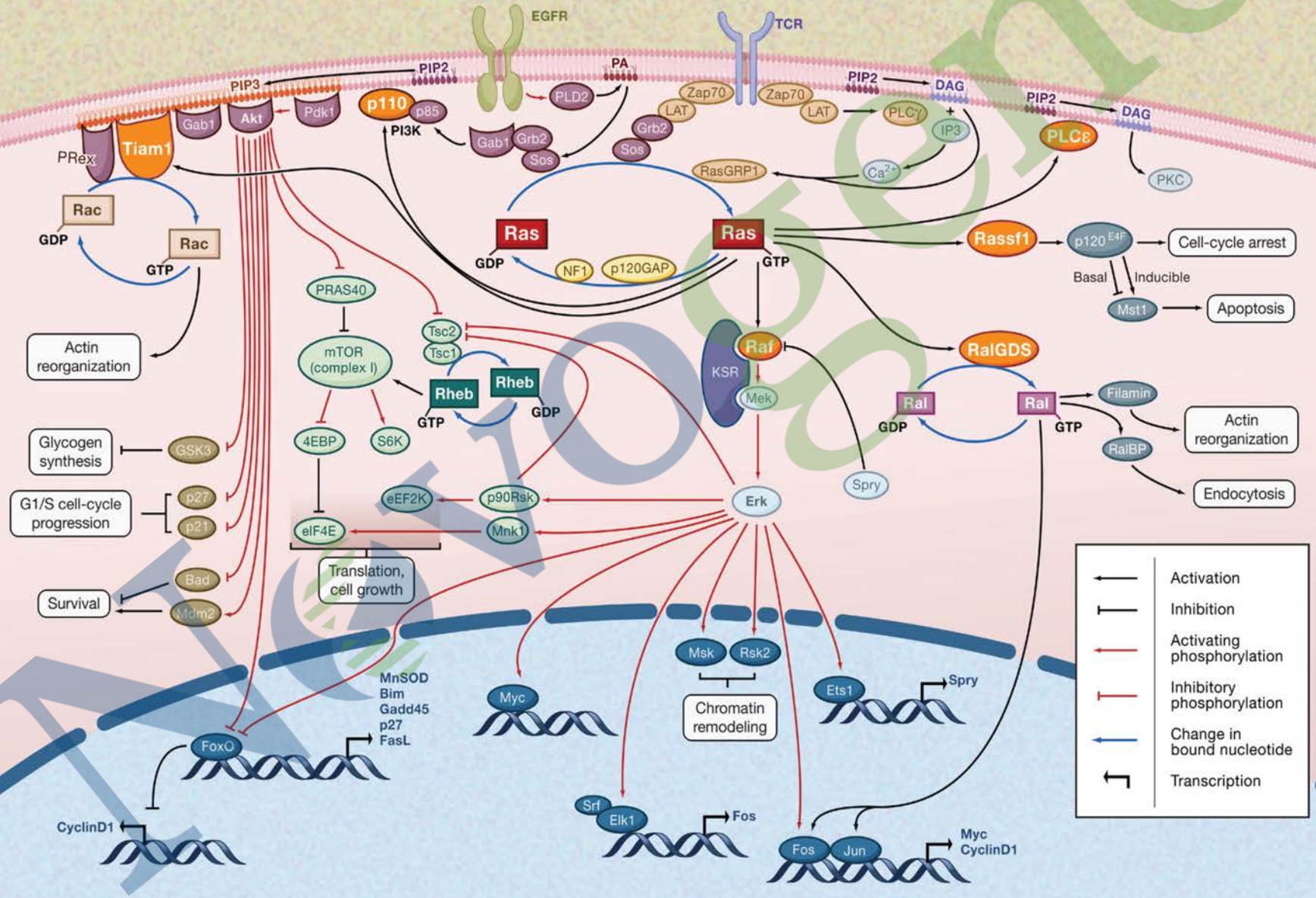
Cancer Research UK London Research Institute, London WC2A 3PX, UK

See online version for legend and references.



frontiers in Molecular Biosciences

ORIGINAL RESEARCH
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Quantitative Proteomic Analysis in Alveolar Type II Cells Reveals the Different Capacities of RAS and TGF-β to Induce Epithelial–Mesenchymal Transition

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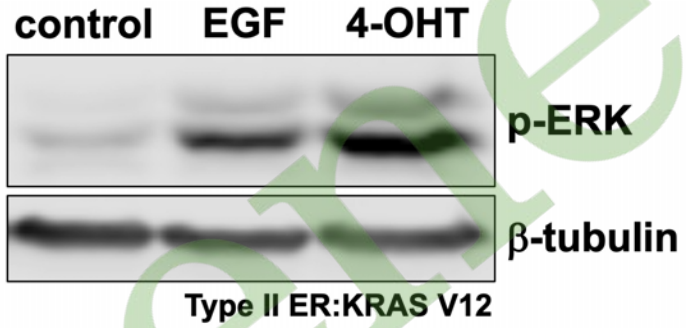
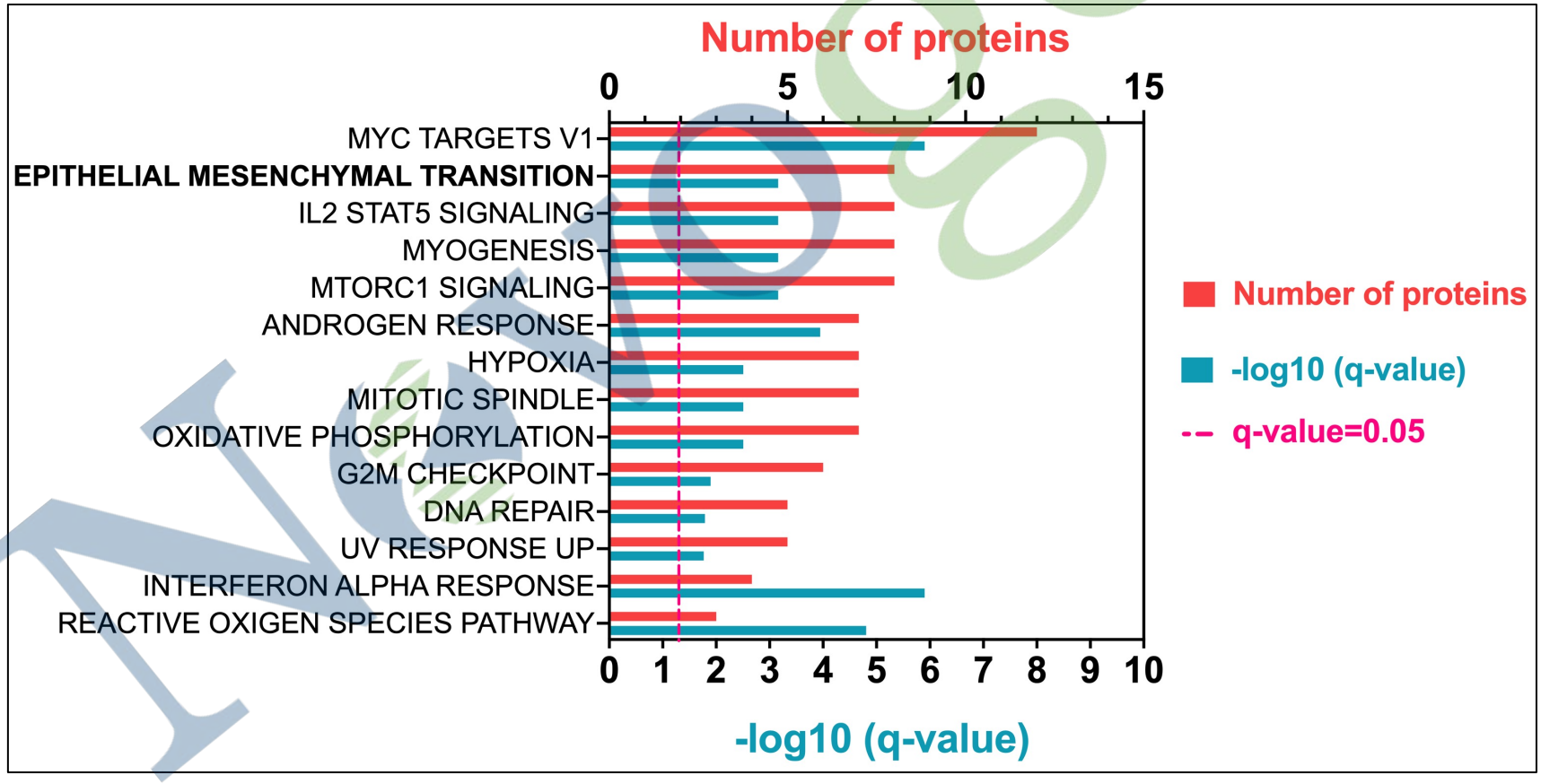
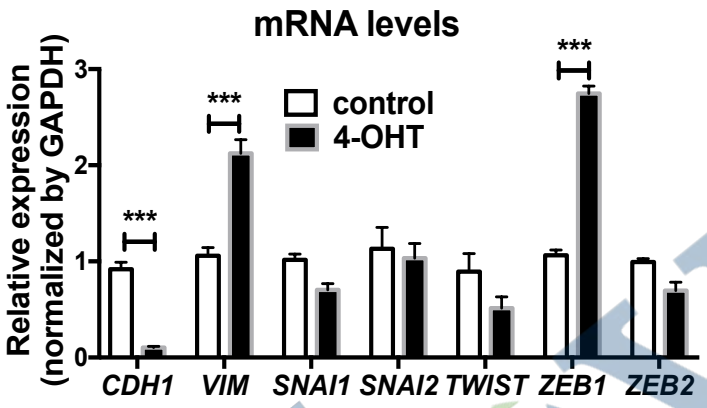
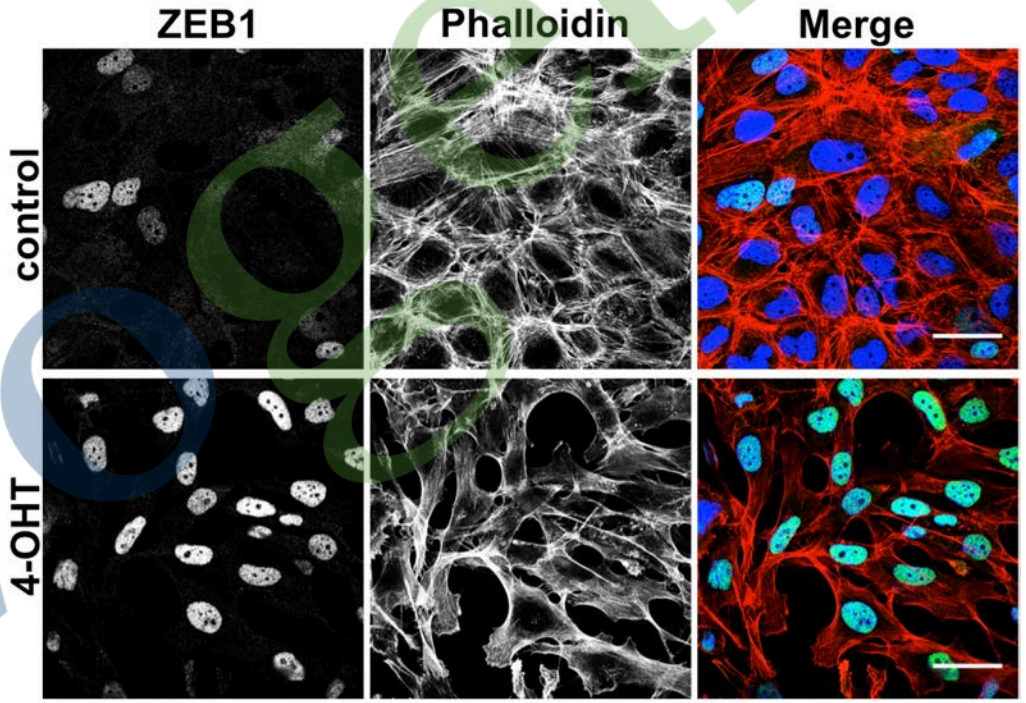


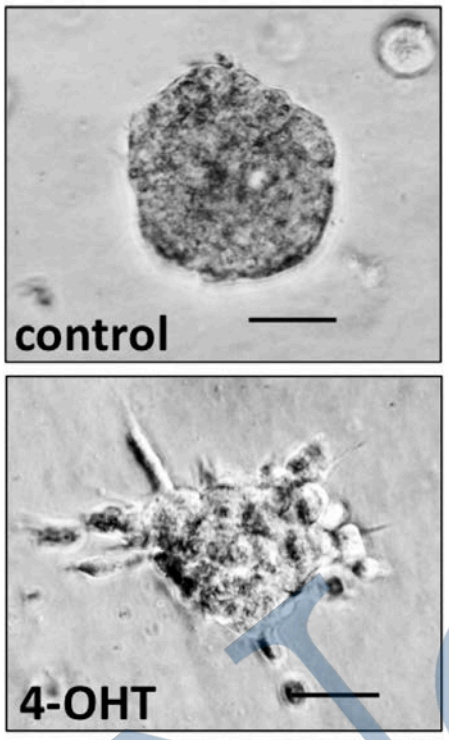


EGFR-RAS activation induces EMT in ATII cells (2D)

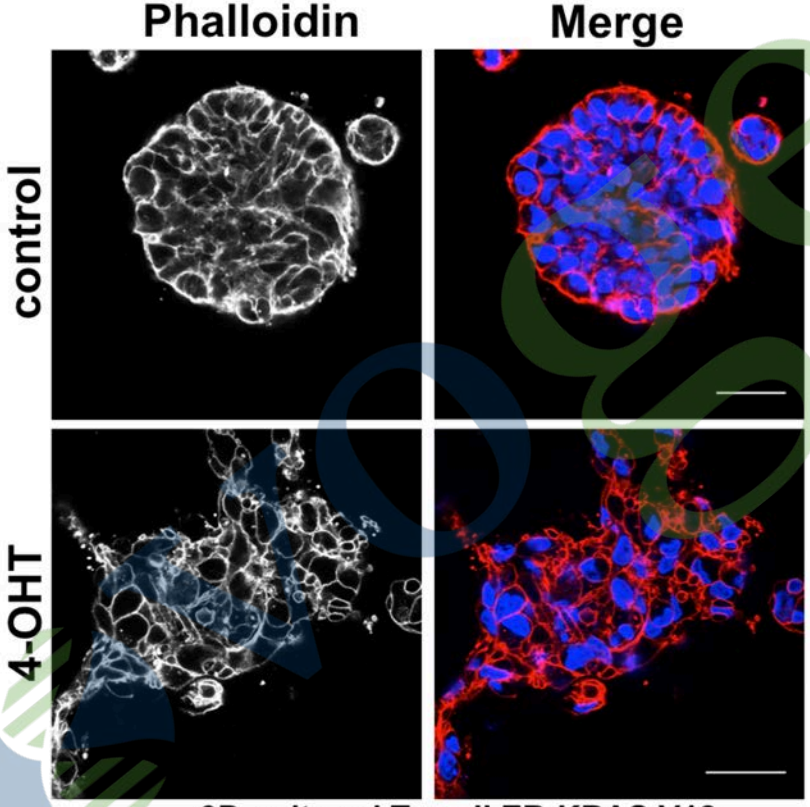




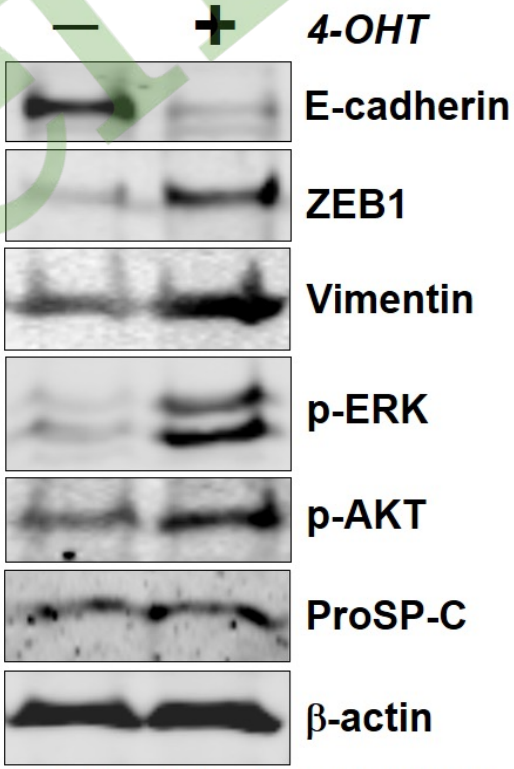
EGFR-RAS activation induces EMT in ATII cells (3D)



Type II ER:KRAS V12

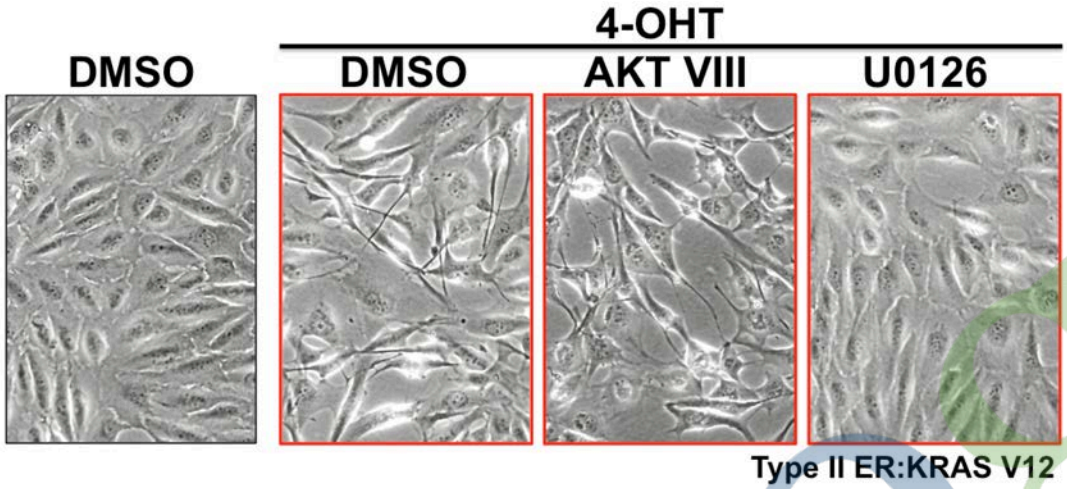


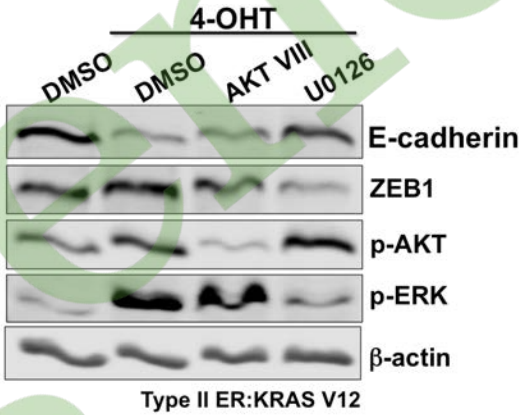
3D-cultured Type II ER:KRAS V12

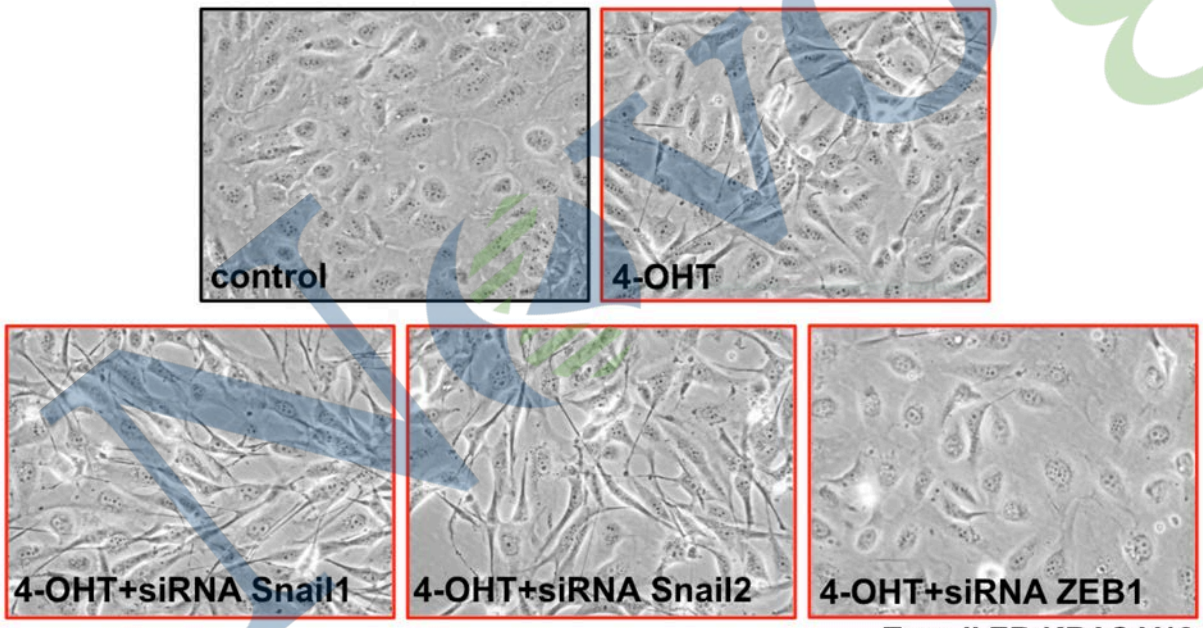


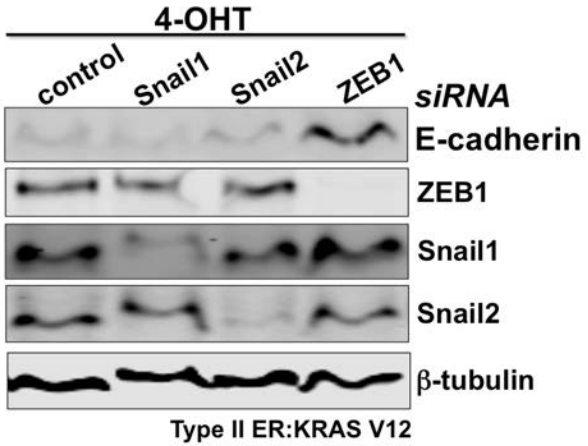
3D cultured Type II ER:KRAS V12

EGFR-RAS induces EMT via ERK-ZEB1 pathway



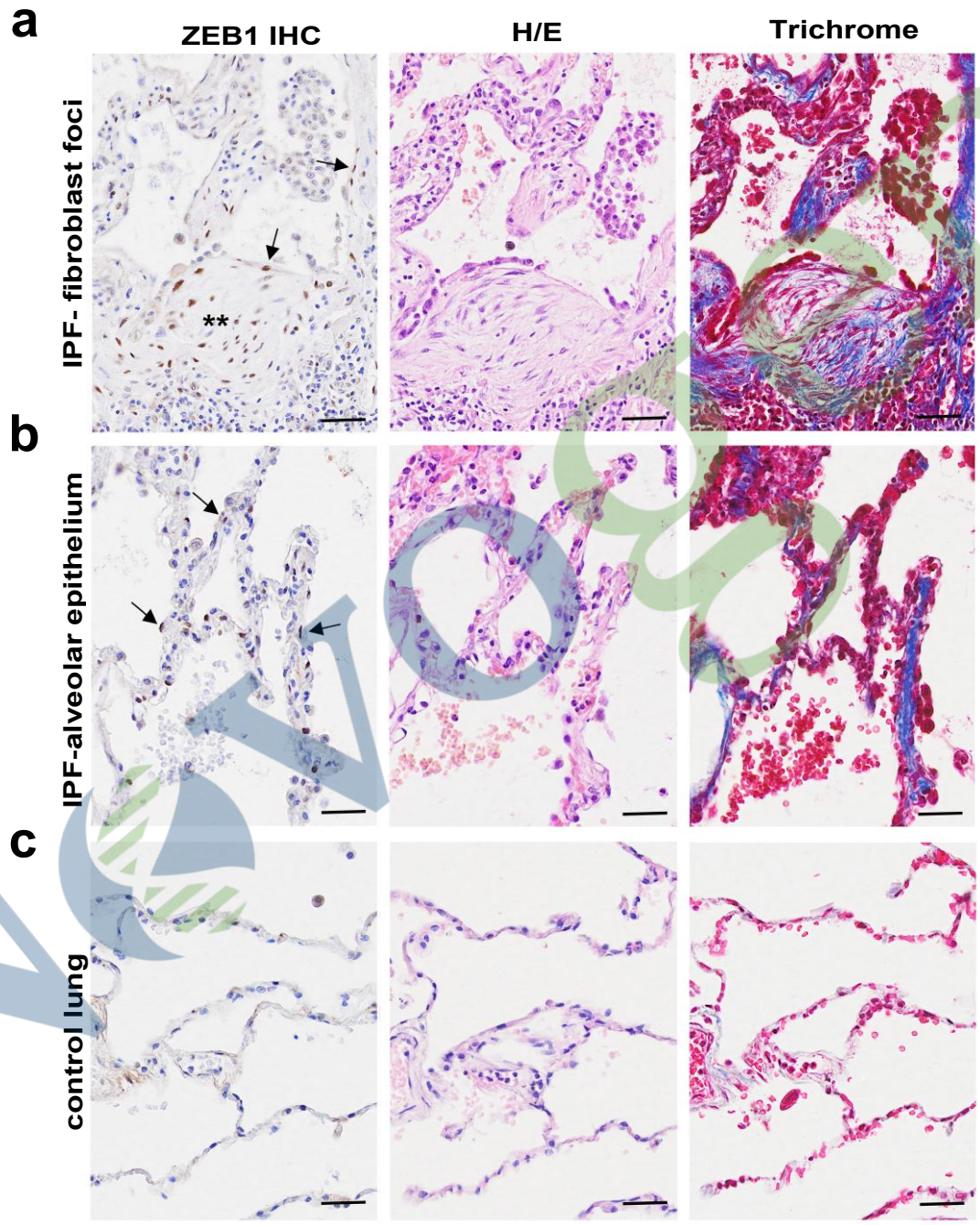




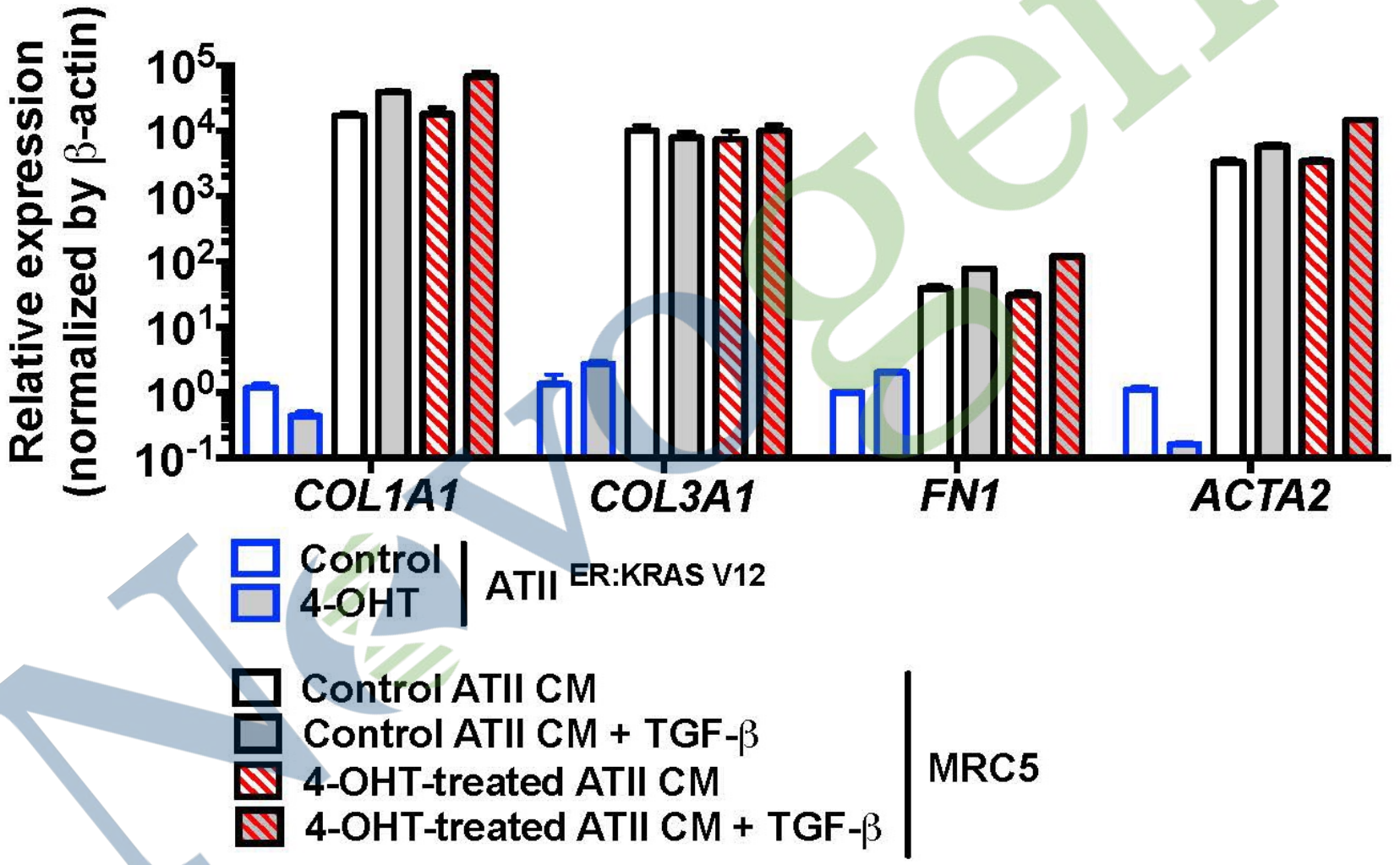


ZEB1 is up-regulated in IPF lungs

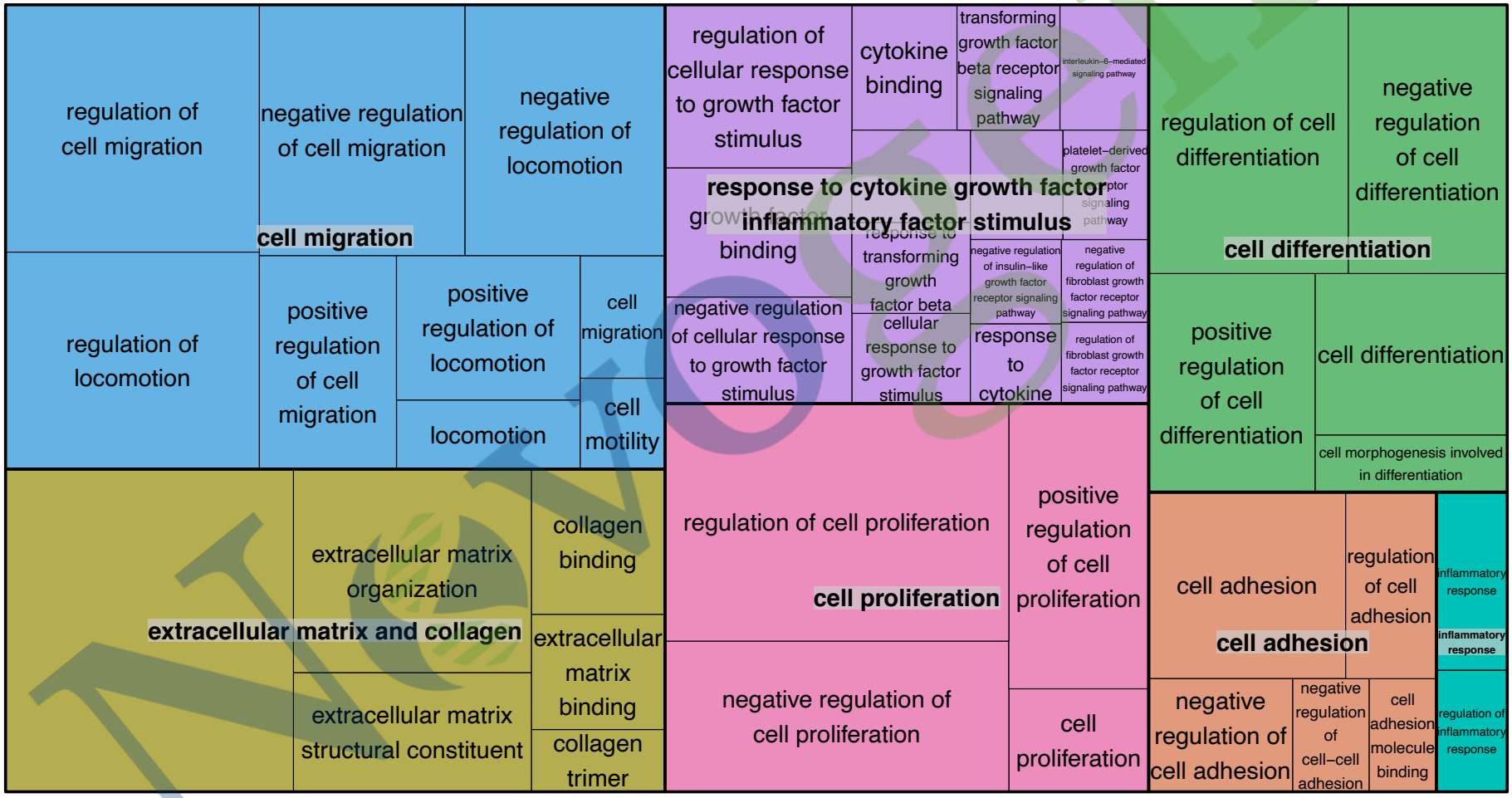
Figure 4



ATII cells produce extremely low levels of ECM genes even after the induction of EMT



Global transcriptomic changes in fibroblasts exposed to conditioned media from RAS-activated ATII cells



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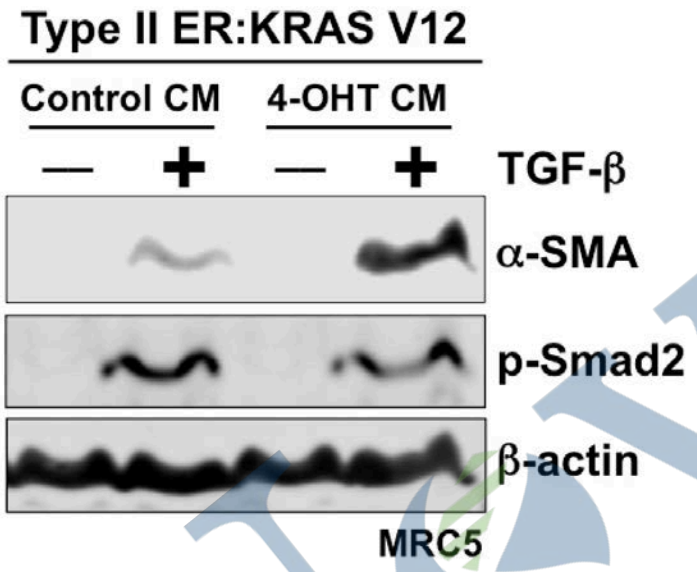
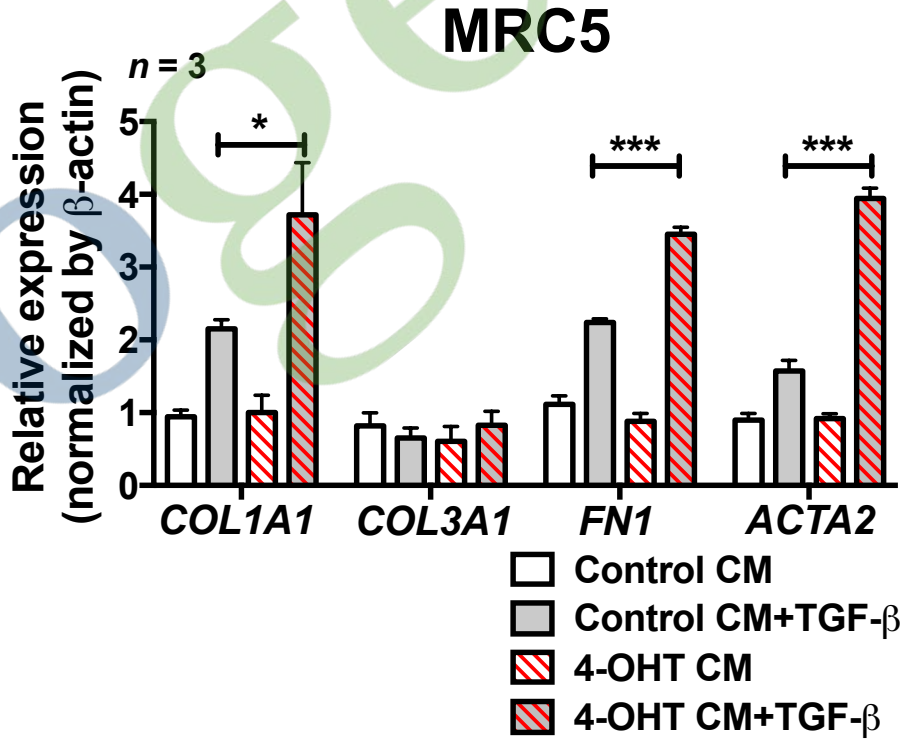
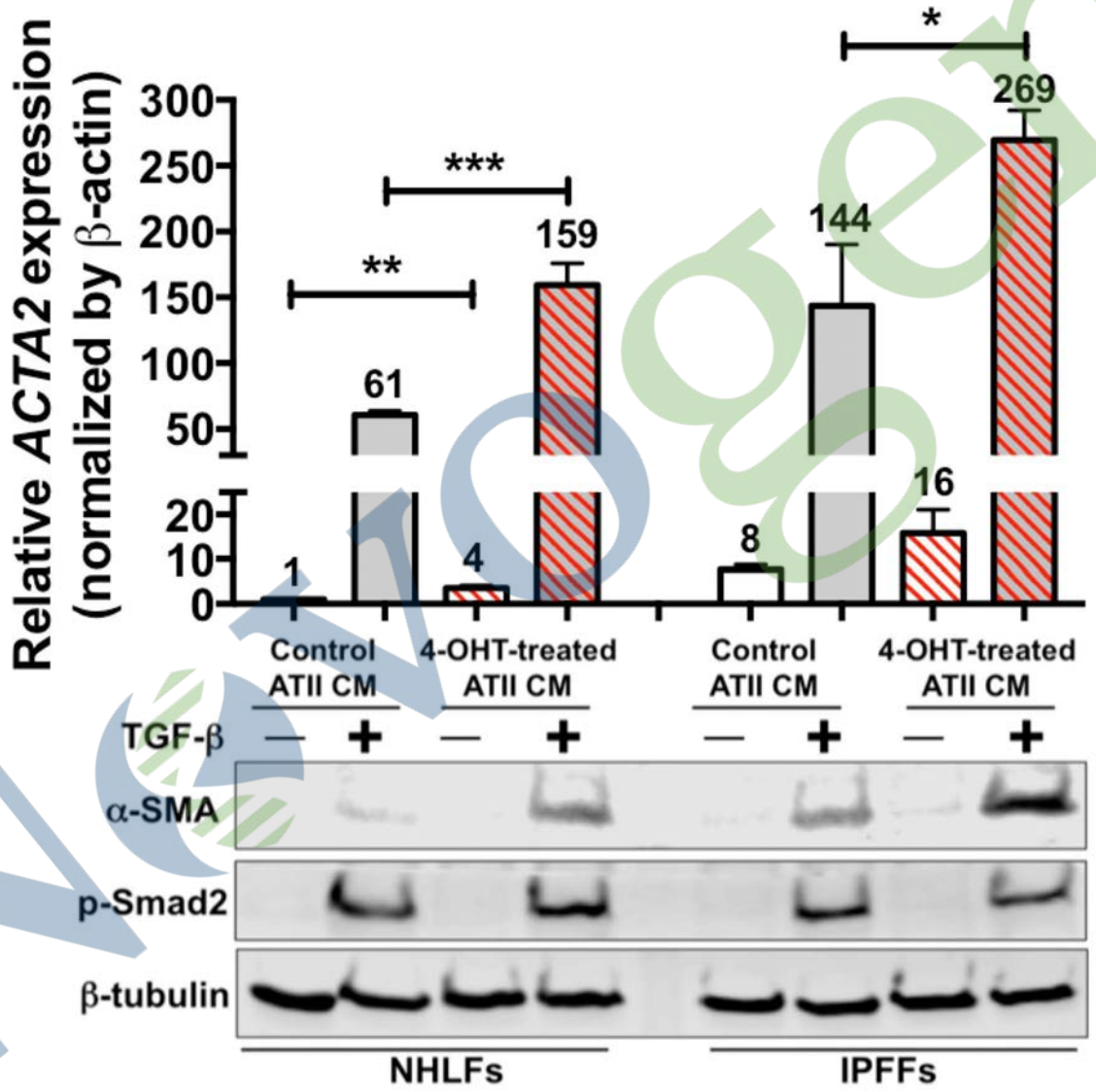
Paracrine signalling during ZEB1-mediated EMT augments local myofibroblast differentiation in lung fibrosis



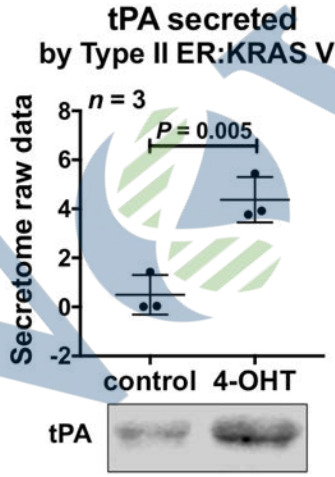


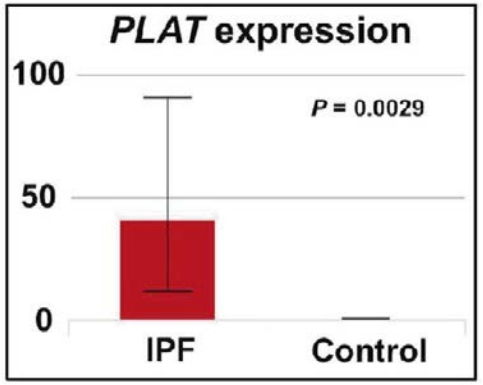
Paracrine signalling during ZEB1-mediated EMT augments local myofibroblast differentiation in lung fibrosis



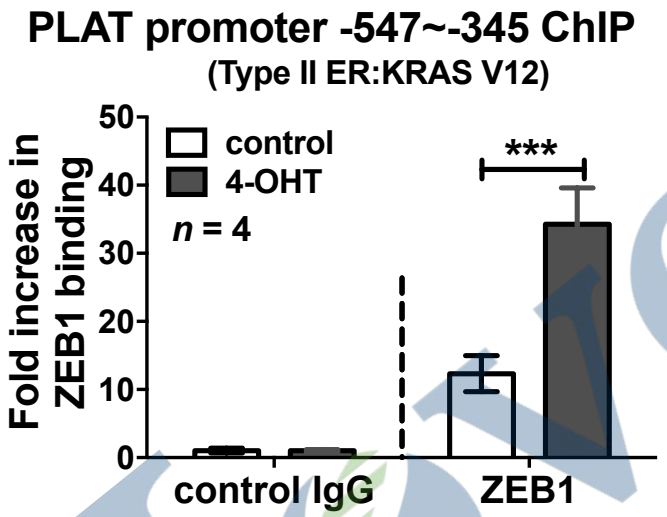
ZEB1 regulates the expression of tissue plasminogen activator (tPA), encoded by PLAT

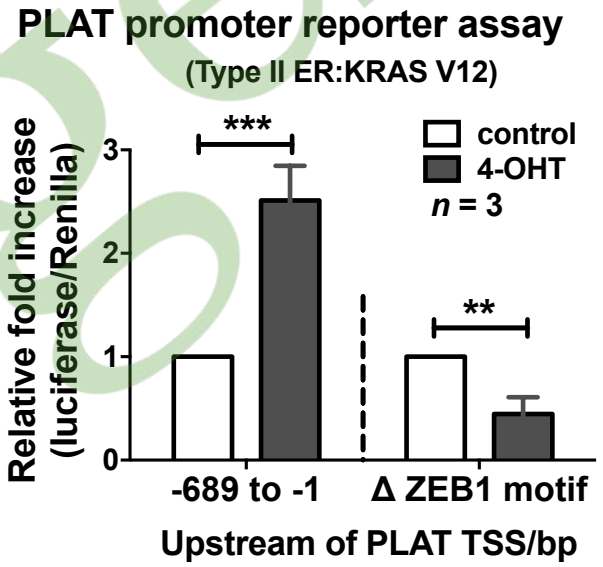
Secretome analysis														LGEA analysis	
protein.Entry	protein.Accession	protein.Description	Control 1	Control 2	Control 3	Mean Control	4OHT_1	4OHT_2	4OHT_3	Mean 4OHT	Present_NumFiles	4OHT/Control	t test	*P* value	fold change
sp	P00750	TPA_HUMAN Tissue-type plasminogen activator OS=Homo sapiens GN=PLAT PE=1 SV=1	0.03805945	0.01625878	1.42580102	0.493373083	5.43590936	3.76467321	3.91557126	4.37205128	4	8.86155209	0.0054235	0.0029	62.186
sp	O43665	RGS10_HUMAN Regulator of G-protein signaling 10 OS=Homo sapiens GN=RGS10 PE=1 SV=2	0.03805945	0.01625878	0.07417637	0.042831532	0.99216271	0.780106	0.60354859	0.7919391	3	18.48962817	0.0027397	0.0173	31.993
sp	Q9UBP4	DKK3_HUMAN Dickkopf-related protein 3 OS=Homo sapiens GN=DKK3 PE=1 SV=2	5.93056295	5.83114799	4.56300733	5.441572754	10.0672589	9.12225748	6.76727499	8.65226378	6	1.590029974	0.0405159	0.0016	22.862
sp	P09382	LEG1_HUMAN Galectin-1 OS=Homo sapiens GN=LGALS1 PE=1 SV=2	26.24369	24.4859987	25.7932936	25.50766077	32.8702499	34.1803729	33.0724352	33.3743527	6	1.30840507	0.0002942	0.0078	21.273
sp	P49006	MRP_HUMAN MARCKS-related protein OS=Homo sapiens GN=MARCKSL1 PE=1 SV=2	0.03805945	0.01625878	0.07417637	0.042831532	1.22915429	0.81883881	1.03388924	1.02729411	3	23.98452876	0.0011912	0.0448	8.948
sp	Q9BUF5	TBB6_HUMAN Tubulin beta-6 chain OS=Homo sapiens GN=TUBB6 PE=1 SV=1	1.59108512	1.6288924	1.70757031	1.642515942	2.42474405	1.99892431	1.96350613	2.12905816	6	1.296217653	0.0329479	0.0085	7.791
sp	Q01813	PFKAP_HUMAN ATP-dependent 6-phosphofructokinase_ platelet type OS=Homo sapiens GN=PFKP PE=1 SV=2	1.41330745	1.34007068	0.99123851	1.248205545	2.99812274	2.50893872	2.45329649	2.65345265	6	2.12581386	0.0029099	0.0103	4.928
sp	O00154	BACH_HUMAN Cytosolic acyl coenzyme A thioester hydrolase OS=Homo sapiens GN=ACOT7 PE=1 SV=3	5.52472907	4.71961366	5.08920541	5.111182716	7.68256975	8.53283108	7.77277898	7.99605994	6	1.564424592	0.0012627	0.0157	4.724
sp	Q16643	DREB_HUMAN Drebrin OS=Homo sapiens GN=DBN1 PE=1 SV=4	1.28240299	1.27421348	0.07417637	0.876930945	2.36175646	2.03966836	1.9269384	2.10945441	5	2.405496598	0.0432139	0.0027	4.643
sp	P08727	K1C19_HUMAN Keratin_ type I cytoskeletal 19 OS=Homo sapiens GN=KRT19 PE=1 SV=4	16.5180996	12.9025304	16.2798462	15.23349207	23.4078944	23.8995049	26.3436831	24.5503608	6	1.611604266	0.003245	0.0206	4.214
sp	O95865	DDAH2_HUMAN N(G)_N(G)-dimethylarginine dimethylaminohydrolase 2 OS=Homo sapiens GN=DDAH2 PE=1 SV=1	0.03805945	0.59171003	0.07417637	0.234648615	1.22556913	3.90442274	4.6763973	3.26879639	4	13.93060167	0.0459206	0.0237	3.299
sp	P08729	K2C7_HUMAN Keratin_ type II cytoskeletal 7 OS=Homo sapiens GN=KRT7 PE=1 SV=5	4.32725875	4.56625134	3.79641725	4.229975778	7.48748748	8.05830553	8.50840587	8.01806629	6	1.8955348	0.0005285	0.0013	3.216
sp	Q9NVA2	SEP11_HUMAN Septin-11 OS=Homo sapiens GN=SEPT11 PE=1 SV=3	1.57415868	1.13117274	0.97297195	1.226101122	2.2307126	3.16447689	2.8112982	2.7354959	6	2.231052436	0.0098376	0.004	2.985
sp	Q16555	DPYL2_HUMAN Dihydropyrimidinase-related protein 2 OS=Homo sapiens GN=DPYSL2 PE=1 SV=1	2.68078712	2.34254329	2.10650798	2.376612799	3.84755891	3.69629067	4.17248673	3.90544543	6	1.643282169	0.0021756	0.009	2.707
sp	Q96HC4	PDLI5_HUMAN PDZ and LIM domain protein 5 OS=Homo sapiens GN=PDLIM5 PE=1 SV=5	0.03805945	0.01625878	0.07417637	0.042831532	1.42312393	1.51615911	1.08566335	1.34164879	3	31.32385725	0.000596	0.0108	2.637
sp	P14618	KPYM_HUMAN Pyruvate kinase PKM OS=Homo sapiens GN=PKM PE=1 SV=4	34.1364177	34.2956157	41.1210583	36.51769721	44.7813329	41.5010682	46.4058265	44.2294092	6	1.211177391	0.046935	0.018	2.134
sp	Q15942	ZYX_HUMAN Zyxin OS=Homo sapiens GN=ZYX PE=1 SV=1	4.62041663	5.84959897	4.55543831	5.008484634	7.11327073	6.31643212	7.42846302	6.95272195	6	1.388188736	0.0221407	0.0048	2.119
sp	P33316	DUT_HUMAN Deoxyuridine 5'-triphosphate nucleotidohydrolase_ mitochondrial OS=Homo sapiens GN=DUT PE=1 SV=4	0.66413732	0.01625878	1.08337868	0.587924926	3.09795096	1.77269097	2.29507769	2.38857321	5	4.062718048	0.0219907	0.0262	2.049
sp	Q9H299	SH3L3_HUMAN SH3 domain-binding glutamic acid-rich-like protein 3 OS=Homo sapiens GN=SH3BGRL3 PE=1 SV=1	10.6936023	11.6126062	10.6132761	10.97316155	13.5005461	13.5527846	12.8667001	13.306677	6	1.212656616	0.0038884	0.0329	1.971
sp	Q9HA64	KT3K_HUMAN Ketosamine-3-kinase OS=Homo sapiens GN=FN3KRP PE=1 SV=2	0.03805945	0.01625878	0.07417637	0.042831532	0.8801573	1.3146447	1.45076137	1.21518779	3	28.3713361	0.0024689	0.011	1.845
sp	P35237	SPB6_HUMAN Serpin B6 OS=Homo sapiens GN=SERPINB6 PE=1 SV=3	1.84898793	2.04193852	1.8771163	1.922680918	2.79704459	2.88861106	3.64011849	3.10859138	6	1.616800455	0.0123326	0.0399	1.781
sp	P67936	TPM4_HUMAN Tropomyosin alpha-4 chain OS=Homo sapiens GN=TPM4 PE=1 SV=3	6.7261055	6.07247215	7.76056393	6.853047193	9.1039629	8.09742761	8.41492282	8.53877111	6	1.245981659	0.0425782	0.0447	1.718
sp	P15311	EZRI_HUMAN Ezrin OS=Homo sapiens GN=EZR PE=1 SV=4	24.1979949	22.4183019	21.3273715	22.64788942	26.6794785	30.7285466	30.7930708	29.4003653	6	1.298150337	0.0133946	0.0204	1.679
sp	O14907	TX1B3_HUMAN Tax1-binding protein 3 OS=Homo sapiens GN=TAX1BP3 PE=1 SV=2	0.03805945	0.01625878	0.07417637	0.042831532	1.88357001	4.36947595	4.53555723	3.59620106	3	83.96153243	0.0143496	0.0023	1.585
sp	O43707	ACTN4_HUMAN Alpha-actinin-4 OS=Homo sapiens GN=ACTN4 PE=1 SV=2	24.6135439	25.0097507	25.5202034	25.04783267	32.0447354	30.9006059	34.5628056	32.5027156	6	1.297625869	0.0025856	0.0246	1.507

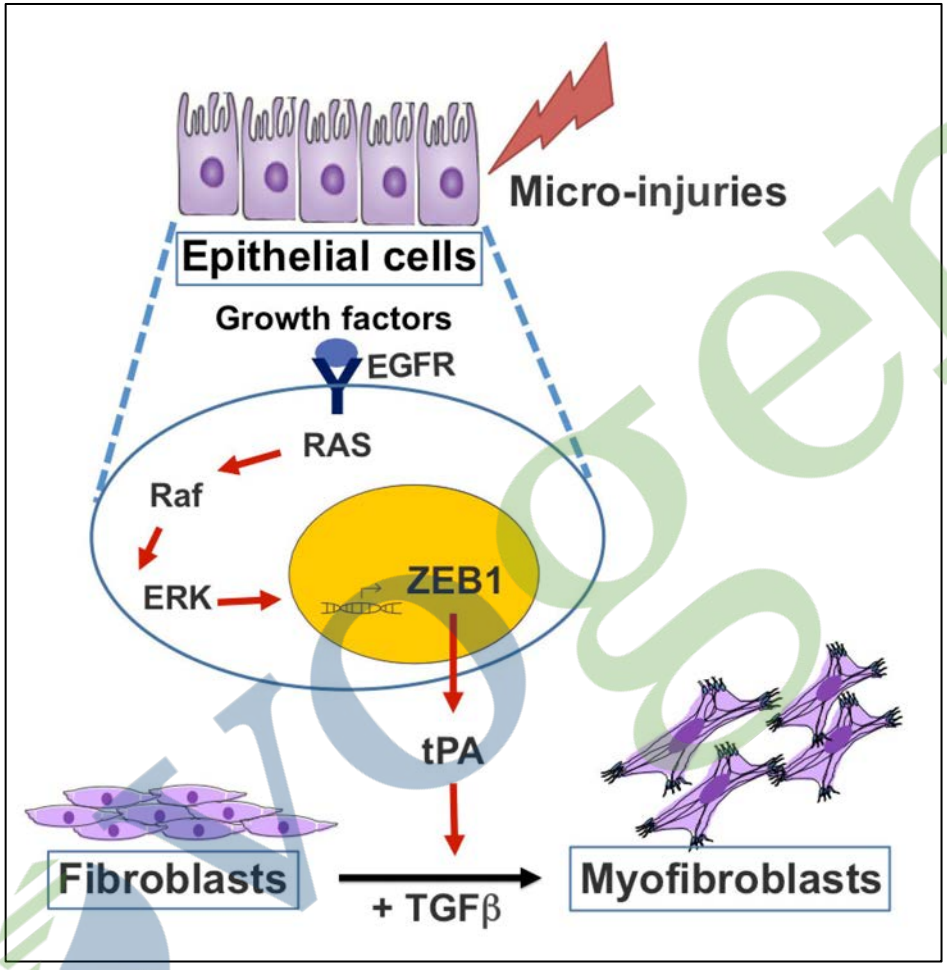




ZEB1 regulates the expression of tissue plasminogen activator (tPA), encoded by PLAT







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ARTICLE

Paracrine signalling during ZEB1-mediated epithelial–mesenchymal transition augments local myofibroblast differentiation in lung fibrosis

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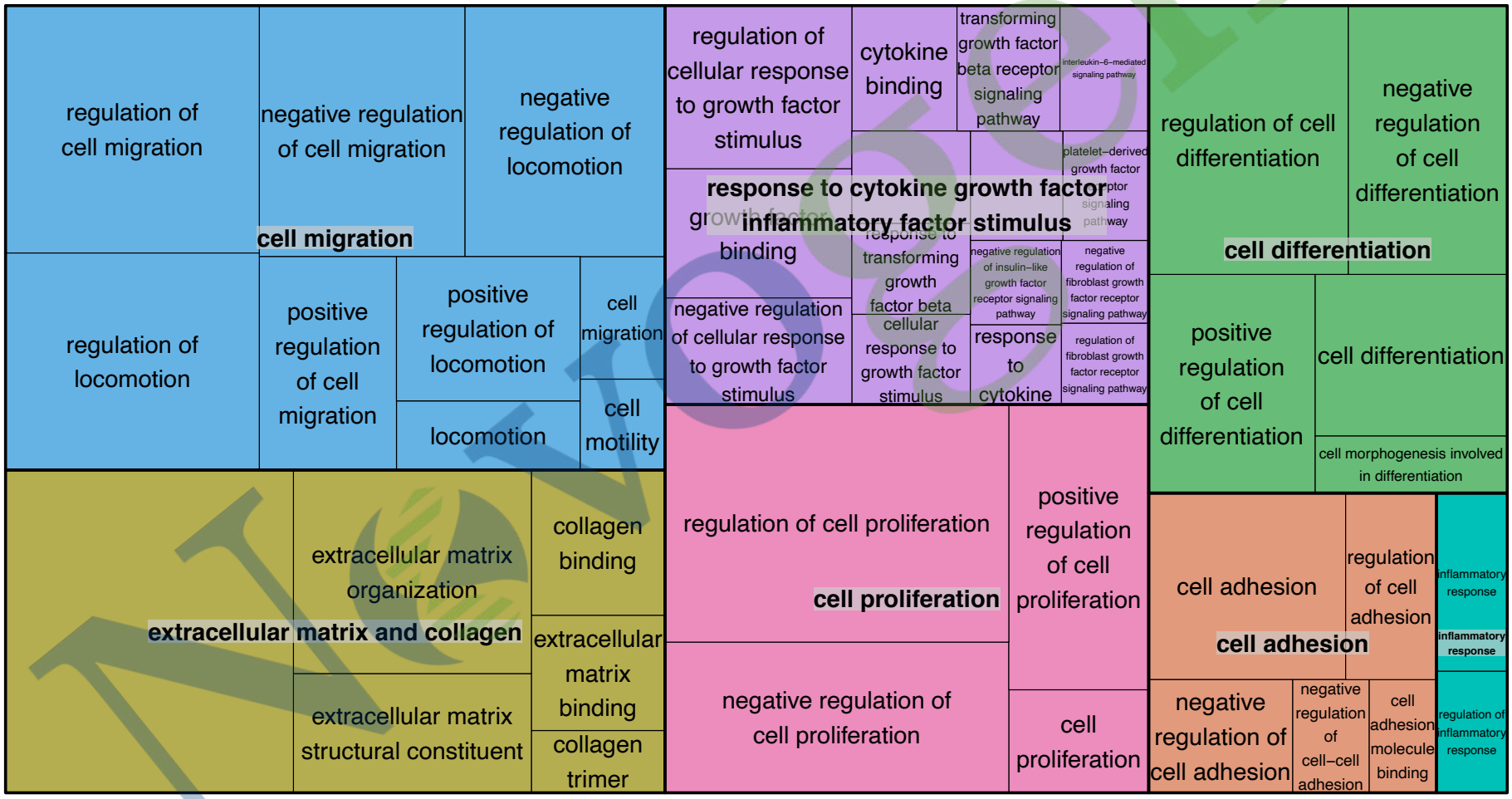
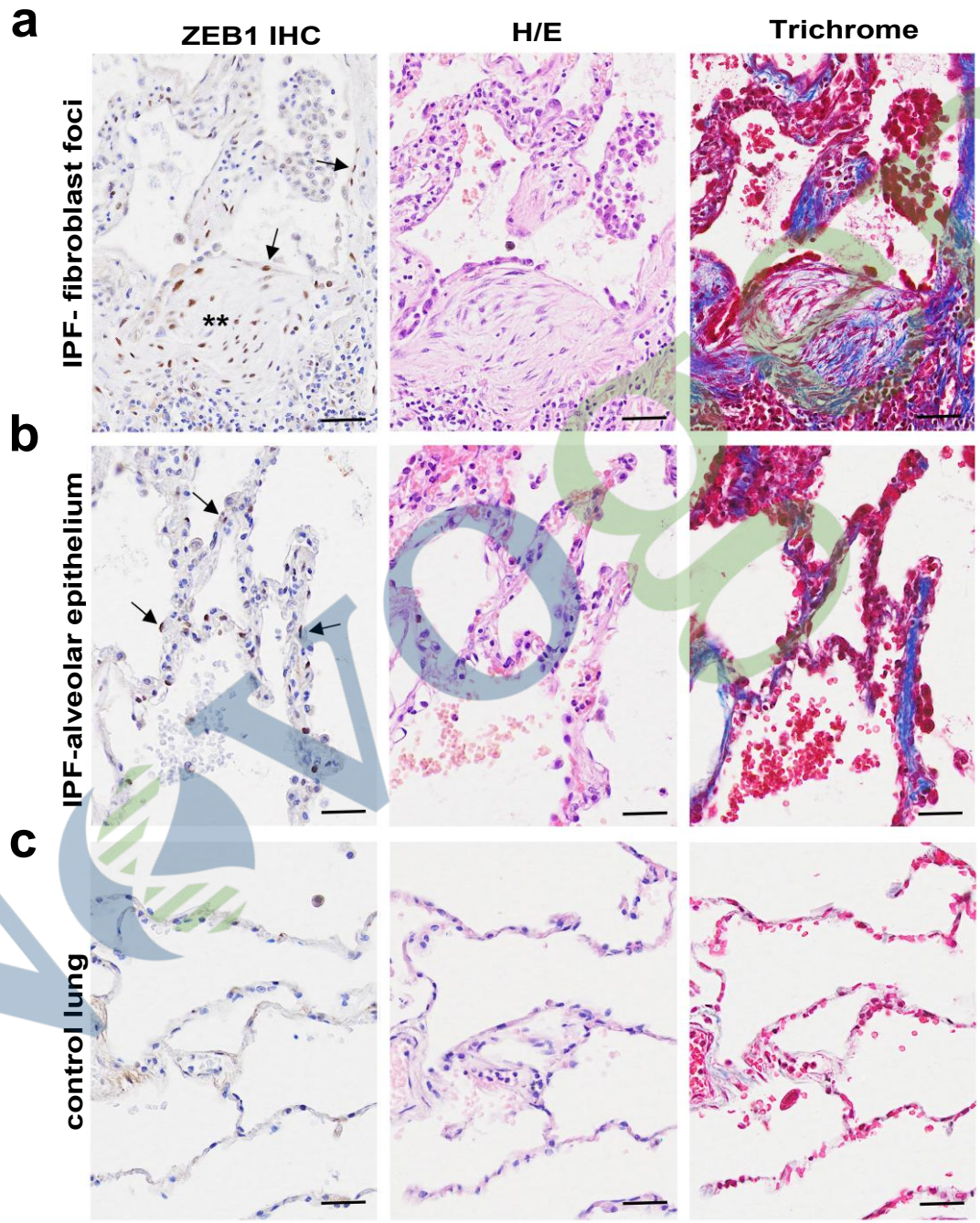
Global transcriptomic changes in fibroblasts exposed to conditioned media from RAS-activated ATII cells

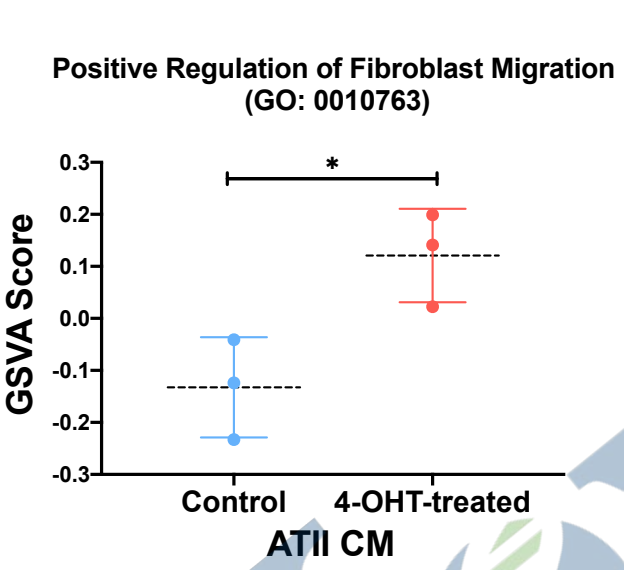


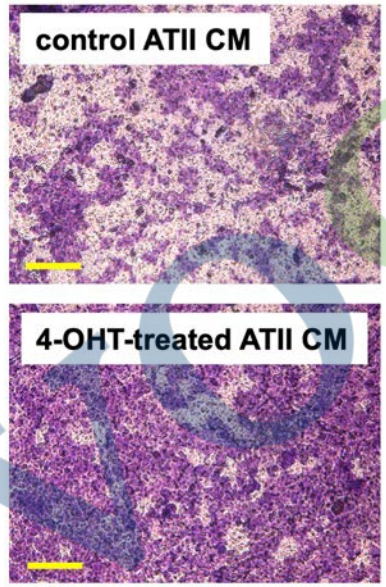
ZEB1 is up-regulated in IPF samples

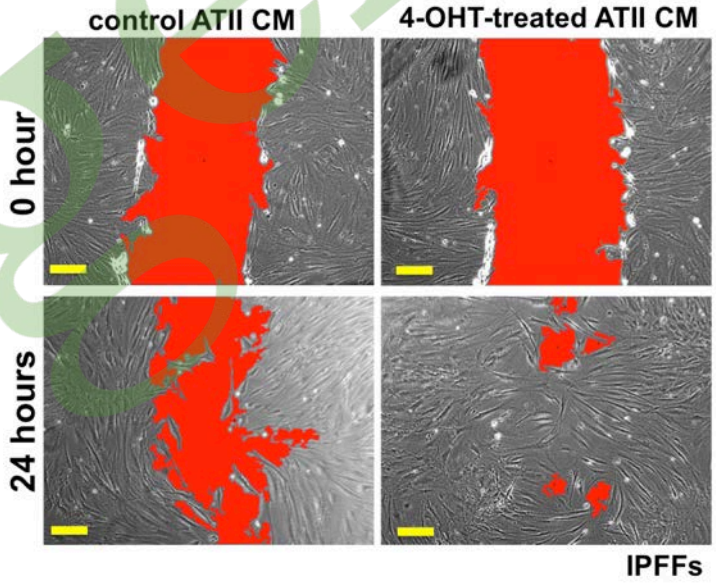
Figure 4

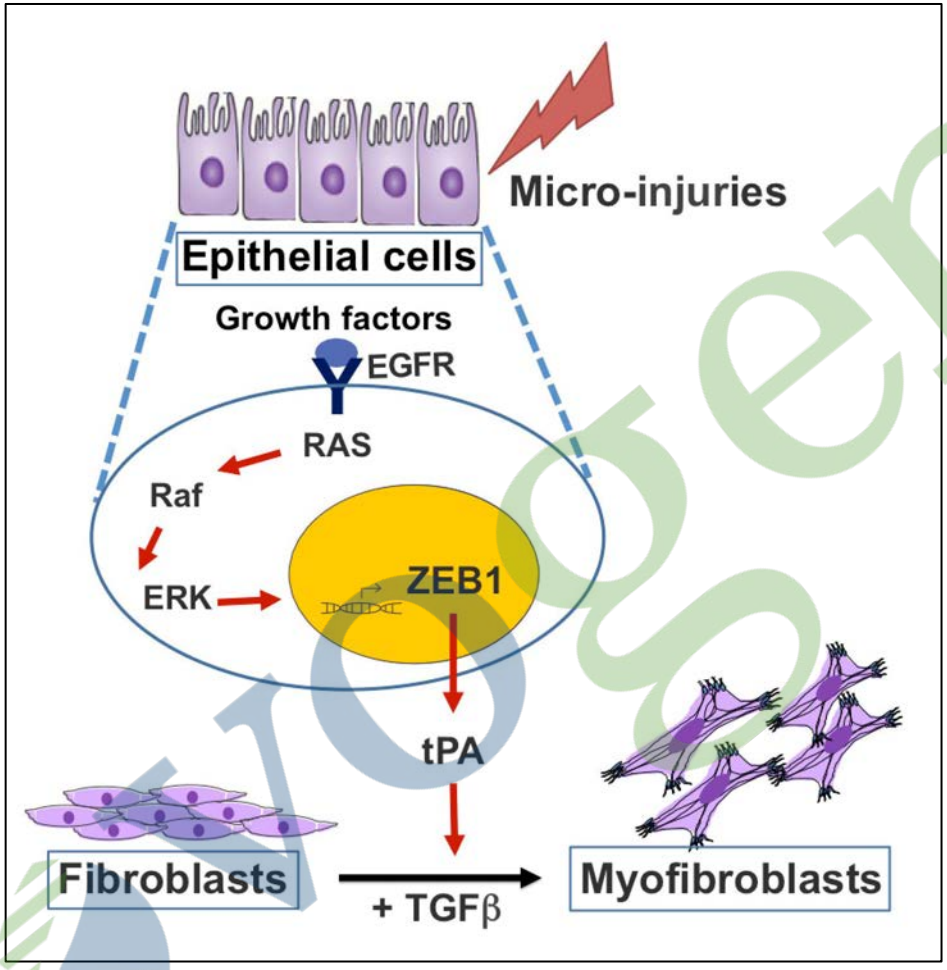


RAS-activated ATII cells augment fibroblast migration via paracrine signalling









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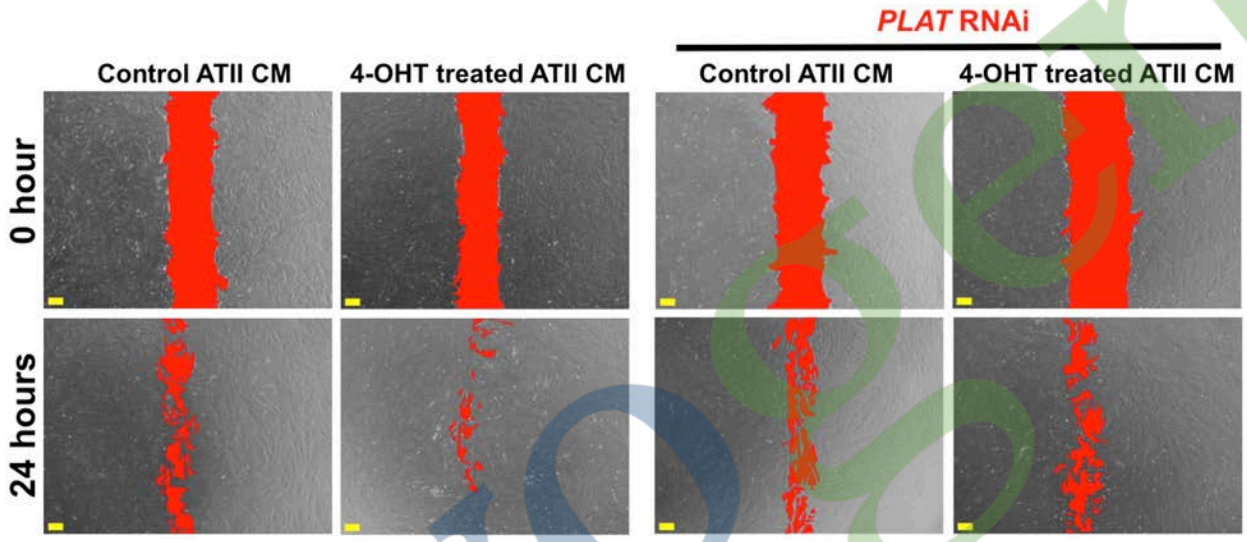
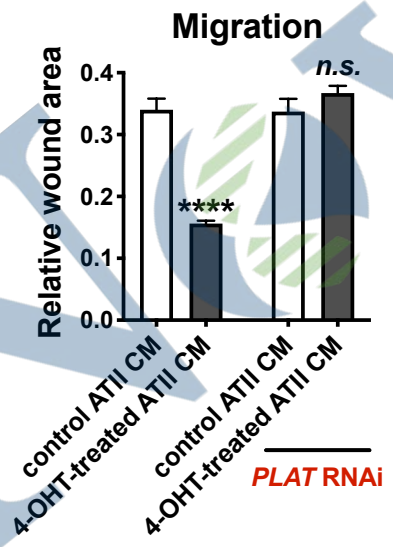
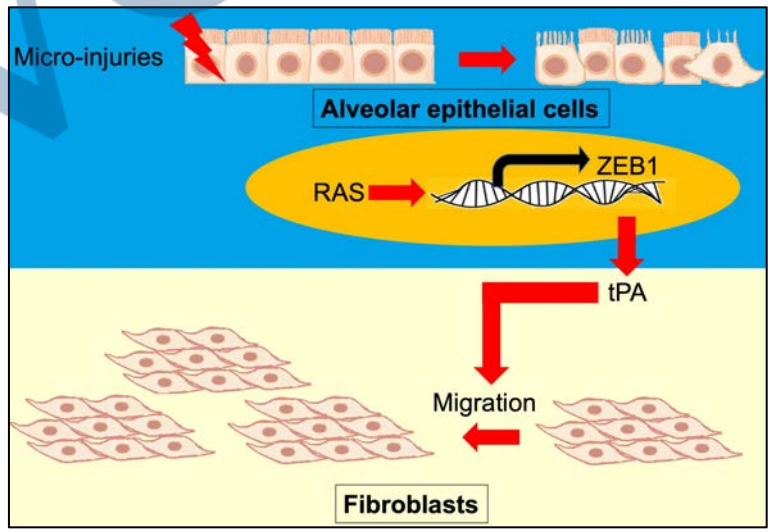
RAS-activated ATII cells augment fibroblast migration via paracrine signalling

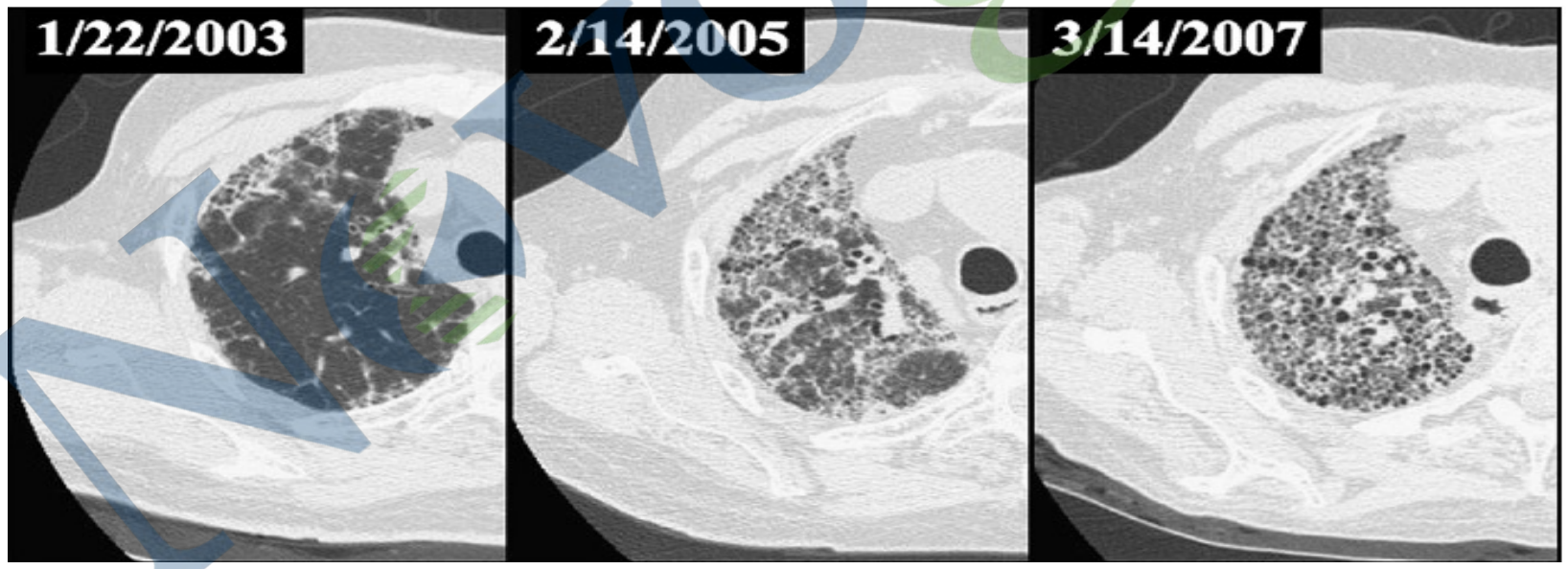






Idiopathic pulmonary fibrosis (IPF)

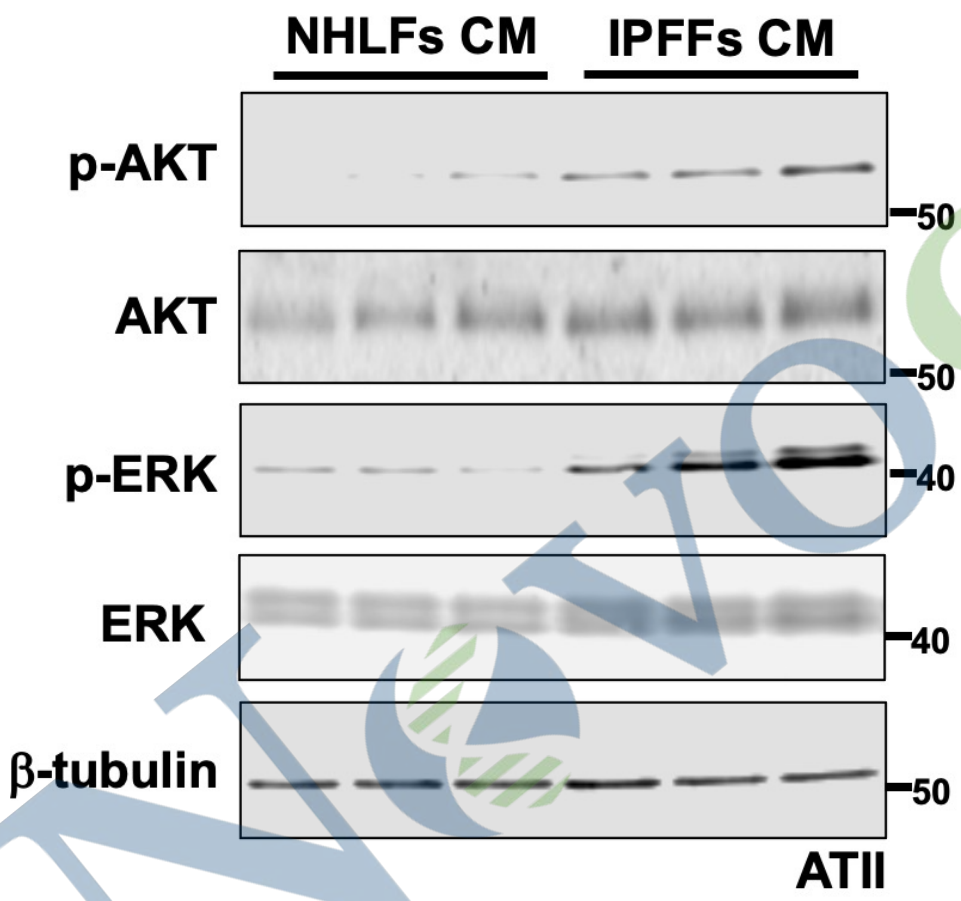
- A progressive fibrotic disease limited to the lungs
- > 5000 cases/year (UK)
- Incidence is increasing
- Median survival from time of diagnosis 3 years

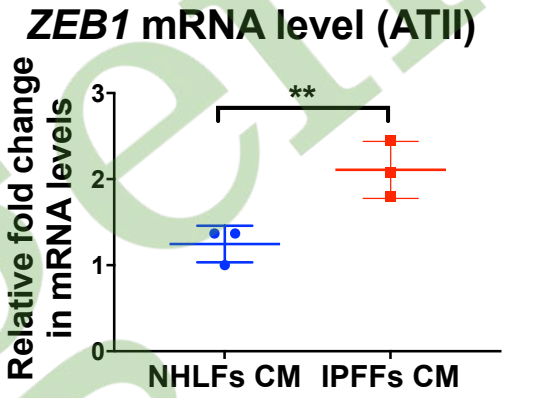


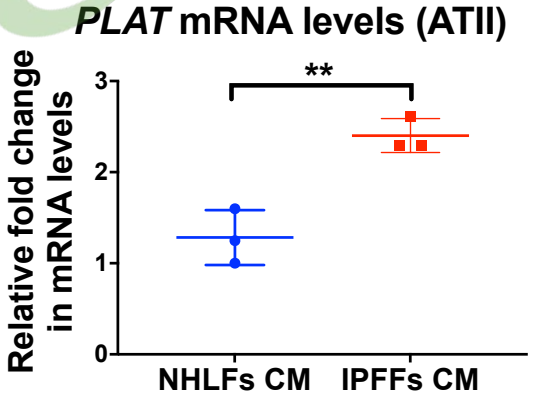
Richeldi L et al. *BMC Medicine* 2015; 13:237

Elicker et al. *Resp Med* 2010; 104:426-33

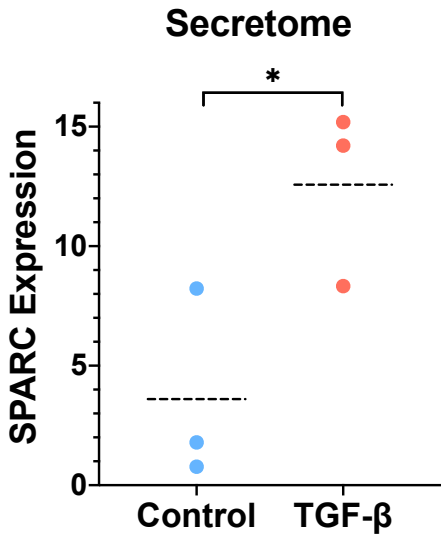
IPF fibroblasts induce RAS activation in ATII cells

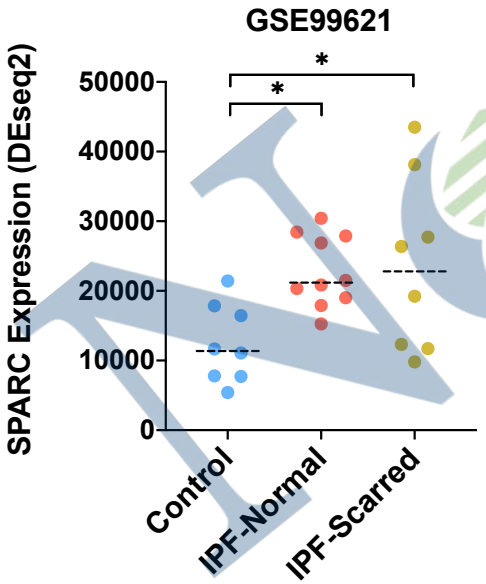


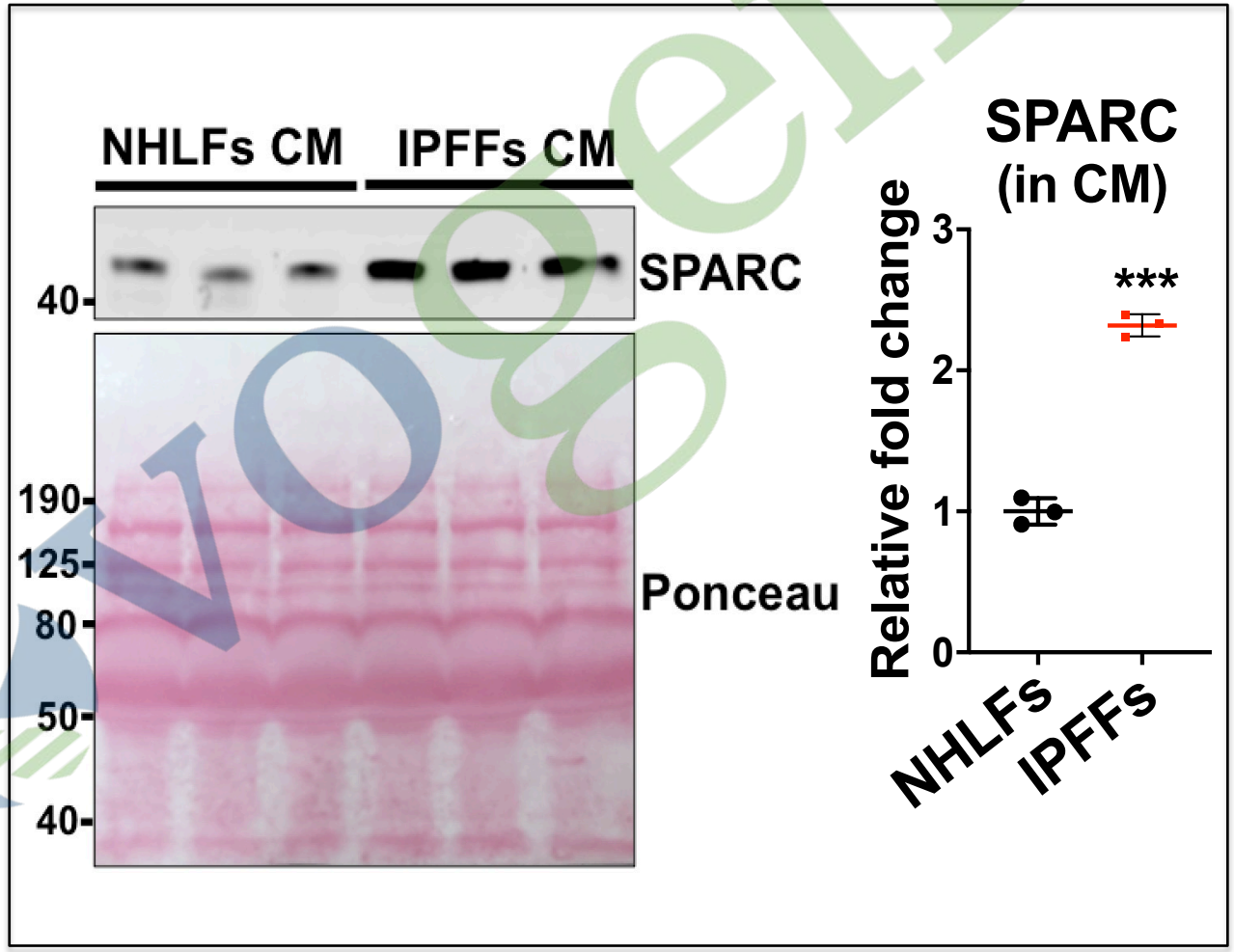




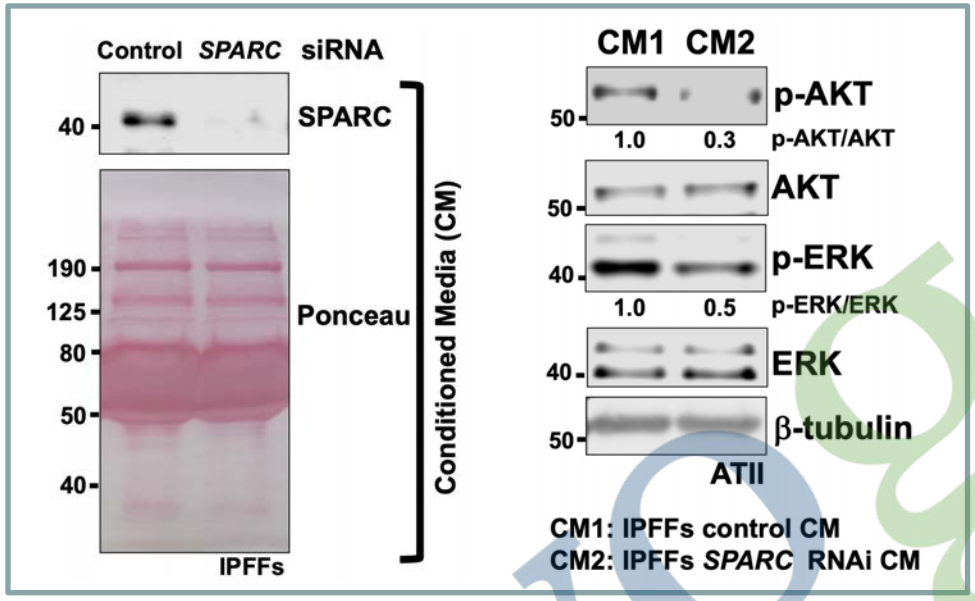
SPARC, a TGF-β-induced secreted protein, is highly expressed in IPF.

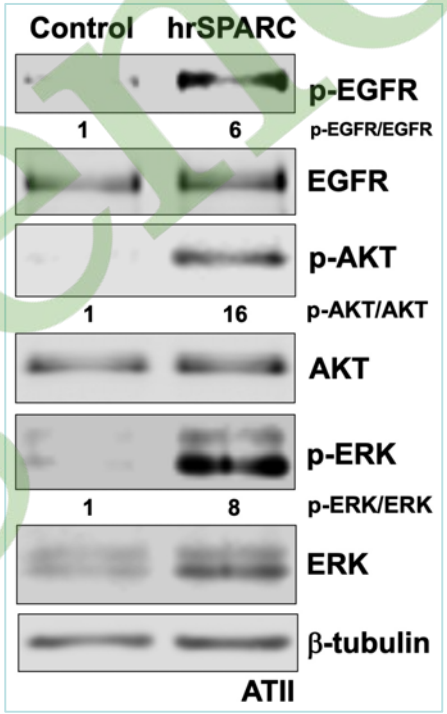


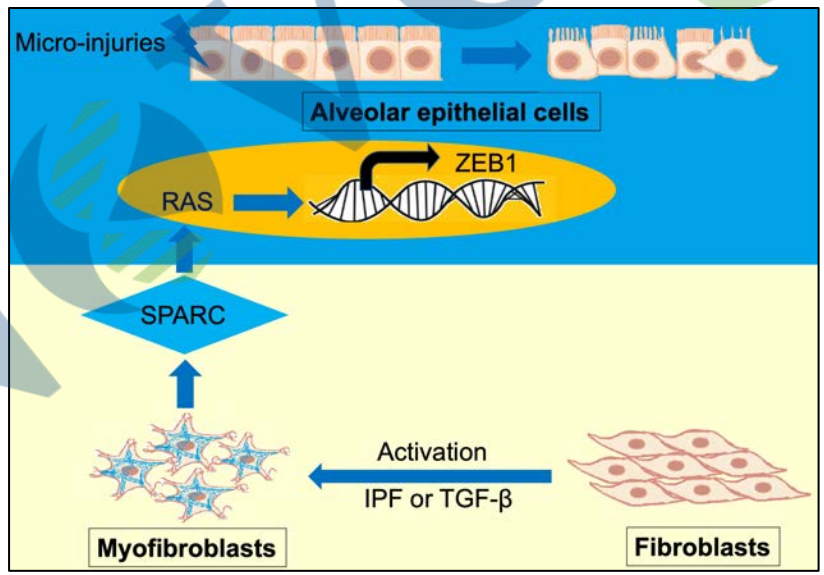




SPARC is a key fibroblast-derived paracrine regulator of RAS activation in ATII cells







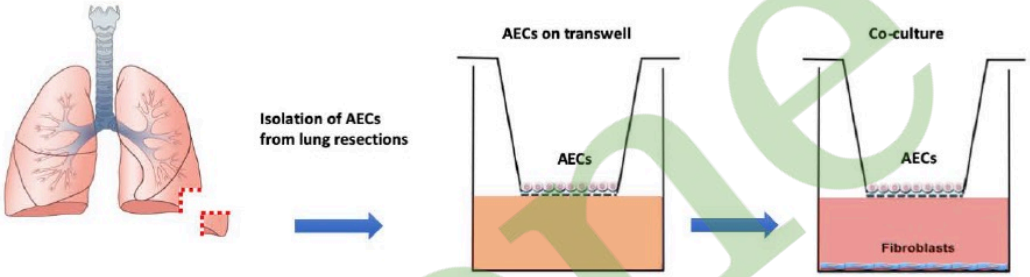
Conforti et al. Cell Death Discovery (2020)6:54
https://doi.org/10.1038/s41420-020-0289-9

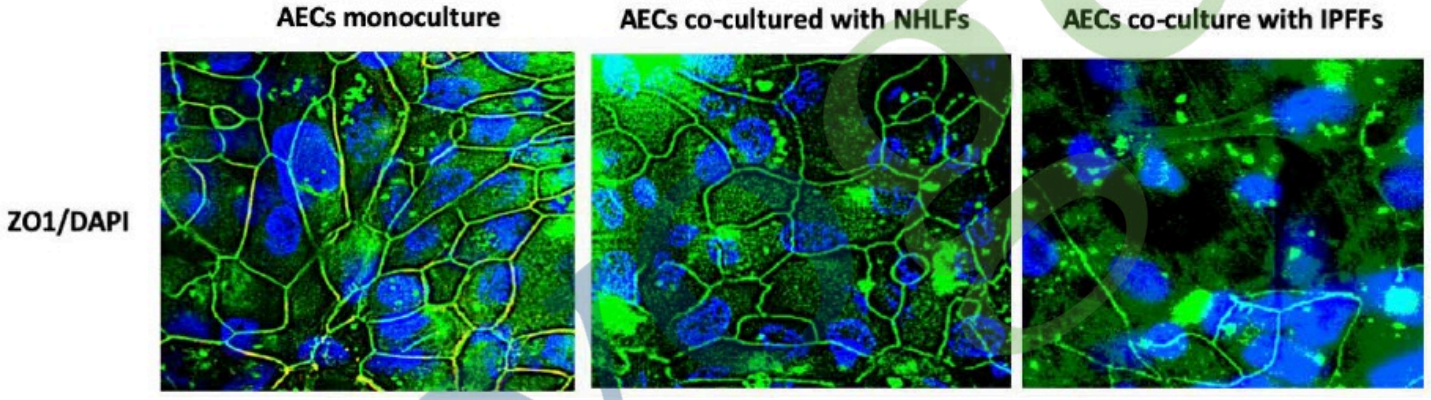
Cell Death Discovery

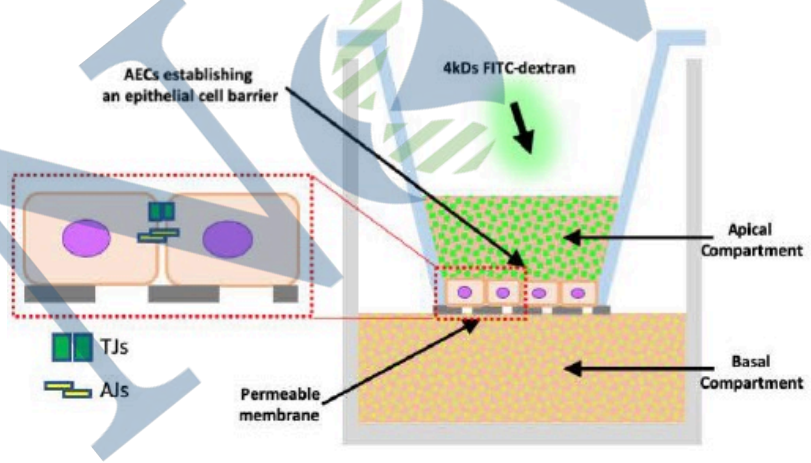
ARTICLE Open Access

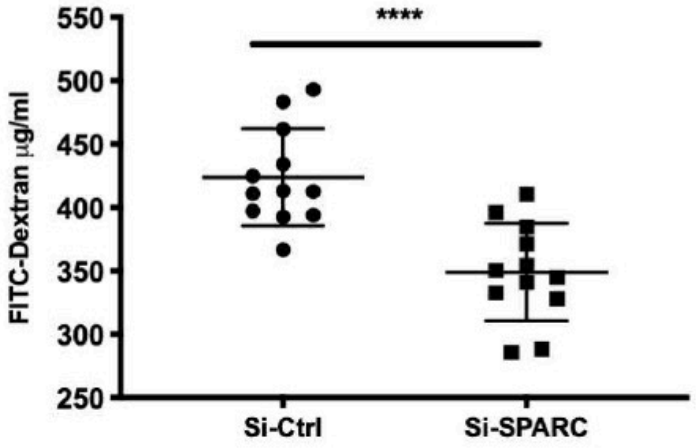
Paracrine SPARC signaling dysregulates alveolar epithelial barrier integrity and function in lung fibrosis

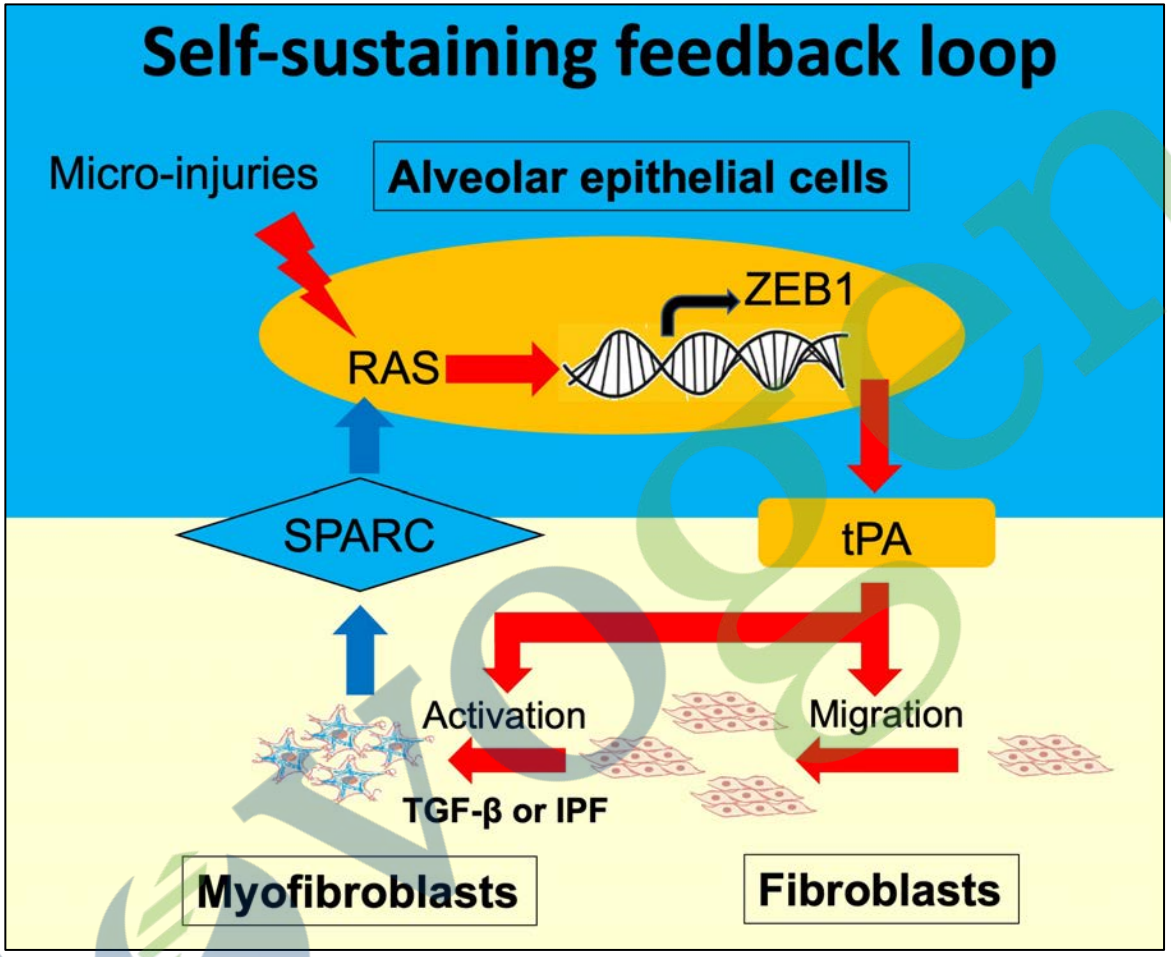
Franco Conforti[1,2], Robert Ridley[1], Christopher Biereton[1,2], Aiman Alzetani[3,4], Benjamin Johnson[5], Ben G. Marshall[3,4], Sophie V. Fletcher[3,4], Christian H. Ottensmeier[4,5], Luca Richeldi[1,2,6], Paul Skipp[7], Yihua Wang[8,9], Mark G. Jones[1,2,4] and Donna E. Davies[1,2,8]

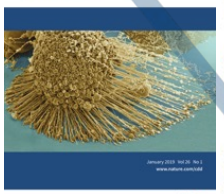












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ARTICLE

Paracrine signalling during ZEB1-mediated epithelial–mesenchymal transition augments local myofibroblast differentiation in lung fibrosis

Liudi Yao[1] · Franco Conforti[2,3] · Charlotte Hill[1] · Joseph Bell[2] · Leena Drawater[1] · Juanjuan Li[1] · Dian Liu[4] · Hua Xiong[4] · Aiman Alzetani[2,10] · Serena J. Chee[5,6] · Ben G. Marshall[3,5] · Sophie V. Fletcher[3,5] · David Hancock[7] · Mark Coldwell[1] · Xianglin Yuan[4] · Christian H. Ottensmeier[6] · Julian Downward[7] · Jane E. Collins[2] · Rob M. Ewing[1] · Luca Richeldi[2,3,8] · Paul Skipp[1,9] · Mark G. Jones[2,3] · Donna E. Davies[2,3,11] · Yihua Wang[1,4,11]

JBC RESEARCH ARTICLE

Bidirectional epithelial–mesenchymal crosstalk provides self-sustaining profibrotic signals in pulmonary fibrosis

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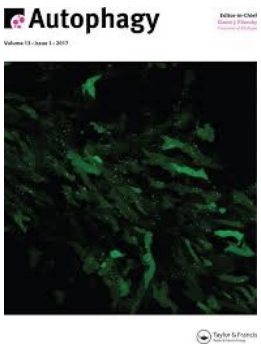

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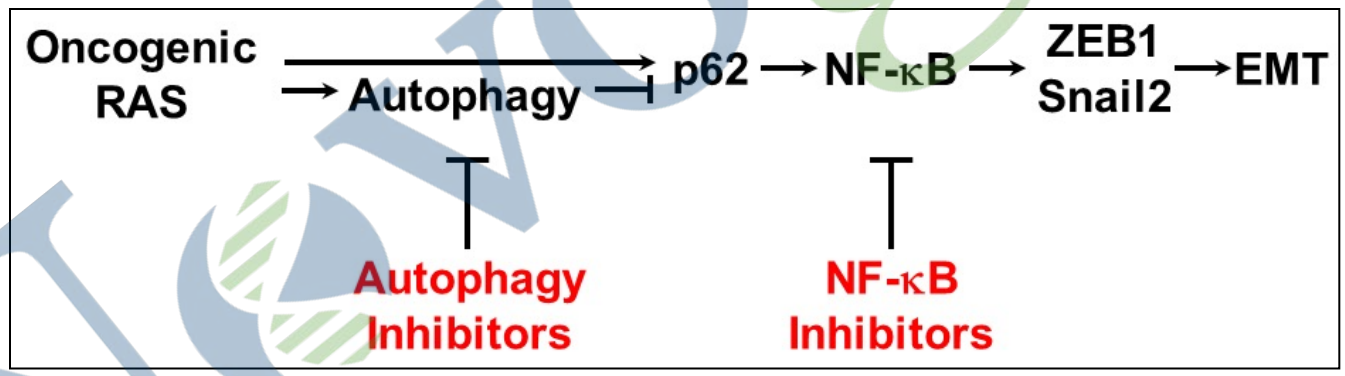
RESEARCH PAPER - TRANSLATIONAL

Autophagy inhibition specifically promotes epithelial-mesenchymal transition and invasion in RAS-mutated cancer cells

Yihua Wang [a,b,c,d], Hua Xiong[a], Dian Liu[a], Charlotte Hill[b], Ayse Ertay[b], Juanjuan Li[b], Yanmei Zou[a], Paul Miller [d], Eileen White[e], Julian Downward [f], Robert D Goldin [g], Xianglin Yuan[a], and Xin Lu [d]



Autophagic activity is downregulated in IPF lungs

Hill et al. *Cell Death and Disease* (2019)10:591
https://doi.org/10.1038/s41419-019-1820-x

Cell Death & Disease

ARTICLE Open Access

Autophagy inhibition-mediated epithelial–mesenchymal transition augments local myofibroblast differentiation in pulmonary fibrosis

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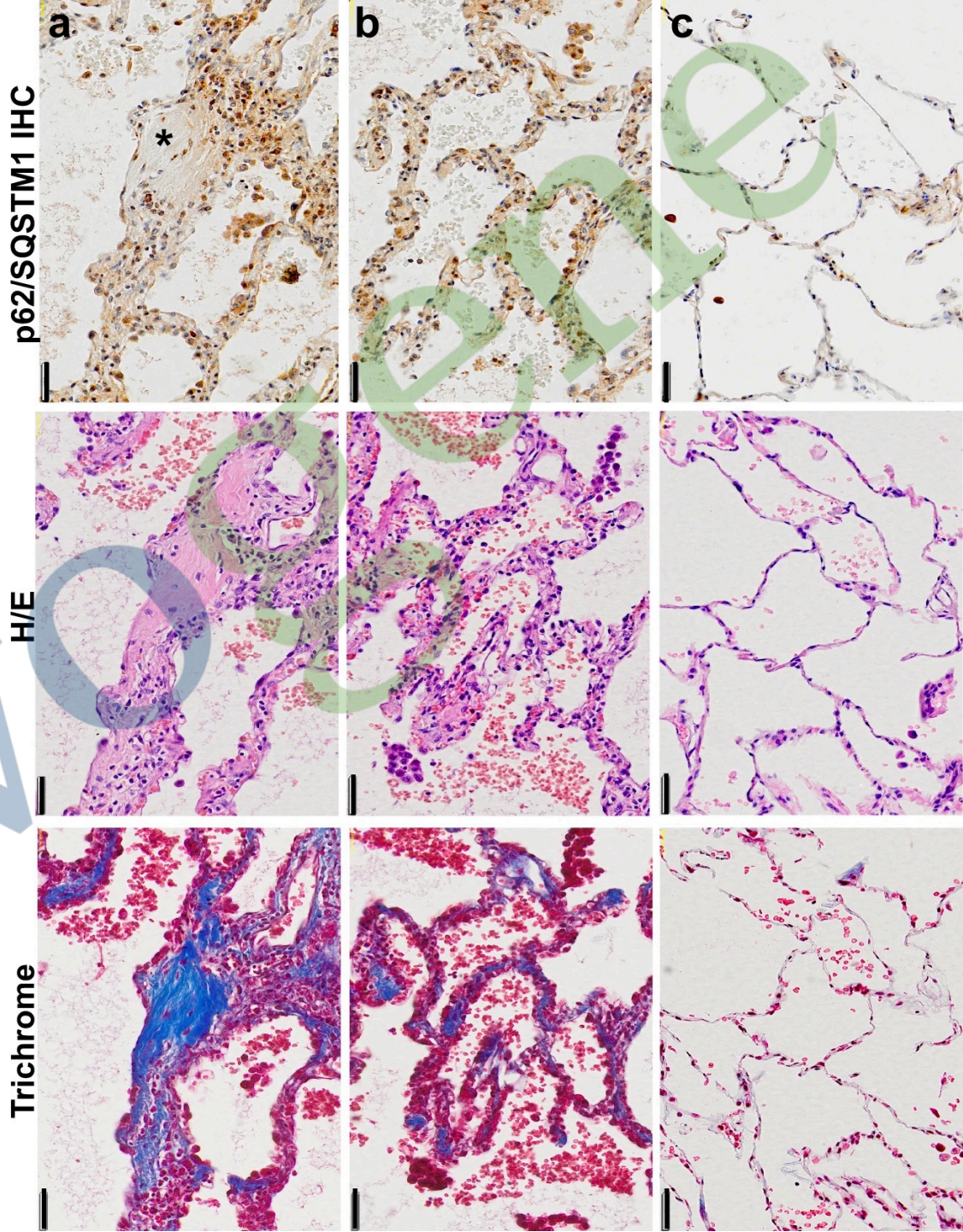
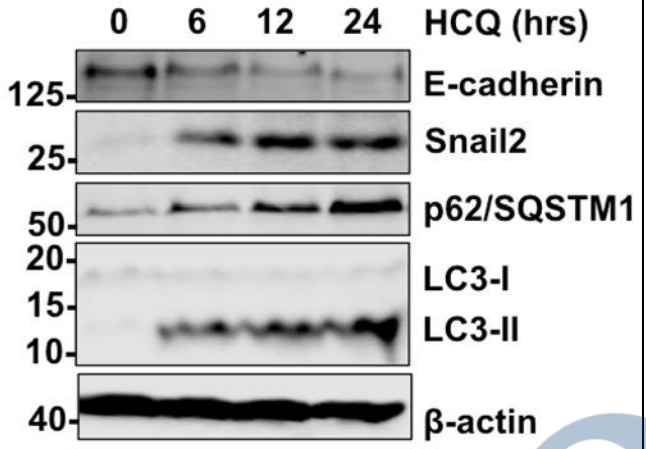
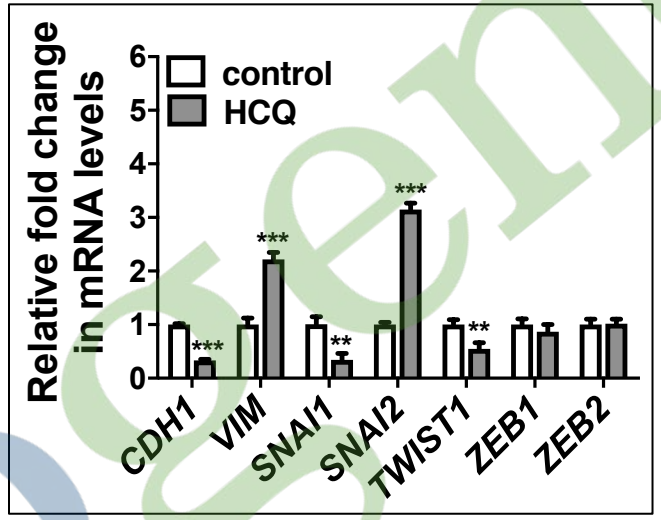
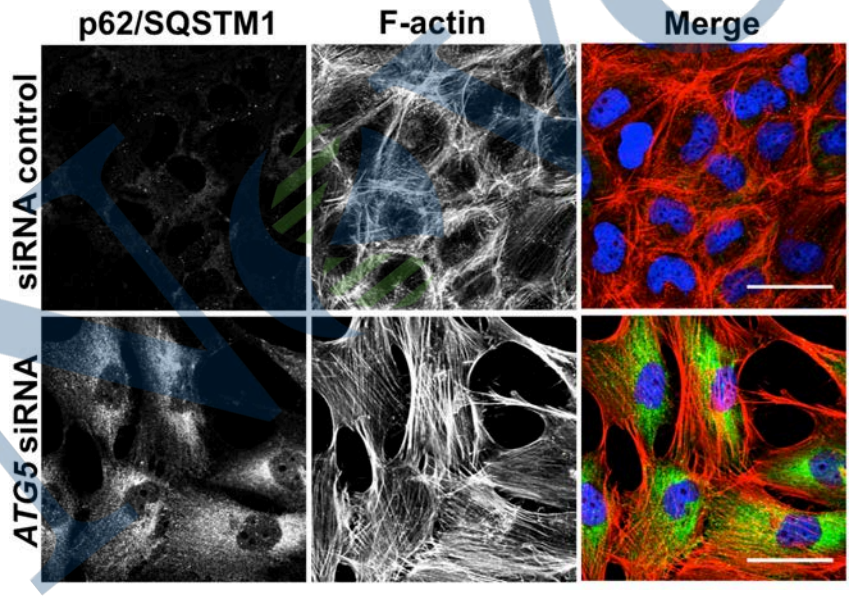
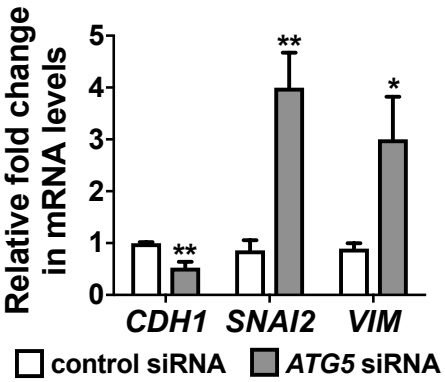


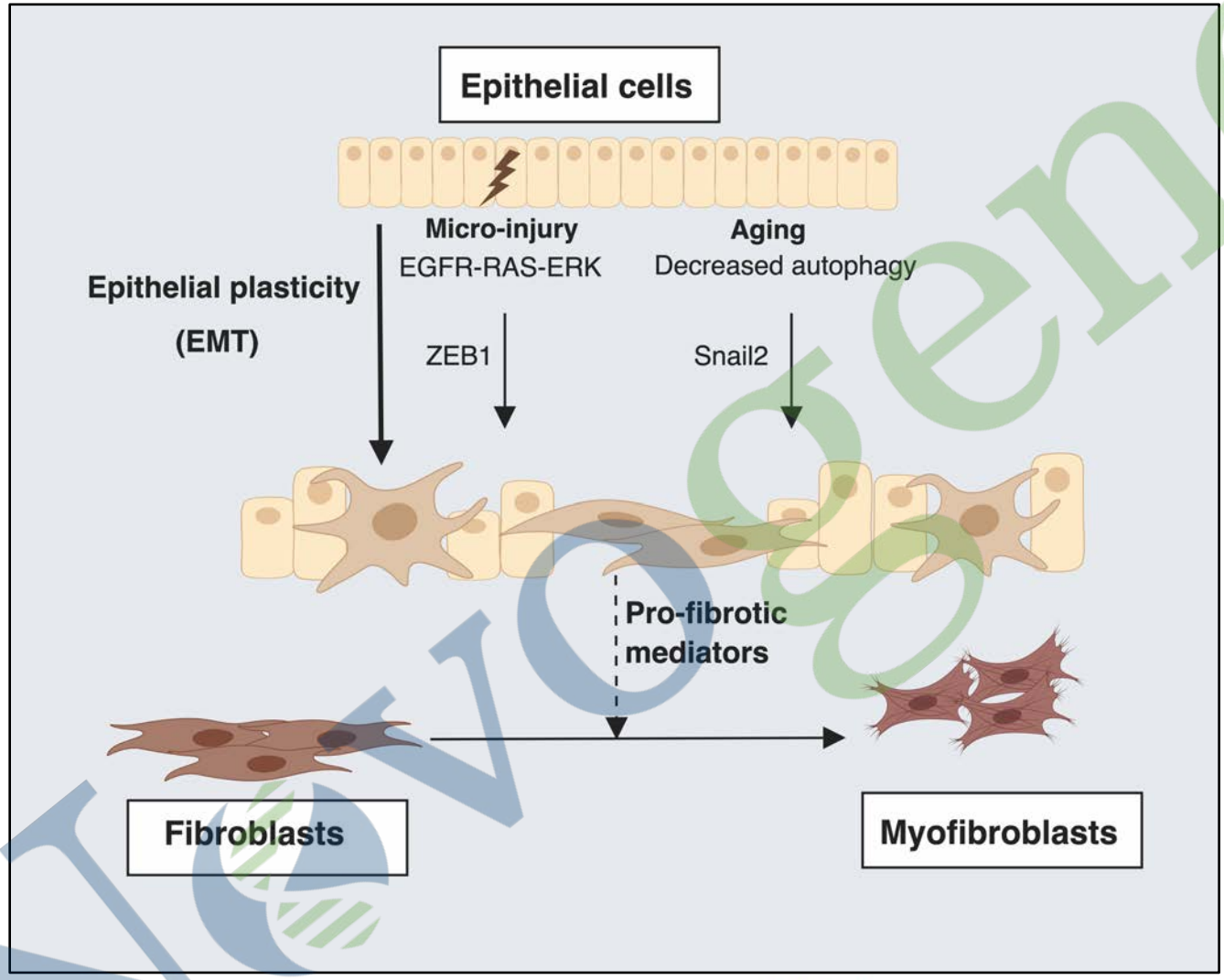
Autophagy inhibition induces EMT via NFκB-Snail2 pathway.











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ARTICLE

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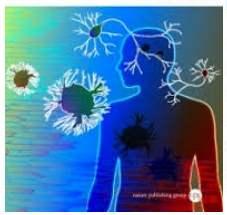

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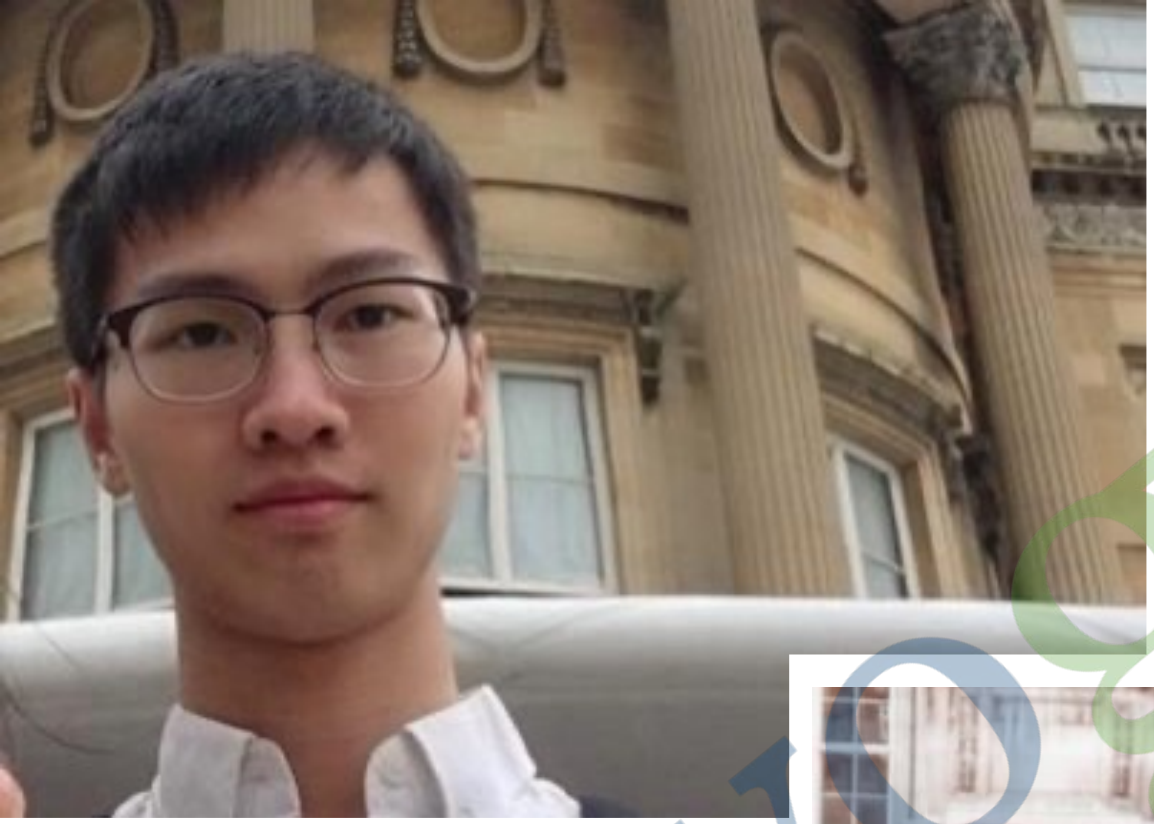

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Proteomics and bioinformatics – Prof Paul Skipp; Dr Rob Ewing

Autophagy – Prof Xin Lu; Prof Eileen White; Dr Andrew Steele

Hypoxia – Prof Sir Peter Ratcliffe; Prof Christopher Schofield; Prof Xin Lu; Prof Ali Tavassoli

Colleagues in China (Dr Dian Liu; Dr Hua Xiong)

Pseudohypoxic HIF pathway activation dysregulates collagen structure-function in human lung fibrosis

Christopher Brereton, Liudi Yao, Yilu Zhou, Milica Vukmirovic, Joseph Bell, Robert A. Ridley, Elizabeth R. Davies, Lareb S.N. Dean, Orestis G. Andriotis, Franco Conforti, Soran Mohammed, Tim Wallis, Ali Tavassoli, R. Ewing, Aiman Alzetani, Ben G. Marshall, Sophie V. Fletcher, Phillipp J. Thurner, Aurelie Fabre, Naftali Kaminski, Luca Richeldi, Atul Bhaskar, Matthew Loxham, Donna E. Davies, Yihua Wang, Mark G. Jones

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Abstract

Extracellular matrix (ECM) stiffening with downstrea
pathways is strongly implicated in fibrosis. We previ
collagen nanoarchitecture is a key determinant of p
in human fibrosis (Jones et al., 2018). Here, through
ex vivo studies we show that hypoxia-inducible facto
critical pathway for this process regardless of oxyge
TGFβ increased rate of fibrillar collagen synthesis, H
to dysregulate post-translational modification of fib
type' cross-linking, altering collagen nanostructure,
vitro, knock down of Factor Inhibiting HIF (FIH) or o
pseudohypoxic HIF activation in normal fibroblasts.
activity was reduced in fibroblasts from patients wit
significantly increased normoxic HIF pathway activa
HIF mediated signalling was increased at sites of ac
subpopulations of IPF lung mesenchymal cells had i
stress scores. Our data demonstrate that oxidative s
pathway activation which is a critical regulator of pa
function in fibrosis.