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Global comparison of chromosome X genes of pulmonary telocytes with mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells, and lymphocytes

Yichun Zhu, Minghuan Zheng, Dongli Song, Ling Ye and Xiangdong Wang*

Abstract

Background: Telocytes (TCs) are suggested as a new type of interstitial cells with specific telopodes. Our previous study evidenced that TCs differed from fibroblasts and stem cells at the aspect of gene expression profiles. The present study aims to search the characters and patterns of chromosome X genes of TC-specific or TC-dominated gene profiles and fingerprints, investigate the network of principle genes, and explore potential functional association.

Methods: We compared gene expression profiles in chromosome X of pulmonary TCs with mesenchymal stem cells (MSC), fibroblasts (Fb), alveolar type II cells (ATII), airway basal cells (ABC), proximal airway cells (PAC), CD8⁺ T cells come from bronchial lymph nodes (T-BL), or CD8⁺ T cells from lungs (T-L) by global analyses, and selected the genes which were consistently up or down regulated (>1 fold) in TCs compared to other cells as TC-specific genes. The functional and characteristic networks were identified and compared by bioinformatics tools.

Results: We selected 31 chromosome X genes as the TC-specific or dominated genes, among which 8 up-regulated (Flna, Msn, Cfp, Col4a5, Mum111, Rnf128, Syn1, and SrpX2) and 23 down-regulated (Abcb7, Atf1, Ddx26b, Drp2, Fam122b, Gyk, Irak1, Lamp2, Mecp2, Ndufb11, Ogt, Pdha1, Pola1, Rab9, Rbmx2, Rhox9, Thoc2, Vbp1, Dkc1, Nkrf, Piga, Tmlhe and Tsr2), as compared with other cells.

Conclusions: Our data suggested that gene expressions of chromosome X in TCs are different with those in other cells in the lung tissue. According to the selected TC-specific genes, we infer that pulmonary TCs function as modulators which may enhance cellular growth and migration, resist senescence, protect cells from external stress, regulate immune responses, participate in tissue remodeling and repair, regulate neural function, and promote vessel formation.

Keywords: Chromosome X, Genes, Lung, Telocytes, Mesenchymal stem cells, Fibroblasts, Alveolar type II cells, Airway epithelial cells, Lymphocytes

Background

Telocytes (TCs) as a new type of interstitial cells are characterized with extensive telopodes [1], and found in multiple organs/tissues, including heart [2], trachea and

lung [3], digestive tract [4, 5], liver [6], skeletal muscle [7], kidney and urinary tract [8, 9], skin [10], mammary gland [11], and others [12–18]. TCs were suggested to play a key role in supporting and nutrition of associated cells through the interconnection in forms of a complex three-dimensional network within organs/tissues [12, 19–21]. TCs are involved in mechanical support, intercellular

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signaling, immune surveillance, stem-cell guidance and tissue regeneration [22–24].

The electrophysiological properties of TCs were reported in recent studies [25]. Ion channels on the membrane of TCs are found to be related with the different function of TCs and are involved in multiple biological courses, e.g., SK3 channel modulates the contractility of myometrial [26], large conductance Ca^{2+} -activated K^{+} current and inwardly rectifying K^{+} current are expressed on TCs in human heart [27], etc.

Our previous studies initially demonstrated that pulmonary TCs were allocated near the basement membrane of the bronchiolar epithelium, between airway smooth muscle cells, or in pulmonary interstitial space [3]. Pulmonary TCs were inferred to play significant roles in lung diseases, e.g. involving in the course of repair after injury, contributing to the development of pulmonary infectious diseases and stimulating the proliferation of fibroblasts during the process of fibrosis, etc. [28]

TCs are mainly identified and defined by the structures of telopodes, podoms and podomers through transmission electron microscopy [4, 22]. CD34/PDGFR α double immunohistochemistry can orientate the diagnosis [29]. The identification course of TCs is relatively complicated and the confusion between TCs and other cells is inevitable. Therefore, there is a need to select several specific biomarkers of TCs to differ between pulmonary TCs and other tissue resident cells, e.g. fibroblasts, stem cells, epithelial cells, and inflammatory cells.

Our previous studies focused on TCs in lung and trachea of the mouse [3] provided genetic evidence that pulmonary TCs differ from stem cells and fibroblasts through comparing the variation of gene expression profiles [30]. Other studies suggested specific microRNA expression signatures as TC-specific biomarkers [31–33]. Our recent studies identified characters and patterns of TC-specific or TC-dominated gene profiles and fingerprints in chromosome 1, 2, 3, 17 and 18, through global comparison between TCs and other cells in the mouse lung tissue [34–36]. The present study aims to search TC-specific or dominated gene profiles and fingerprints of chromosome X, investigate the network of principle genes, and explore potential functional association. We globally compared gene expression profiles of TCs, mesenchymal stem cells (MSCs), fibroblasts (Fbs), alveolar type II cells (ATII), airway basal cells (ABCs), proximal airway cells (PACs), CD8 $^{+}$ T cells from bronchial lymphnodes (T-BL), and CD8 $^{+}$ T cells from lung (T-L), which may interact with TCs in the lung and trachea.

Methods

Isolation and primary culture of TCs from lung tissues

TCs were isolated from mouse lung tissues, cultured in a density of 1×10^5 cells/cm 2 . TCs usually begin forming

telopodes on day 5 and start overlapping and apoptosis on day 10, therefore TCs were harvested on day 5 (TC5) and day 10 (TC10), as described previously [30, 34]. RNAs were isolated and prepared, labeled, and hybridized for DNA microarray (The Mouse 4x44K Gene Expression Array, Agilent, Shanghai, China) with about 39,000+ mouse genes and transcripts represented with public domain annotations, according to the protocol of One-Color Microarray-Based Gene Expression Analysis. The hybridized arrays were washed, fixed and scanned with using the Agilent DNA Microarray Scanner (part number G2505B).

Data collection and mining

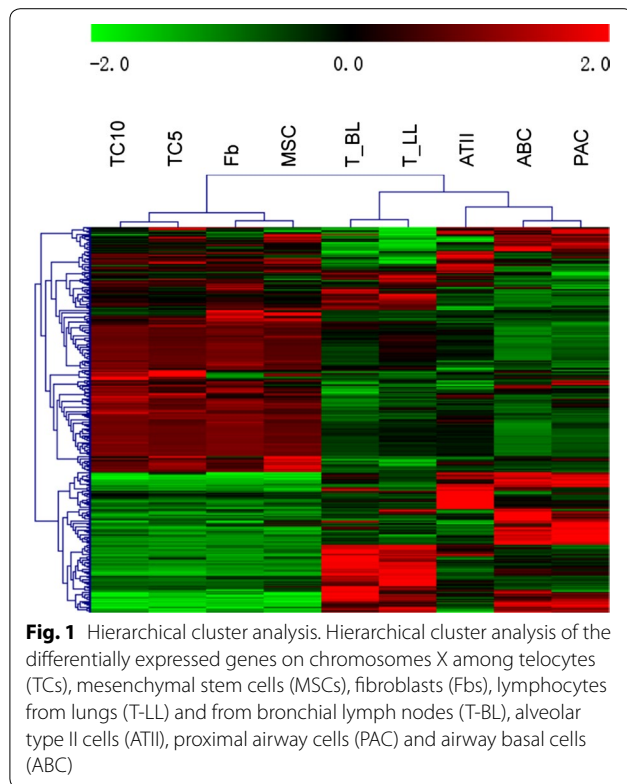
We obtained gene expression profiles of pulmonary TCs on days 5 and 10, MSCs, Fbs from our previous study [30], ATII, ABCs, PACs, T-BL, and T-LL from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus database (GSE6846 [37], GSE27379 [38], GSE28651). The microarray was composed of 45,101 probes. Our first filter eliminated the probe sets without corresponding official symbol, leaving 39,417 probes and 21,680 genes.

Our earlier study have made the gene expression profile, composed of 23,861 probes, of mouse lung TCs, Fbs and stromal stem/progenitor cells [30]. After eliminating the probes without corresponding official symbol, there are 13,236 probes and 11,532 genes. Only those genes whose expressions were measured in all cells were considered in our analysis. In total, 11,532 genes were analyzed and 335 genes of chromosome X were focused and furthermore analyzed in the present study.

Identification of differentially expressed genes

The present study compared gene expression profiles in chromosome X of pulmonary TCs with MSCs, Fbs, ATII, ABCs, PACs, T-BL, or T-L by global analyses, investigated gene expression profiles of chromosome X in different cells to seek for the TC-specific regulated genes and explored potential association of selected genes.

Hierarchical clustering of genes in chromosomes X was performed by TIGR Multi-experiment Viewer (MeV v4.9) (Fig. 1). Gene expression data were normalized and imported into Agilent GeneSpring GX software (version 11.5.1) for further analysis. Up- or down-regulated folds of TCs genes were calculated by comparing with other cells, after the averages of gene expression in cells were obtained from the raw data of multi-databases. The up-regulated folds were defined as the normalized gene expression values of TC5 or TC10 divide those of other cells, while the down-regulated folds were defined as the expression values of other cells divide those of TC5 or TC10. We selected the genes which were consistently



up or down regulated (>1 fold) in both TC5 and TC10 as compared to other cells as TC-specific genes (Additional file 1: Table S1).

Results

Hierarchical clustering of genes in chromosomes X was performed, as shown in Fig. 1. The result of clustering showed a close relationship of TC5 and TC10, and obvious difference between TCs and other kind of cells.

Gene expression array data showed that 8 chromosome X genes (e.g. *Flna*, *Msn*, *Cfp*, *Col4a5*, *Mum11l*, *Rnf128*, *Syn1*, and *Srpx2*) up-regulated in both TC5 and TC10, as compared with those in other cells (Table 1). Of them, *Cfp*, *Col4a5*, *Mum11l*, *Rnf128*, and *Syn1* up-regulated 2–5 folds, and *Srpx2* more than 5 folds as compared with other cells (Table 1B). 23 genes (e.g. *Abcb7*, *Atf1*, *Ddx26b*, *Drp2*, *Fam122b*, *Gyk*, *Irak1*, *Lamp2*, *Mecp2*, *Ndufb11*, *Ogt*, *Pdha1*, *Pola1*, *Rab9*, *Rbmx2*, *Rhox9*, *Thoc2*, *Vbp1*, *Dkc1*, *Nkrf*, *Piga*, *Tmlhe* and *Tsr2*) down-regulated in TCs, of which 5 chromosome X genes (*Dkc1*, *Nkrf*, *Piga*, *Tmlhe*, and *Tsr2*) in TCs were more than 2 folds lower than in other cells, as compared with other cells (Table 2).

A set of genes were found specifically up- or down-regulated in pulmonary TCs, as compared with MSCs, Fbs, ATII, ABCs, PACs, T-BL, or T-L, respectively, as

listed in Table 3. A set of genes up- or down-regulated more than one fold in TC5 were 178 or 157, 224 or 111, 101 or 234, 99 or 236, 109 or 226, 68 or 267, or 88 or 247 and in TC10 123 or 212, 180 or 155, 75 or 260, 87 or 248, 86 or 249, 51 or 284, or 71 or 264, as compared with MSCs, Fbs, ATII, T-BL, T-L, ABCs, PACs, respectively. Up- or down-regulated genes in both TC5 and TC10 were 119 or 153, 172 or 103, 72 or 231, 79 or 228, 81 or 221, 43 or 259, or 65 or 241, as compared with MSCs, Fbs, ATII, T-BL, T-L, ABCs, PACs, respectively. Details of up- or down-regulated gene variations of chromosome X were listed in Additional file 2: Table S2, including the number and names of up- or down-regulated genes among different cells.

We picked out the top 15 % high-expressed genes in chromosome X of TC10, and compared the distribution of such active gene group with other cells, as shown in Fig. 2. The distribution of the high expressed genes in TC10 was similar to those in TC5, while quite different from MSCs, Fbs, ATII, ABCs, PACs, T-BL or T-L. These high expressed genes are mostly involved in gene transcription, energy metabolism, apoptosis and protein degradation, cell migration and intracellular trafficking, and DNA repair. The relationships, including direct (physical) and indirect (functional) associations, of these genes were analyzed by String Network analysis (<http://www.string-db.org>). The interaction and potential functional links of those genes are also displayed in Fig. 2.

Thirty-one genes were selected as TC-specific or dominated genes, which were up- or down-regulated more than one fold in both TC5 and TC10, as compared with other cells. Among those genes in TCs, 8 were up-regulated, while 23 were down-regulated. Figure 3 demonstrated the distribution of such distinct TC-specific or dominated genes in chromosome X of all cells. The interaction and potential functional links between those genes are also displayed in Fig. 3.

Discussion

Chromosome X is one of the two sex-determining chromosomes, which exists in both gender, with one copy in male and two copies in female, spanning about 156 million base pairs and 1805 genes in human cells. Although chromosome X contains only 4 % of all human genes, a large number of disease condition are related with chromosome X, including X-linked diseases and 10 % of diseases with a mendelian pattern of inheritance [39]. There are 20,000–25,000 genes in mouse, and the similarity of genes between human and mouse is about 85 %. Among 2059 genes in chromosome X of the mouse, 335 were measured by bioinformatics tools in the present study. There were about 8 or 23 up- or down-regulated genes

Table 1 Summary of genes up-regulated in TCs, as compared with others

Compared pairs/fold up-regulated		>1	>2	>5	
TC5 vs others		24	9	1	
TC10 vs others		12	8	2	
TCs vs others		8	6	1	
Gene symbol	Folds (TC5 vs others/TC10 vs others)	ATI1	T_LL	ABC	PAC
(A) Genes up-regulated between 1- and 2-folds in TCs as compared with others					
Flha	14.13/8.85	16.21/10.15	49.80/31.18	26.52/16.60	22.41/14.03
Msn	5.43/3.93	3.45/2.50	4.11/2.97	8.02/5.80	7.86/5.69
(B) Genes up-regulated between 2- and 5-folds in TCs as compared with other					
Cfp	6.05/8.22	2.15/2.92	9.46/12.85	41.52/56.38	36.31/49.30
Col4a5	11.55/9.00	5.20/4.05	81.54/63.50	2.89/2.25	7.92/6.16
Mum111	2.67/2.60	4.31/4.19	35.42/34.50	17.91/17.44	81.21/79.09
Rnf128	161.75/297.77	8.99/16.55	11.83/21.77	2.07/3.82	2.52/4.63
Syn1	34.19/35.13	6.66/6.84	3.26/3.35	3.36/3.46	2.77/2.85
(C) Genes up-regulated between 5- and 10-folds in TCs as compared with other					
SrpX2	32.62/54.91	82.00/138.03	55.79/93.92	6.25/10.52	23.63/39.77

Table 2 Summary of genes down-regulated in TCs, as compared with others

Compared pairs/fold down-regulated	>1	>2	>5
TC5 vs others	41	6	0
TC10 vs others	91	22	1
TCs vs others	23	5	0

Gene symbol	Folds (TC5 vs others/TC10 vs others)						
	Fb	MSC	ATII	T_BL	T_LL	ABC	PAC
(A) Genes down-regulated between 1- and 2-folds in TCs as compared with others							
Abcb7	1.37/1.97	1.50/2.15	17.81/25.48	26.27/37.59	15.70/22.47	26.13/37.39	23.93/34.24
Atf1	1.89/2.00	1.86/1.97	6.57/6.95	11.93/12.62	13.90/14.70	23.09/24.43	17.32/18.32
Ddx26b	1.32/1.22	4.39/4.06	5.57/5.15	8.24/7.62	14.11/13.05	4.48/4.14	2.93/2.71
Drp2	1.26/1.79	1.43/2.04	2.58/3.67	2.32/3.30	4.42/6.29	3.67/5.22	2.11/3.01
Fam122b	5.05/6.22	1.08/1.32	1.52/1.87	4.03/4.96	2.87/3.53	6.53/8.03	1.59/1.96
Gyk	2.01/1.79	1.59/1.42	24.83/22.14	6.30/5.62	8.25/7.36	5.35/4.77	16.66/14.85
Irak1	1.31/1.28	1.70/1.66	4.59/4.50	6.03/5.90	5.61/5.49	5.66/5.54	3.52/3.45
Lamp2	1.23/1.36	2.07/2.30	3.91/4.34	1.02/1.14	1.31/1.45	4.49/4.99	3.49/3.88
Mecp2	1.59/1.84	2.35/2.72	1.98/2.29	3.26/3.77	2.79/3.23	2.60/3.01	1.48/1.71
Ndufb11	1.34/1.80	1.05/1.42	4.64/6.26	3.74/5.05	2.71/3.65	5.41/7.30	4.84/6.53
Ogt	1.48/1.63	5.10/5.64	3.73/4.11	15.00/16.56	14.45/15.96	10.01/11.06	6.00/6.63
Pdha1	1.08/1.13	1.16/1.21	9.30/9.73	14.59/15.28	12.53/13.11	10.88/11.39	10.18/10.66
Pola1	1.45/2.04	1.30/1.83	1.31/1.84	1.96/2.76	1.48/2.09	1.69/2.38	2.71/3.82
Rab9	1.03/1.14	1.53/1.70	5.01/5.56	2.89/3.21	2.83/3.14	2.65/2.95	2.84/3.15
Rbmx2	1.01/1.54	1.85/2.81	4.23/6.43	14.71/22.35	10.64/16.17	8.91/13.54	9.89/15.03
Rhox9	1.49/1.53	1.12/1.15	13.98/14.39	13.94/14.35	20.54/21.15	21.07/21.69	8.39/8.64
Thoc2	1.40/1.66	2.54/3.00	1.83/2.17	10.15/12.00	12.25/14.49	7.73/9.14	6.27/7.42
Vbp1	1.04/1.22	1.44/1.70	4.70/5.53	17.42/20.48	16.14/18.98	7.87/9.26	7.10/8.35
(B) Genes down-regulated between 2- and 5-folds in TCs as compared with others							
Dkc1	2.05/2.62	3.58/4.57	8.45/10.78	20.66/26.35	14.18/18.09	28.20/35.98	38.11/48.61
Nkrf	2.36/2.47	2.38/2.50	10.62/11.12	25.28/26.46	14.63/15.32	10.10/10.57	10.10/10.57
Piga	3.52/4.74	3.16/4.25	2.05/2.75	3.41/4.59	3.83/5.16	3.24/4.36	13.95/18.76
Tmlhe	2.62/5.24	3.80/7.61	2.47/4.94	11.75/23.51	8.01/16.03	10.56/21.13	9.27/18.55
Tsr2	3.65/3.27	3.22/2.89	24.69/22.09	24.70/22.10	23.11/20.69	33.31/29.81	26.16/23.41

of chromosome X in TCs, as compared with stem cells, lung interstitial cells, pneumocytes, airway cells, or lymphocytes (Fig. 4).

Srp2, Cfp, Col4a5, Mum111, Rnf128 and Syn1 over-expressed in chromosome X of TCs, as compared with other cells. Srp2 (sushi-repeat-containing protein, X-linked 2) gene was the only one of chromosome X that expressed more than 5 folds in pulmonary TCs as compared with all the other cells. The Srp2-encoded protein was found to be the key factor in the development of speech and language centers in the brain [40], the important mediator in endothelial cell migration and tube formation, and the predictor for tumor growth and metastasis [41–43]. The enrichment of Srp2 in pulmonary TCs suggests the potential role of TCs in the regulation of neuron function, promotion of vessel

formation, and enhance of cellular growth and migration. Those could be performed through the complicated three-dimensional network constructed by the telopodes with other cells. Cfp, Col4a5, Mum111, Rnf128 and Syn1 over-expressed 2–5 folds in TCs within the lung tissue. Cfp (complement factor properdin) encodes a plasma glycoprotein that positively regulates the alternative complement pathway of the innate immune system [44]. TCs were found to be associated with the immune cells including lymphocytes [45], basophiles [46], eosinophils and plasma cells [7]. The high-expressed Cfp suggested that TCs might participate in immune responses and play a potential role in the lung infectious diseases. Col4a5 (collagen, type IV, alpha 5) encodes type IV collagen, which is the major structural component of basement membranes and is critical for tissue remodeling

Table 3 The number of genes specifically up- or down-regulated in pulmonary telocytes, as compared with other cells

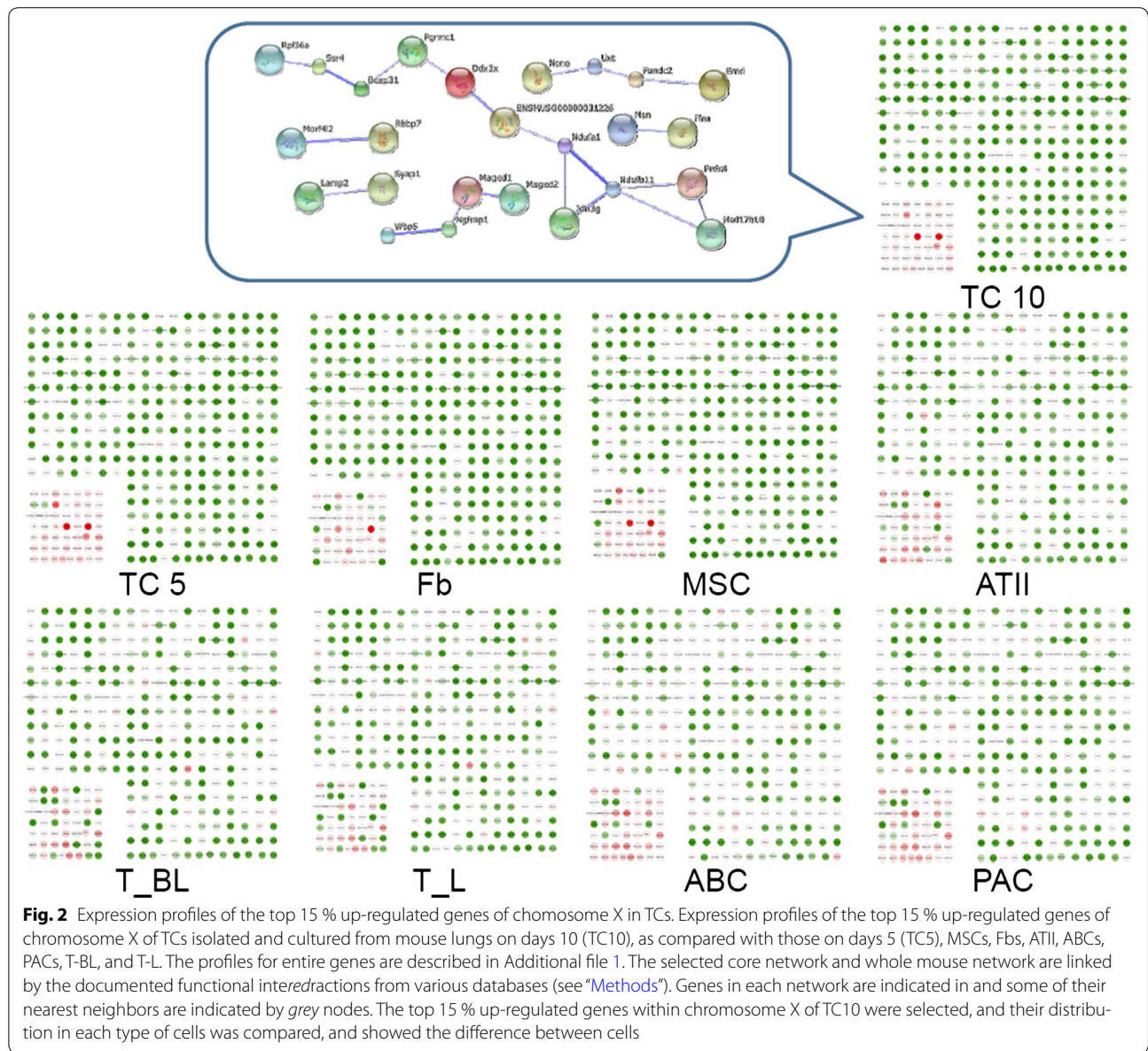
Compared pairs	Up >1	Up >2	Up >5	Down >1	Down >2	Down >5	Down >10
TC5 vs MSC	178	58	21	157	56	9	3
TC10 vs MSC	123	49	18	212	92	14	8
TCs vs MSC	119	36	13	153	45	9	3
TC5 vs Fb	224	100	65	111	28	9	6
TC10 vs Fb	180	81	34	155	65	14	7
TCs vs Fb	172	68	29	103	25	8	5
TC5 vs ATII	101	47	19	234	167	85	42
TC10 vs ATII	75	38	15	260	199	102	56
TCs vs ATII	72	33	12	231	163	73	40
TC5 vs T_BL	99	68	46	236	168	90	54
TC10 vs T_BL	87	59	36	248	201	109	66
TCs vs T_BL	79	54	34	228	166	85	52
TC5 vs T_LL	109	66	35	226	176	103	56
TC10 vs T_LL	86	56	31	249	201	122	75
TCs vs T_LL	81	54	27	221	172	98	55
TC5 vs ABC	68	40	14	267	210	121	67
TC10 vs ABC	51	31	14	284	230	146	90
TCs vs ABC	43	28	11	259	199	116	65
TC5 vs PAC	88	47	22	247	180	89	46
TC10 vs PAC	71	43	20	264	210	111	67
TCs vs PAC	65	37	16	241	174	84	44

and repair [47]. The *Col4a5* gene was also found as a TC-dominant gene as compared with Fbs or MSCs in our previous study [30].

Rnf128 (ring finger protein 128, E3 ubiquitin protein ligase) is associated with cellular apoptosis and cytokine regulation, of which over-expression inhibits the production of activation-induced IL2 and IL4 cytokine, and may converse T cells to the anergic phenotype [48, 49]. This implies that TCs may be involved in inflammation, immune surveillance, or tissue repair after injury by regulating immune function and inflammatory cell. Syn1 (synapsin I) encodes neuronal phosphoproteins associated with the cytoplasmic surface of synaptic vesicles, by which TCs may establish synapses as a special type of heterocellular junctions with other neighbouring cells, including lymphocytes, macrophages, or mast cells [46, 50, 51]. Through those connections to immune cells, TCs could integrate signals, and behave as an immune system modulator. Mum1l1 (melanoma associated antigen (mutated) 1-like 1) is a gene related with melanoma or some other tumors, its function in TCs is not quite clear yet.

Genes down-regulated in chromosome X of pulmonary TCs mainly contribute to gene transcription, protein synthesis and energy metabolism. Nkrf (NFKB

repressing factor) encodes a transcriptional repressor of nuclear factor kappa B (NF- κ B) and is activated for cell survival, proliferation and immune responses. It indicates that TCs per se have relatively high capacities of proliferation and involvements of immune reactions in physiological conditions, although there are needs of direct evidences to show roles and changes of TCs in cancers, infection, autoimmune diseases, or injury [52–55]. Tsr2 [TSR2, 20S rRNA accumulation, homolog (*S. cerevisiae*)] is another inhibitor of NF- κ B, and induces cell apoptosis [56]. Pulmonary TCs may be more involved in activities and processes dominated by NF- κ B such as the production of inflammatory mediators, due to the down-regulation of NF- κ B inhibitors in TCs. Dkc1 (dyskeratosis congenita 1, dyskerin) plays an important role in telomerase stabilization and DNA damage response, regulation of a subset of microRNAs, nucleo-cytoplasmic shuttling, and cell adhesion [57]. It suggested that TCs have better abilities to resist senescence and external stresses. Piga (phosphatidylinositol glycan anchor biosynthesis, class A) is a gene related with paroxysmal nocturnal hemoglobinuria and encodes a protein required for synthesis of *N*-acetylglucosaminyl phosphatidylinositol, the first intermediate in the biosynthetic pathway



of a glycolipid on blood cells and to anchor proteins to the cell surface [58]. Tmlhe (trimethyllysine hydroxylase, epsilon) encodes the first enzyme in the carnitine biosynthesis pathway related with the transport of activated fatty acids across the inner mitochondrial membrane [59]. The significance of those two down-regulated genes in TCs still remains unclear. Based on the level of gene expression, the limitation of the study is inevitable, since gene expression level cannot equally reflect the protein level or the function change in the cells. Fold changes of gene expression may not be in direct proportion to the functional significance. More studies will be conducted in the future to detect

the relationships among TC-specific genes, TC-specific proteins and the function of TCs.

Conclusions

In conclusion, the present study initially compared genetic variations of chromosome X of pulmonary TCs with MSCs, Fbs, ATII, ABCs, PACs, or bronchial and lung lymphocytes by global analyses. Our data demonstrated that 8 or 23 genes of TC chromosome X up- or down-regulated, respectively, indicating that biological functions of TCs may be mainly fulfilled through the network constructed by the telopodes with connecting cells and act as an integrated modulator to regulate neural

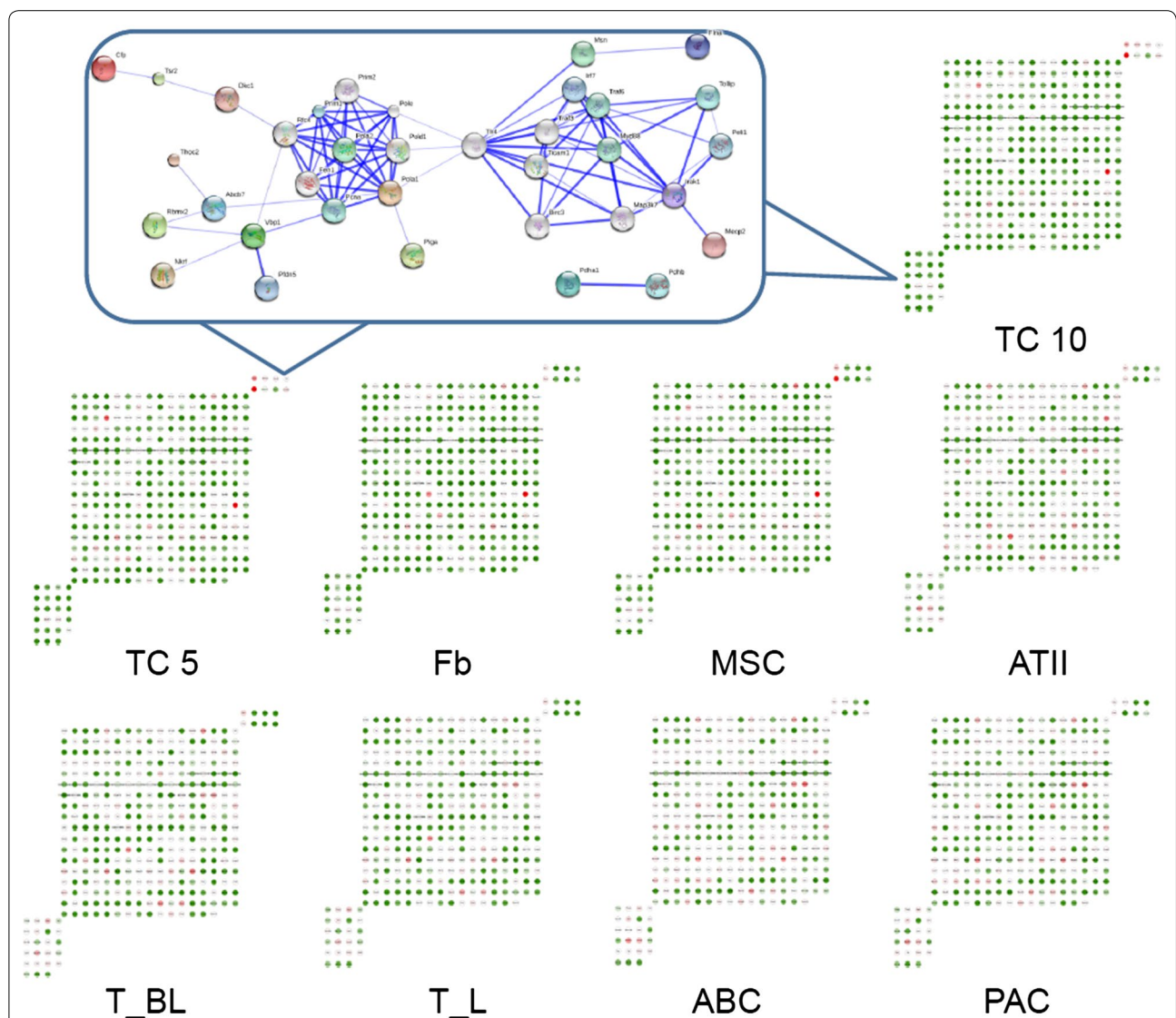
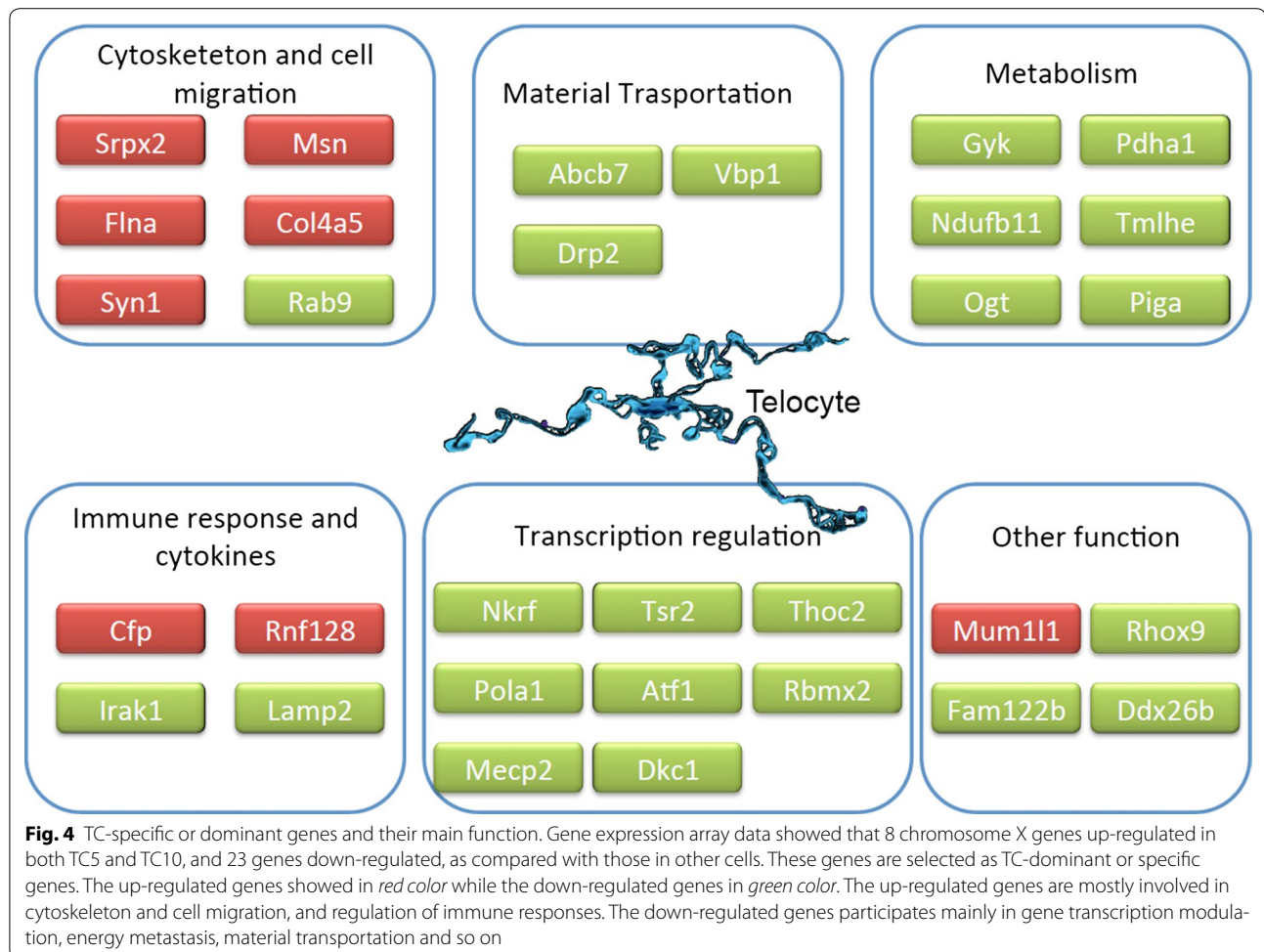


Fig. 3 Expression profiles of TC-specific or dominant genes. Expression profiles of the up- or down-regulated genes (more than one fold) in both TC5 and TC10 as compared with MSCs, Fbs, ATII, ABCs, PACs, T-BL and T-L. The profiles for entire genes are described in Additional file 1. The selected core network and whole mouse network are linked by the documented functional interactions from various databases (see “Methods”). Genes in each network are indicated in *red* and some of their nearest neighbors are indicated by *grey* nodes. The 8 up-regulated genes in TCs were shown in the *upper right corner*, while the 23 down-regulated genes in the *lower left* and their distribution in each type of cells showed in Fig. 2b. These up- or down-regulated genes were considered as TC-specific or TC-dominant genes. The connections between these genes were analyzed and illustrated

function and immune responses, promote vessel formation and cellular growth and migration, and participate in tissue remodeling and repair. TCs may have the potential

function to support cell survival, anti-senescence, and protection from stresses. Pulmonary TCs with stronger NF-κB-dominant activities may play the important and



critical roles in pathogenesis of lung diseases, although further studies on those chromosome X genes of pulmonary TC are needed.

Additional files

Additional file 1. Data profiles for all genes in chromosome X.

Additional file 2. Details of up-regulated or down-regulated gene expression variations in chromosome X.

Abbreviations

TC: telocyte; TC10: telocytes isolated and cultured from mouse lungs on days 10; TC5: telocytes isolated and cultured from mouse lungs on days 5; MSC: mesenchymal stem cell; Fb: fibroblast; ATI: alveolar type II cell; ABC: airway basal cell; PAC: proximal airway cell; T-BL: CD8⁺ T cells come from bronchial lymph node; T-L: CD8⁺ T cells from lungs.

Authors' contributions

YCZ planned and performed studies, analyzed data and wrote the manuscript; and XDW made study plans, overviewed data, and prepare the manuscript. MHZ, DLS, and LY analysed data and performed data mining. All authors read and approved the final manuscript.

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Compliance with ethical guidelines

Competing interests

The authors declare that they have no competing interests.

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References

- Popescu L, Faussone-Pellegrini MS. TELOCYTES—a case of serendipity: the winding way from Interstitial Cells of Cajal (ICC), via Interstitial Cajal-Like Cells (ICLC) to TELOCYTES. *J Cell Mol Med*. 2010;14:729–40.
- Gherghiceanu M, Popescu L. Cardiomyocyte precursors and telocytes in epicardial stem cell niche: electron microscope images. *J Cell Mol Med*. 2010;14:871–7.

3. Zheng Y, Li H, Manole CG, Sun A, Ge J, Wang X. Telocytes in trachea and lungs. *J Cell Mol Med*. 2011;15:2262–8. doi:10.1111/j.1582-4934.2011.01404.x.
4. Cantarero Carmona I, Luesma Bartolomé MJ, Junquera Escribano C. Identification of telocytes in the lamina propria of rat duodenum: transmission electron microscopy. *J Cell Mol Med*. 2011;15:26–30. doi:10.1111/j.1582-4934.2010.01207.x.
5. Rusu MC, Nicolescu MI, Jianu AM, Lighezan R, Manoiu VS, Paduraru D. Esophageal telocytes and hybrid morphologies. *Cell Biol Int*. 2012;36:1079–88. doi:10.1042/cbi20120007.
6. Xiao J, Wang F, Liu Z, Yang C. Telocytes in liver: electron microscopic and immunofluorescent evidence. *J Cell Mol Med*. 2013;17:1537–42. doi:10.1111/jcmm.12195.
7. Popescu LM, Manole E, Serboiu CS, Manole CG, Suciuc LC, Gherghiceanu M, et al. Identification of telocytes in skeletal muscle interstitium: implication for muscle regeneration. *J Cell Mol Med*. 2011;15:1379–92. doi:10.1111/j.1582-4934.2011.01330.x.
8. Gevaert T, De Vos R, Van Der Aa F, Joniau S, van den Oord J, Roskams T, et al. Identification of telocytes in the upper lamina propria of the human urinary tract. *J Cell Mol Med*. 2012;16:2085–93. doi:10.1111/j.1582-4934.2011.01504.x.
9. Qi G, Lin M, Xu M, Manole CG, Wang X, Zhu T. Telocytes in the human kidney cortex. *J Cell Mol Med*. 2012;16:3116–22. doi:10.1111/j.1582-4934.2012.01582.x.
10. Rusu MC, Mirancea N, Manoiu VS, Valcu M, Nicolescu MI, Paduraru D. Skin telocytes. *Ann Anat*. 2012;194:359–67. doi:10.1016/j.aanat.2011.11.007.
11. Mou Y, Wang Y, Li J, Lu S, Duan C, Du Z, et al. Immunohistochemical characterization and functional identification of mammary gland telocytes in the self-assembly of reconstituted breast cancer tissue in vitro. *J Cell Mol Med*. 2013;17:65–75. doi:10.1111/j.1582-4934.2012.01646.x.
12. Nicolescu MI, Popescu LM. Telocytes in the interstitium of human exocrine pancreas: ultrastructural evidence. *Pancreas*. 2012;41:949–56. doi:10.1097/MPA.0b013e31823fbded.
13. Popescu BO, Gherghiceanu M, Kostin S, Ceafalan L, Popescu LM. Telocytes in meninges and choroid plexus. *Neurosci Lett*. 2012;516:265–9. doi:10.1016/j.neulet.2012.04.006.
14. Hatta K, Huang ML, Weisel RD, Li RK. Culture of rat endometrial telocytes. *J Cell Mol Med*. 2012;16:1392–6. doi:10.1111/j.1582-4934.2012.01583.x.
15. Suciuc L, Popescu LM, Gherghiceanu M, Regalia T, Nicolescu MI, Hinescu ME, et al. Telocytes in human term placenta: morphology and phenotype. *Cells Tissues Organs*. 2010;192:325–39. doi:10.1159/000319467.
16. Nicolescu MI, Bucur A, Dinca O, Rusu MC, Popescu LM. Telocytes in parotid glands. *Anat Rec Hoboken*. 2012;295:378–85. doi:10.1002/ar.21540.
17. Corradi LS, Jesus MM, Fochi RA, Vilamaior PS, Justulin LA Jr, Goes RM, et al. Structural and ultrastructural evidence for telocytes in prostate stroma. *J Cell Mol Med*. 2013;17:398–406. doi:10.1111/jcmm.12021.
18. Luesma MJ, Gherghiceanu M, Popescu LM. Telocytes and stem cells in limbus and uvea of mouse eye. *J Cell Mol Med*. 2013;17:1016–24. doi:10.1111/jcmm.12111.
19. Gherghiceanu M, Popescu LM. Cardiac telocytes—their junctions and functional implications. *Cell Tissue Res*. 2012;348:265–79.
20. Crețoiu SM, Crețoiu D, Popescu LM. Human myometrium—the ultrastructural 3D network of telocytes. *J Cell Mol Med*. 2012;16:2844–9.
21. Popescu L, Gherghiceanu M, Crețoiu D, Radu E. The connective connection: interstitial cells of Cajal (ICC) and ICC-like cells establish synapses with immunoreactive cells: electron microscope study in situ. *J Cell Mol Med*. 2005;9:714–30.
22. Popescu LM, Gherghiceanu M, Suciuc LC, Manole CG, Hinescu ME. Telocytes and putative stem cells in the lungs: electron microscopy, electron tomography and laser scanning microscopy. *Cell Tissue Res*. 2011;345:391–403.
23. Hinescu ME, Gherghiceanu M, Suciuc L, Popescu LM. Telocytes in pleura: two- and three-dimensional imaging by transmission electron microscopy. *Cell Tissue Res*. 2011;343:389–97. doi:10.1007/s00441-010-1095-0.
24. Vannucchi MG, Bani D, Fausson-Pellegrini MS. Telocytes contribute as cell progenitors and differentiation inductors in tissue regeneration. *Curr Stem Cell Res Ther* 2015 [Epub ahead of print].
25. Crețoiu SM, Popescu LM. Telocytes revisited. *Biomol Concept*. 2014;5:353–69.
26. Rosenbaum ST, Svalø J, Nielsen K, Larsen T, Jørgensen JC, Bouchelouche P. Immunolocalization and expression of small-conductance calcium-activated potassium channels in human myometrium. *J Cell Mol Med*. 2012;16:3001–8.
27. Sheng J, Shim W, Lu J, Lim SY, Ong BH, Lim TS, et al. Electrophysiology of human cardiac atrial and ventricular telocytes. *J Cell Mol Med*. 2014;18:355–62.
28. Zheng Y, Bai C, Wang XD. Potential significance of telocytes in the pathogenesis of lung diseases. *Expert Rev Respir Med*. 2012;6(1):45–9. doi:10.1586/ers.11.91.
29. Vannucchi MG, Traini C, Manetti M, Ibba-Manneschi L, Fausson-Pellegrini MS. Telocytes express PDGFR α in the human gastrointestinal tract. *J Cell Mol Med*. 2013;17:1099–108.
30. Zheng Y, Zhang M, Qian M, Wang L, Cismasiu VB, Bai C, et al. Genetic comparison of mouse lung telocytes with mesenchymal stem cells and fibroblasts. *J Cell Mol Med*. 2013;17:567–77. doi:10.1111/jcmm.12052.
31. Cismasiu VB, Radu E, Popescu LM. miR-193 expression differentiates telocytes from other stromal cells. *J Cell Mol Med*. 2011;15:1071–4. doi:10.1111/j.1582-4934.2011.01325.x.
32. Gherghiceanu M, Popescu LM. Cardiac telocytes—their junctions and functional implications. *Cell Tissue Res*. 2012;348:265–79. doi:10.1007/s00441-012-1333-8.
33. Manole CG, Cismasiu V, Gherghiceanu M, Popescu LM. Experimental acute myocardial infarction: telocytes involvement in neo-angiogenesis. *J Cell Mol Med*. 2011;15:2284–96. doi:10.1111/j.1582-4934.2011.01449.x.
34. Sun X, Zheng M, Zhang M, Qian M, Zheng Y, Li M, et al. Differences in the expression of chromosome 1 genes between lung telocytes and other cells: mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells and lymphocytes. *J Cell Mol Med*. 2014;18:801–10.
35. Zheng M, Sun X, Zhang M, Qian M, Zheng Y, Li M, et al. Variations of chromosomes 2 and 3 gene expression profiles among pulmonary telocytes, pneumocytes, airway cells, mesenchymal stem cells and lymphocytes. *J Cell Mol Med*. 2014;18:2044–60.
36. Wang J, Ye L, Jin M, Wang X. Global analyses of Chromosome 17 and 18 genes of lung telocytes compared with mesenchymal stem cells, fibroblasts, alveolar type II cells, airway epithelial cells, and lymphocytes. *Biol Direct*. 2015;10:9.
37. Xu Y, Ikegami M, Wang Y, Matsuzaki Y, Whittsett JA. Gene expression and biological processes influenced by deletion of Stat3 in pulmonary type II epithelial cells. *BMC Genom*. 2007;8:455. doi:10.1186/1471-2164-8-455.
38. Chen W, Ware LB. Prognostic factors in the acute respiratory distress syndrome. *Clin Transl Med*. 2015;4(1):65. doi:10.1186/s40169-015-0065-2.
39. Ross MT, Grafham DV, Coffey AJ, Scherer S, McLay K, Muzny D, et al. The DNA sequence of the human X chromosome. *Nature*. 2005;434:325–37.
40. Sia GM, Clem RL, Haganir RL. The human language-associated gene SRPX2 regulates synapse formation and vocalization in mice. *Science*. 2013;342:987–91. doi:10.1126/science.1245079.
41. Yamada T, Oshima T, Yoshihara K, Sato T, Nozaki A, Shiozawa M, et al. Impact of overexpression of Sushi repeat-containing protein X-linked 2 gene on outcomes of gastric cancer. *J Surg Oncol*. 2014;109:836–40. doi:10.1002/jso.23602.
42. Tanaka K, Arai T, Tamura D, Aomatsu K, Furuta K, Matsumoto K, et al. SRPX2 is a novel chondroitin sulfate proteoglycan that is overexpressed in gastrointestinal cancer. *PLoS One*. 2012;7:e27922. doi:10.1371/journal.pone.0027922.
43. Tanaka K, Arai T, Maegawa M, Matsumoto K, Kaneda H, Kudo K, et al. SRPX2 is overexpressed in gastric cancer and promotes cellular migration and adhesion. *Int J Cancer*. 2009;124:1072–80. doi:10.1002/ijc.24065.
44. Saggiu G, Cortes C, Emch HN, Ramirez G, Worth RG, Ferreira VP. Identification of a novel mode of complement activation on stimulated platelets mediated by properdin and C3(H2O). *J Immunol*. 2013;190:6457–67. doi:10.4049/jimmunol.1300610.
45. Wang XY, Berezin I, Mikkelsen HB, Der T, Berck P, Collins SM, et al. Pathology of interstitial cells of Cajal in relation to inflammation revealed by ultrastructure but not immunohistochemistry. *Am J Pathol*. 2002;160:1529–40.
46. Popescu LM, Gherghiceanu M, Crețoiu D, Radu E. The connective connection: interstitial cells of Cajal (ICC) and ICC-like cells establish synapses with immunoreactive cells. Electron microscope study in situ. *J Cell Mol Med*. 2005;9:714–30.
47. Massella L, Muda AO, Faraggiana T, Bette C, Renieri A, Rizzoni G. Epidermal basement membrane alpha 5(IV) expression in females with Alport

- syndrome and severity of renal disease. *Kidney Int.* 2003;64:1787–91. doi:10.1046/j.1523-1755.2003.00251.x.
48. Su LL, Iwai H, Lin JT, Fathman CG. The transmembrane E3 ligase GRAIL ubiquitinates and degrades CD83 on CD4 T cells. *J Immunol.* 2009;183:438–44. doi:10.4049/jimmunol.0900204.
 49. MacKenzie DA, Schartner J, Lin J, Timmel A, Jennens-Clough M, Fathman CG, et al. GRAIL is up-regulated in CD4 + CD25 + T regulatory cells and is sufficient for conversion of T cells to a regulatory phenotype. *J Biol Chem.* 2007;282:9696–702. doi:10.1074/jbc.M604192200.
 50. Rusu MC, Jianu AM, Mirancea N, Didilescu AC, Manoiu VS, Paduraru D. Tracheal telocytes. *J Cell Mol Med.* 2012;16:401–5. doi:10.1111/j.1582-4934.2011.01465.x.
 51. Chen X, Zheng Y, Manole CG, Wang X, Wang Q. Telocytes in human oesophagus. *J Cell Mol Med.* 2013;17:1506–12. doi:10.1111/jcmm.12149.
 52. King PT. Inflammation in chronic obstructive pulmonary disease and its role in cardiovascular disease and lung cancer. *Clin Transl Med.* 2015;4:26.
 53. Ho SC, Lee KY, Chan YF, Kuo LW, Ito K, Adcock IM, et al. Neutrophil elastase represses IL-8/CXCL8 synthesis in human airway smooth muscle cells through induction of NF-kappa B repressing factor. *J Immunol.* 2009;183:411–20. doi:10.4049/jimmunol.0803729.
 54. Swindell WR, Sarkar MK, Stuart PE, Voorhees JJ, Elder JT, Johnston A, Gudjonsson JE. Psoriasis drug development and GWAS interpretation through in silico analysis of transcription factor bindingsites. *Clin Transl Med.* 2015;4:13. doi:10.1186/s40169-015-0054-5.
 55. López E, Muñoz S, Pascual J, Madero L. Relevant phosphoproteomic and mass spectrometry: approaches useful in clinical research. *Clin Transl Med.* 2012;1:2.
 56. Graves CA, Abboodi FF, Tomar S, Wells J, Pirisi L. The translational significance of epithelial-mesenchymal transition in head and neck cancer. *Clin Transl Med.* 2014;3:39.
 57. Gu BW, Bessler M, Mason PJ. A pathogenic dyskerin mutation impairs proliferation and activates a DNA damage response independent of telomere length in mice. *Proc Natl Acad Sci U S A.* 2008;105:10173–8. doi:10.1073/pnas.0803559105.
 58. Johnston JJ, Gropman AL, Sapp JC, Teer JK, Martin JM, Liu CF, et al. The phenotype of a germline mutation in PIGA: the gene somatically mutated in paroxysmal nocturnal hemoglobinuria. *Am J Hum Genet.* 2012;90:295–300. doi:10.1016/j.ajhg.2011.11.031.
 59. Nava C, Lamari F, Heron D, Mignot C, Rastetter A, Keren B, et al. Analysis of the chromosome X exome in patients with autism spectrum disorders identified novel candidate genes, including TMLHE. *Transl Psychiatry.* 2012;2:e179. doi:10.1038/tp.2012.102.

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