Tumor Biology

COL11A1/(pro)collagen 11A1 expression is a remarkable biomarker of human invasive carcinoma-associated stromal cells and carcinoma progression

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Corresponding Author:	Juan R de los Toyos, Ph. D. Universidad de Oviedo Oviedo, Asturias SPAIN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Universidad de Oviedo
Corresponding Author's Secondary Institution:	
First Author:	Fernando Vázquez-Villa
First Author Secondary Information:	
Order of Authors:	Fernando Vázquez-Villa
	Marcos García-Ocaña
	José A Galván
	Jorge García-Martínez
	Carmen García-Pravia
	Primitiva Menéndez-Rodríguez
	Carmen González-del Rey
	Luis Barneo-Serra
	Juan R de los Toyos, Ph. D.
Order of Authors Secondary Information:	
Abstract:	The COL11A1 human gene codes for the α1 chain of procollagen 11A1 and mature collagen 11A1, an extracellular minor fibrillar collagen. Under regular conditions, this gene and its derived products are mainly expressed by chondrocytes and mesenchymal stem cells as well as osteoblasts. Normal epithelial cells and quiescent fibroblasts from diverse locations do not express them. Mesenchyme-derived tumours and related conditions such as scleroderma and keloids, are positive for COL11A1/(pro)collagen 11A1 expression, as well as high grade human gliomas/glioblastomas. This expression is almost absent in benign pathological processes such as breast hyperplasia, sclerosing adenosis, idiopathic pulmonary fibrosis, cirrhosis, pancreatitis, diverticulitis, and inflammatory bowel disease. By contrast, COL11A1/(pro)collagen 11A1 is highly expressed by activated stromal cells of the desmoplastic reaction of different human invasive carcinomas, and this expression is correlated with carcinoma aggressiveness and progression, and lymph node metastasis. COL11A1 up-regulation has been shown to be associated to TGF-β1, Wnt and Hh signalling pathways, which are especially active in cancer-associated stromal cells. At the front of invasive carcinomas, neoplastic epithelial cells, putatively undergoing epithelial-to-mesenchymal transition, and carcinoma-derived cells with highly

	metastatic capabilities, can express COL11A1. Thus, in established metastases, the expression of COL11A1/(pro)collagen 11A1 could rely on both the metastatic epithelial cells and/or the accompanying activated stromal cells. Conclusion: COL11A1/(pro)collagen 11A1 expression is a remarkable biomarker of human carcinoma-associated stromal cells and carcinoma progression.
Response to Reviewers:	Reviewer #1: The review titled "COL11A1/(pro)collagen 11A1 expression is a remarkable biomarker of human invasive carcinoma-associated stromal cells and carcinoma progression" details the current knowledge of this topic and reference 97 previous studies. The authors are have been involved with this research topic and therefore can contribute with their own experience. The topic is important in cancer biology and has clinical implications. Reply to comments The figures that are now included are suboptimal. Figure 1 and 2 should be reconsidered with the aim of generating one figure with the necessary information. We have now combined former Figures 1 and 2 in just one new Figure 1, which has been redrawn, keeping the information we have considered as most relevant. Figure 3 is unclear and does not convey the information provided in text that both stromal and epithelial cells within the tumor may express col11a1. We have partially redrawn former Figure 3 -now Figure 2- , making a reference to the putative expression of COL11A1/(pro)collagen11A1 in the epithelial front of invasive carcinomas. The example of immunohistochemistry (fig. 4) could be improved given the authors previous experience. The Authors could display examples of human primary tumors (and stroma) as well as cell lines. We have now added more photos of examples of the expression of procollagen 11A1 in different kind of human tumors and cell lines -new Figure 3-. Some data on different tumors could be shown with a table, which could facilitate comparative analysis. We have now tried to summarize in a new Table 1 the up-regulation of COL11A1/(pro)collagen 11A1 expression in different human tumours, according to the current literature. There are 9 authors listed: this is unusual for a review paper. What are the contributions of all these authors? This review was intended as an update of those aspects of the biology of COL11A1/(pro)collagen 11A1 in which our team has been involved for the last years. It is the result of experimental observations, clinical findings, literature revisions and discussions, in which all of us have participated and have been actively engaged. For these reasons, we think that all the members of our team are entitled to be acknowledged as authors. Reviewer #3 : The presented article is perfectly writed, designed, explained and defended. For myself I find no more comments to add.

	Reply to comments Perhaps slightly revise of the abstract since its reading becomes a little difficult because is so sketchy. According to Reviewer #3 comment(s), we now provide a longer version of the Abstract to make it easier to read.

COL11A1/(pro)collagen 11A1 expression is a remarkable biomarker of human invasive carcinoma-associated stromal cells and carcinoma progression

Fernando Vázquez-Villa[1,2], Marcos García-Ocaña[2,3], José A. Galván[1,2*], Jorge García-Martínez[1,2], Carmen García-Pravia[2,4], Primitiva Menéndez-Rodríguez[4], Carmen González-del Rey[4], Luis Barneo-Serra[1,2], and Juan R. de los Toyos[2,5]

[1]Surgery Department, School of Medicine and Health Sciences, University of Oviedo, 33006 Oviedo, Spain; [2]Oncology University Institute of the Principality of Asturias (IUOPA), 33006 Oviedo, Spain; [3]Preparative Biotechnology Unit, Technical-Scientific Services, University of Oviedo, 33006 Oviedo, Spain; [4]Pathological Anatomy Service, Asturias Central University Hospital (HUCA), 33006 Oviedo, Spain; and [5]Immunology Department, School of Medicine and Health Sciences, University of Oviedo, 33006 Oviedo, Spain.

*Present address: Translational Research Unit (TRU), Institute of Pathology, University of Bern, Bern, Switzerland

Corresponding author: Prof. Juan R. de los Toyos, Área de Inmunología, Facultad de Medicina y Ciencias de la Salud, Universidad de Oviedo, c/ Julián Clavería s/n, 33006 Oviedo, Spain

E-mail: jrtoyos@uniovi.es; Phone: +34 985 106244; Fax: +34 985 103534

Abstract

The *COL11A1* human gene codes for the α1 chain of procollagen 11A1 and mature collagen 11A1, an extracellular minor fibrillar collagen.

Under regular conditions, this gene and its derived products are mainly expressed by chondrocytes and mesenchymal stem cells as well as osteoblasts. Normal epithelial cells and quiescent fibroblasts from diverse locations do not express them.

Mesenchyme-derived tumours and related conditions such as scleroderma and keloids, are positive for *COL11A1*/(pro)collagen 11A1 expression, as well as high grade human gliomas/glioblastomas. This expression is almost absent in benign pathological processes such as breast hyperplasia, sclerosing adenosis, idiopathic pulmonary fibrosis, cirrhosis, pancreatitis, diverticulitis, and inflammatory bowel disease. By contrast, *COL11A1*/(pro)collagen 11A1 is highly expressed by activated stromal cells of the desmoplastic reaction of different human invasive carcinomas, and this expression is correlated with carcinoma aggressiveness and progression, and lymph node metastasis.

COL11A1 up-regulation has been shown to be associated to TGF-β1, Wnt and Hh signalling pathways, which are especially active in cancer-associated stromal cells.

At the front of invasive carcinomas, neoplastic epithelial cells, putatively undergoing epithelial-to-mesenchymal transition, and carcinoma-derived cells with highly metastatic capabilities, can express *COL11A1*. Thus, in established metastases, the expression of *COL11A1*/(pro)collagen 11A1 could rely on both the metastatic epithelial cells and/or the accompanying activated stromal cells.

Conclusion: *COL11A1*/(pro)collagen 11A1 expression is a remarkable biomarker of human carcinoma-associated stromal cells and carcinoma progression.

Keywords: *COL11A1*; (pro)collagen 11A1; stromal cells; human invasive carcinoma

(Pro)collagen 11A1 structure and normal tissue distribution

The *COL11A1* human gene codes for the α1 chain of procollagen and mature collagen of type XI, which is an extracellular minor fibrillar collagen.

Each collagen protomer is usually made of three different polypeptides, designed as α1, α2, and α3, and coded by specific gene sequences. In collagen of type XI, the α1 and α2 chains are coded by the *COL11A1* and *COL11A2* genes, respectively; however, the α3 chain is identical to α1(II), coded by the *COL2A1* gene, which is the main component of collagen of type II. These polypeptides are synthesized as procollagens, which include the globular N- and C-propeptides flanking the prototypical collagen triple helix. Upon secretion, the propeptides are excised by proteolytic cleavage; at the ends of the triple-helical collagen molecule, short N- and C-telopeptides remain [1]. Then, the mature collagen molecules self-assemble into fibrils, on the cell surface and/or in the extracellular matrix, through covalent cross-links between telopeptides and specific Triple-helical Telopeptide-Binding Regions [2] (Fig. 1).

Minor fibrillar collagens of type V and XI are considered to act as nucleators, controlling the assembly of collagen fibrils, in such a way that they become mostly buried, under major fibrillar collagens I, II and III, in the core of the mature heterotypic extracellular fibril [3]. Extracellular collagens are main components of the extracellular matrix, along with proteoglycans and glycoproteins such as fibronectin and tenascin C, among others.

In the adult, (pro)collagen 11A1 is present in the ocular vitreous, in the inner ear, in hyaline cartilage, and in the *nucleus pulposus* of the intervertebral disc [4]. In the latter, it is mainly produced by chondrocytes; in the case of the ocular vitreous, by keratocytes (corneal fibroblasts). It is also expressed by mesenchymal stem cells and osteoblasts [5-6] (Fig. 2).

Under regular conditions, normal epithelial cells and quiescent fibroblasts, from diverse locations, do not express *COL11A1*/(pro)collagen 11A1.

Regulation of the expression of *COL11A1*/(pro)collagen 11A1

So far, two transcription factors have been reported to interact with the *COL11A1* promoter. Matsuo et al. [7] and Hida et al. [8] have shown that the transcription factor NF-Y regulates the proximal promoter activity of the *COL11A1* gene in both cartilage and non-cartilage cells. Lymphocyte enhancer-binding factor 1 (Lef1), which participates in the Wnt signalling pathway, and is important in osteoblast maturation [9], indirectly activates *COL11A1*.

Human mesenchymal stem cells (HMSCs), upon exposure to TGF-β1, differentiate to carcinoma-associated fibroblast-like cells and up-regulate their *COL11A1* expression [10-12]. In line with this, in fibroblasts, it was confirmed that TGF-β signalling activates the transcription of the *COL11A1* gene [13]. Recently, TGF-β1 has been shown to up-regulate NF-Y and to modulate its binding to the *COL11A1* promoter, resulting in induction of *COL11A1* mRNA [14]. Similarly, the activation of the Hedgehog (Hh) pathway increases the expression of *COL11A1* [15].

In cancer-associated stromal cells, several signalling activation pathways, such as the TGF-β1, Wnt or Hh, have been identified to be active [16-19]. The expression of *WISP*-1, a downstream mediator of the Wnt signalling pathway has been found to be correlated with the expression of *COL11A1* in sporadic colorectal carcinomas [20]. Activation of Wnt signalling in stroma from pancreatic cancer is also associated to high *COL11A1* expression [21]. Hh signalling promotes desmoplasia and is restricted to the stromal compartment in pancreatic cancer [22-23].

The *COL11A1* gene is expressed in mesenchymal-type/soft tissue human tumours such as rhabdomyosarcoma, chondrosarcoma, fibrosarcoma, osteosarcoma or Ewing´s sarcoma [24-25], as well as in solitary fibrous tumours [26].

A high expression of *COL11A1* has been found as well in at least some human gliomas/glioblastomas, especially of high-grade; these tumours are thought to be derived from mesenchymal stem cells [27-30].

Keloids are benign dermal fibroproliferative tumours, characterised by dense nodules of collagens and fibroblasts; the TGFβ/Smad pathway is paramount in this disease. *COL11A1* has been found to be overexpressed in human keloid fibroblasts related to normal skin fibroblasts [31-33].

In scleroderma skin, another condition with extensive fibroblast activation and up-regulation of the TGFβ and Wnt signalling pathways, the overexpression of *COL11A1* has also been reported [34].

Thus, according to all these observations, *COL11A1* expression is mainly restricted to mesenchyme-derived cells (Fig. 2).

***COL11A1*/(pro)collagen 11A1 expression as biomarker of carcinoma-associated stromal cells and carcinoma progression**

Classically, fibroblasts are described as spindle-shaped stromal cells, which express mesenchymal biomarkers such as *VIM*/vimentin.

They can be activated under a number of conditions, and they express some additional biomarkers, such as fibroblast activation protein (FAP).

One of the conditions which leads to the activation of fibroblasts is their association to malignant tumours. They are then generically called cancer-associated fibroblasts (CAFs), a heterogeneous group which includes various stromal cell types,

which along with the accompanying extracellular matrix components, build up the desmoplastic reaction. According to Togo et al., 2013 [35], "Several different markers, such as α-SMA, tenascin-C (TN-C), periostin (POSTN), neuron-glial antigen2 (NG2), PDGFRα/β, fibroblast activated protein (FAP), palladin and podoplanin are reported to be useful for detecting activated stromal fibroblast populations in CAFs"; however, *in strictu sensu*, some of these markers are not exclusive to CAFs.

α-SMA is a general biomarker of myofibroblasts, either resting or activated. Tenascin C is highly expressed in tissue repair and chronic inflammation [36]. Periostin is expressed by airway epithelial cells [37]. In the adult intestine, NG-2/CSPG4/MCSP expression is observed within myofibroblasts and pericytes [38]. PDGFRα/β is also expressed by fibroblasts of the idiopathic pulmonary fibrosis [39]. FAP has increased expression during tissue damage, wound healing, fibrosis and inflammation [40]. According to Rönty [41], palladin is widely expressed in both epithelial and mesenchymal tissues, in muscle cells and in non-muscle cells. As shown by Schacht et al. [42], the lymphatic marker podoplanin is expressed by different cell types, and by alveolar epithelial type I cells in lung. Some other markers, such as Fibroblast Surface Protein and fibroblast specific protein-1 (FSP-1)/S100A4, are not either specific of CAFs.

Under normal regular conditions, *COL11A1*/(pro)collagen 11A1 is not expressed in stromal cells of head and neck, breast, lung, stomach, liver, pancreas and colon; and it is almost absent in benign pathological processes such as breast hyperplasia, sclerosing adenosis [43], idiopathic pulmonary fibrosis, cirrhosis [44], pancreatitis [45], diverticulitis, and inflammatory bowel disease [46].

In invasive carcinomas, the extracellular collagens are key players of tumour behaviour and are subjected to continuous remodelling in such a way that they both

inhibit and promote tumour progression depending on the stage of tumour development [47].

COL11A1/(pro)collagen 11A1 is highly expressed by activated stromal cells of the desmoplastic reaction of human invasive carcinomas of oral cavity/pharynx [48], head and neck [49-50], breast [43, 51-55], lung [56-60], esophagus [61], stomach [62-63], pancreas [44, 64-66], colon [20, 67-71], and ovary [14, 72] (Fig. 2). In these scenarios, the expression of *COL11A1*/(pro)collagen 11A1 is correlated with carcinoma aggressiveness and progression, and lymph node metastasis (Table 1).

According to Vecci et al. [62], *COL11A1* was the gene with the overall highest fold-change in advanced gastric cancer in comparison with early gastric cancer. These observations were confirmed later on by Zhao et al. [63] as *COL11A1* was found to be expressed by stromal cells in the vicinity of developing carcinoma *in situ* in stomach, increasingly with the progression of the carcinoma, allowing to distinguish between premalignant and malignant lesions.

Similarly, Freire et al. [55], Stuetz et al. [73], Ma et al. [74], Lee et al. [75], Castellana et al. [76], and Vargas et al. [77], reported that *COL11A1/*(pro)collagen 11A1 is overexpressed in invasive ductal carcinoma (IDC) of the breast relative to ductal carcinoma *in situ* (DCIS).

The expression of *COL11A1* has also been shown to be associated with progression and poor survival of ovarian cancer patients [14, 72]. Based on *in vitro* observations, Sok et al. [50] reached similar conclusions regarding head and neck squamous cell cancer growth and invasion. More recently, Galván et al. [71] found that the immunodetection of procollagen 11A1 is associated with the development of distant metastases and advanced Dukes staging of human colon adenocarcinoma.

Through co-immunostainings on pancreatic ductal adenocarcinoma samples, procollagen 11A1+ cells have been shown to express some other mesenchymal markers, such as vimentin, α-SMA or desmin in different proportions [66], which confers to them an "activated myofibroblast-like" phenotype. In all the different types of human invasive carcinomas so far studied, these cells are mainly peritumoral, located around the tumor foci. It is intriguing that only a fraction of the peritumoral spindle-shaped α-SMA+ myofibroblast-like cells are procollagen 11A1+. Since it has been shown that some carcinoma-associated stromal cells are in part derived from mesenchymal progenitors and some of these progenitors express *COL11A1/*(pro)collagen 11A1, it has been suggested that peritumoral procollagen 11A1+ cells could be a more especialized subpopulation of activated myofibroblasts [71].

Although *COL11A1* has been reported to be expressed to some extent by vascular smooth muscle cells [78] and tumour endothelial cells [79], immunostaining of blood vessel walls has never been observed with the highly specific anti-human procollagen 11A1 DTMX1/1E8.33 mAb [54, 55, 66, 71].

COL11A1/(pro)collagen 11A1 in epithelial-to-mesenchymal transition (EMT) and metastases

At present, there are three recognized subtypes of "Epithelial-to-Mesenchymal Transition" (EMT) [80-81]. Type 3 EMT occurs at the invasive front of carcinomas in such a way that carcinoma cells lose adhesiveness and acquire motility and migration capabilities. Traits associated with a Type 3 EMT are the acquisition of a spindle shape, the up-regulation of vimentin (*VIM*), and the "cadherin switching", consisting in the progressive loss of E-cadherin (*CDH1*) and the increase in N-cadherin and OB-cadherin or cadherin-11 (*CDH11*) expression. Together with this, EMT is also associated with

the up-regulation of some transcription regulators such as *SNAI1* (Snail), *SNAI2* (Slug), *TWIST1* (Twist) and *ZEB2* (SIP1) [81-82].

It remains a matter of speculation and controversy what the origin and/or nature of the cells is which, at the front of human invasive carcinomas, express *COL11A1*/(pro)collagen 11A1 [72, 77, 83-84]; this aspect warrants further detailed study (see more below).

The development of distant metastases is the major cause of death from some carcinomas. These metastases originate from small tumour emboli, which separate from the primary tumour mass, and, through bloodstream or lymphatics, reach and nestle into another body location. These emboli are not usually accompanied by stromal components but, in the establishment of pancreatic cancer metastasis, the co-migration of pancreatic stellate cells and tumour cells has been demonstrated [85].

Transcription profiling observations from circulating breast and prostate cancer cells indicate that these cells do not express *COL11A1*; in contrast, expression of cadherin-11 – a surface adhesion molecule, which establishes interactions with stromal cells for anchorage and nesting of distant metastases – has been shown to be associated with a circulating and metastasizing phenotype of these cancer cells [86-89].

The overexpression of *COL11A1* has been correlated with a multi-cancer metastasis-associated gene expression signature [90], and with lymph node metastasis of non-small lung cancer [57]. Reports on the differential expression of *COL11A1* between primary breast tumours and lymph node metastases have pointed toward a higher expression in the primary tumours [91-93].

These studies did not pay especial attention to the kind of cells which express *COL11A1* in metastases; and moreover, so far there have not been detailed reports on

the immunodetection of (pro)collagen 11A1 in metastases of human invasive carcinomas.

While *COL11A1*/(pro)collagen 11A1+ cells seem to be predominantly activated stromal cells in the primary tumour, some observations indicate that carcinoma-derived cells, with high metastatic capabilities, can express *COL11A1* [94-95]. The SNU182 poorly differentiated hepatocellular carcinoma cell line expresses high levels of *COL11A1*, along with cadherin-1 and mesenchymal markers such as vimentin, *SNAI1* (Snail), *SNAI2* (Slug), *TWIST1* (Twist) and *TWIST2* [94]. Lung-metastatic LM2 cells, originally derived from the clear cell renal (RCC) carcinoma SN12C cell line, have been shown to have a highly up-regulated *COL11A1* gene [95].

According to the Gene Expression Atlas, ArrayExpress E-MTAB-37 [96], one of the human cancer cell lines with the highest *COL11A1*-specific mRNA expression is the large cell lung carcinoma NCI-H661. This cell line was derived from the lymph node of a patient with large cell cancer of the lung. We have assessed by immunocytochemistry that this cell line expresses high levels of procollagen 11A1 as well (Fig. 3).

Therefore, in established metastases, the expression of *COL11A1*/(pro)collagen 11A1 could originate from both the metastatic epithelial cells and/or the accompanying activated stromal cells.

Conclusion

In summary, under the influence of various growth factors and signalling pathways which are known to be active in carcinomas and promote *COL11A1* expression, we may conclude that *COL11A1*/(pro)collagen 11A1 expression is a remarkable biomarker of human carcinoma-associated stromal cells and carcinoma progression.

In agreement with this, a very recent review by Raglow and Thomas [97] highlights the role of *COL11A1*/(pro)collagen 11A1 in cancer.

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Conflicts of interest The authors declare no conflicts of interest.

References

1. Fan D, Takawale A, Lee J, Kassiri Z. Cardiac fibroblasts, fibrosis and extracellular matrix remodeling in heart disease. Fibrogenesis Tissue Repair 2012; 5:15. doi: 10.1186/1755-1536-5-15.
2. Canty EG, Kadler KE. Procollagen trafficking, processing and fibrillogenesis. J Cell Sci. 2005;118:1341-53.
3. Kadler KE, Hill A, Canty-Laird EG. Collagen fibrillogenesis: fibronectin, integrins, and minor collagens as organizers and nucleators. Curr Opin Cell Biol. 2008; 20:495-501.
4. GeneCards: http://www.genecards.org/cgi-bin/carddisp.pl?gene=COL11A1&search=60c7972800f65b34c22171d38f22a63f. Accessed 23 Dec 2014.
5. Kao L-P, Yu S-L, Singh S, Wang K-H, Kao A-P, Li SS. Comparative profiling of mRNA and microRNA expression in human mesenchymal stem cells derived

from adult adipose and lipoma tissues. The Open Stem Cell Journal 2009;1:1-9. doi: 10.2174/1876893800901010001.

6. Grundberg E, Brändström H, Lam KC, Gurd S, Ge B, Harmsen E, Kindmark A, Ljunggren O, Mallmin H, Nilsson O, Pastinen T. Systematic assessment of the human osteoblast transcriptome in resting and induced primary cells. Physiol Genomics 2008;33:301-11.

7. Matsuo N, Yu-Hua W, Sumiyoshi H, Sakata-Takatani K, Nagato H, Sakai K, Sakurai M, Yoshioka H. The transcription factor CCAAT-binding factor CBF/NF-Y regulates the proximal promoter activity in the human alpha 1(XI) collagen gene (COL11A1). J Biol Chem. 2003;278:32763-70.

8. Hida M, Hamanaka R, Okamoto O, Yamashita K, Sasaki T, Yoshioka H, Matsuo N. Nuclear factor Y (NF-Y) regulates the proximal promoter activity of the mouse collagen α1(XI) gene (Col11a1) in chondrocytes. In Vitro Cell Dev Biol Anim. 2014;50:358-66. doi: 10.1007/s11626-013-9692-3.

9. Kahler RA, Yingst SM, Hoeppner LH, Jensen ED, Krawczak D, Oxford JT, Westendorf JJ. Collagen 11a1 is indirectly activated by lymphocyte enhancer-binding factor 1 (Lef1) and negatively regulates osteoblast maturation. Matrix Biol. 2008;27:330-8. doi: 10.1016/j.matbio.2008.01.002.

10. Emura M, Ochiai A, Horino M, Arndt W, Kamino K, Hirohashi S. Development of myofibroblasts from human bone marrow mesenchymal stem cells cocultured with human colon carcinoma cells and TGF beta 1. In Vitro Cell Dev Biol Anim. 2000;36:77-80.

11. Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, Richardson AL, Polyak K, Tubo R, Weinberg RA. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature 2007;449:557-63.

12. Mishra PJ, Mishra PJ, Humeniuk R, Medina DJ, Alexe G, Mesirov JP, Ganesan S, Glod JW, Banerjee D. Carcinoma-associated fibroblast-like differentiation of human mesenchymal stem cells. Cancer Res. 2008;68:4331-9. doi: 10.1158/0008-5472.CAN-08-0943.

13. Gardner H, Strehlow D, Bradley L, Widom R, Farina A, de Fougerolles A, Peyman J, Koteliansky V, Korn JH. Global expression analysis of the fibroblast transcriptional response to TGFbeta. Clin Exp Rheumatol. 2004;22 (3 Suppl 33): S47-S57.

14. Wu YH, Chang TH, Huang YF, Huang HD, Chou CY. COL11A1 promotes tumor progression and predicts poor clinical outcome in ovarian cancer. Oncogene 2014;33:3432-40. doi: 10.1038/onc.2013.307.

15. Oliveira FS, Bellesini LS, Defino HL, da Silva Herrero CF, Beloti MM, Rosa AL. Hedgehog signaling and osteoblast gene expression are regulated by purmorphamine in human mesenchymal stem cells. J Cell Biochem. 2012;113: 204-8. doi: 10.1002/jcb.23345.

16. Kojima Y, Acar A, Eaton EN, Mellody KT, Scheel C, Ben-Porath I, Onder TT, Wang ZC, Richardson AL, Weinberg RA, Orimo A. Autocrine TGF-beta and stromal cell-derived factor-1 (SDF-1) signaling drives the evolution of tumor-promoting mammary stromal myofibroblasts. Proc Natl Acad Sci USA 2010; 107: 20009-14. doi: 10.1073/pnas.1013805107.

17. Mishra P, Banerjee D, Ben-Baruch A. Chemokines at the crossroads of tumor-fibroblast interactions that promote malignancy. J Leukoc Biol. 2011;89:31-9. doi: 10.1189/jlb.0310182.

18. Margolin DA, Silinsky J, Grimes C, Spencer N, Aycock M, Green H, Cordova J, Davis NK, Driscoll T, Li L. Lymph node stromal cells enhance drug-resistant

colon cancer cell tumor formation through SDF-1α/CXCR4 paracrine signaling. Neoplasia 2011;13:874-86.

19. Polanska UM, Orimo A. Carcinoma-associated fibroblasts: non-neoplastic tumour-promoting mesenchymal cells. J Cell Physiol. 2013;228:1651-7. doi: 10.1002/jcp.24347.

20. Fischer H, Salahshor S, Stenling R, Björk J, Lindmark G, Iselius L, Rubio C, Lindblom A. COL11A1 in FAP polyps and in sporadic colorectal tumors. BMC Cancer 2001;1:17. http://www.biomedcentral.com/1471-2407/1/17.

21. Pilarsky C, Ammerpohl O, Sipos B, Dahl E, Hartmann A, Wellmann A, Braunschweig T, Löhr M, Jesenofsky R, Friess H, Wente MN, Kristiansen G, Jahnke B, Denz A, Rückert F, Schackert HK, Klöppel G, Kalthoff H, Saeger HD, Grützmann R. Activation of Wnt signalling in stroma from pancreatic cancer identified by gene expression profiling. J Cell Mol Med. 2008;12:2823-35.

22. Bailey JM, Swanson BJ, Hamada T, Eggers JP, Singh PK, Caffery T, Ouellette MM, Hollingsworth MA. Sonic hedgehog promotes desmoplasia in pancreatic cancer. Clin Cancer Res. 2008;14:5995-6004. doi: 10.1158/1078-0432.CCR-08-0291.

23. Tian H, Callahan CA, DuPree KJ, Darbonne WC, Ahn CP, Scales SJ, de Sauvage FJ. Hedgehog signaling is restricted to the stromal compartment during pancreatic carcinogenesis. Proc Natl Acad Sci USA 2009;106:4254-9. doi: 10.1073/pnas.0813203106.

24. Gene Expression Atlas- Summary for COL11A1 (Homo sapiens). http://www-test.ebi.ac.uk/gxa/gene/ENSG00000060718. Accessed 23 Dec 2014.

25. Lin PP, Wang Y, Lozano G. Mesenchymal stem cells and the origin of Ewing's sarcoma. Sarcoma 2011;pii:276463. doi: 10.1155/2011/276463.

26. Hajdu M, Singer S, Maki RG, Schwartz GK, Keohan ML, Antonescu CR. IGF2 over-expression in solitary fibrous tumours is independent of anatomical location and is related to loss of imprinting. J Pathol. 2010;221:300-7.

27. An JH, Lee SY, Jeon JY, Cho KG, Kim SU, Lee MA. Identification of gliotropic factors that induce human stem cell migration to malignant tumor. J Proteome Res. 2009;8:2873-81.

28. Chernov AV, Baranovskaya S, Golubkov VS, Wakeman DR, Snyder EY, Williams R, Strongin AY. Microarray-based transcriptional and epigenetic profiling of matrix metalloproteinases, collagens, and related genes in cancer. J Biol Chem. 2010;285:19647-59.

29. Pope WB, Mirsadraei L, Lai A, Eskin A, Qiao J, Kim HJ, Ellingson B, Nghiemphu PL, Kharbanda S, Soriano RH, Nelson SF, Yong W, Phillips HS, Cloughesy TF. Differential gene expression in glioblastoma defined by ADC histogram analysis: relationship to extracellular matrix molecules and survival. AJNR Am J Neuroradiol. 2012;33:1059-64. doi: 10.3174/ajnr.A2917.

30. Seemann L, Shulman J, Gunaratne GH. A robust topology-based algorithm for gene expression profiling. ISRN Bioinformatics 2012; Article ID 381023. doi:10.5402/2012/381023.

31. Chen W, Fu X, Sun X, Sun T, Zhao Z, Sheng Z. Analysis of differentially expressed genes in keloids and normal skin with cDNA microarray. J Surg Res. 2003;113:208-16.

32. Seifert O, Bayat A, Geffers R, Dienus K, Buer J, Löfgren S, Matussek A. Identification of unique gene expression patterns within different lesional sites

of keloids. Wound Repair Regen. 2008;16:254-65. doi: 10.1111/j.1524-475X.2007.00343.x.

33. Yagi Y, Muroga E, Naitoh M, Isogai Z, Matsui S, Ikehara S, Suzuki S, Miyachi Y, Utani A. An ex vivo model employing keloid-derived cell-seeded collagen sponges for therapy development. J Invest Dermatol. 2013;133:386-93. doi: 10.1038/jid.2012.314.

34. Gardner H, Shearstone JR, Bandaru R, Crowell T, Lynes M, Trojanowska M, Pannu J, Smith E, Jablonska S, Blaszczyk M, Tan FK, Mayes MD. Gene profiling of scleroderma skin reveals robust signatures of disease that are imperfectly reflected in the transcript profiles of explanted fibroblasts. Arthritis Rheum. 2006;54:1961-73.

35. Togo S, Polanska UM, Horimoto Y, Orimo A. Carcinoma-associated fibroblasts are a promising therapeutic target. Cancers (Basel) 2013; 5:149-69. doi: 10.3390/cancers5010149.

36. Midwood KS, Orend G. The role of tenascin-C in tissue injury and tumorigenesis. J Cell Commun Signal. 2009;3:287-310. doi: 10.1007/s12079-009-0075-1.

37. Sidhu SS, Yuan S, Innes AL, Kerr S, Woodruff PG, Hou L, Muller SJ, Fahy JV. Roles of epithelial cell-derived periostin in TGF-beta activation, collagen production, and collagen gel elasticity in asthma. Proc Natl Acad Sci U S A 2010;107:14170-5. doi: 10.1073/pnas.1009426107.

38. Mifflin RC, Pinchuk IV, Saada JI, Powell DW. Intestinal myofibroblasts: targets for stem cell therapy. Am J Physiol Gastrointest Liver Physiol. 2011;300: G684–G696. doi:10.1152/ajpgi.00474.2010.

39. Nishioka Y, Azuma M, Kishi M, Aono Y. Targeting platelet-derived growth factor as a therapeutic approach in pulmonary fibrosis. J Med Invest. 2013;60: 175-83.

40. Keane FM, Yao TW, Seelk S, Gall MG, Chowdhury S, Poplawski SE, Lai JH, Li Y, Wu W, Farrell P, Vieira de Ribeiro AJ, Osborne B, Yu DM, Seth D, Rahman K, Haber P, Topaloglu AK, Wang C, Thomson S, Hennessy A, Prins J, Twigg SM, McLennan SV, McCaughan GW, Bachovchin WW, Gorrell MD. Quantitation of fibroblast activation protein (FAP)-specific protease activity in mouse, baboon and human fluids and organs. FEBS Open Bio. 2013;4:43-54. doi: 10.1016/j.fob.2013.12.001.

41. Rönty M. Palladin, a novel microfilament protein. PhD thesis. University of Helsinki, Department of Pathology; 2008.

42. Schacht V, Dadras SS, Johnson LA, Jackson DG, Hong YK, Detmar M. Up-regulation of the lymphatic marker podoplanin, a mucin-type transmembrane glycoprotein, in human squamous cell carcinomas and germ cell tumors. Am J Pathol. 2005;166:913-21.

43. Fuentes-Martínez N, García-Pravia C, García-Ocaña M, Menéndez-Rodríguez P, Del Amo J, Suárez-Fernández L, Galván JA, De Los Toyos JR, Barneo L. Overexpression of proCOL11A1 as a stromal marker of breast cancer. Histol Histopathol. 2015;30: 87-93.

44. Erkan M, Weis N, Pan Z, Schwager C, Samkharadze T, Jiang X, Wirkner U, Giese NA, Ansorge W, Debus J, Huber PE, Friess H, Abdollahi A, Kleeff J. Organ-, inflammation- and cancer specific transcriptional fingerprints of pancreatic and hepatic stellate cells. Mol Cancer 2010;9:88. http://www.molecular-cancer.com/content/9/1/88.

45. Prenzel KL, Ribati M, Warnecke-Ebers U, Stöcklein N, Vallböhmer D, Stippel D, Knoefel WT, Hölscher AH. Differential expression of COL11A1 in chronic pancreatitis and periampullary adenocarcinomas. Deutsche Gesellschaft für Chirurgie 2009;38:209-10. Chirurgisches Forum und DGAV Forum 2009.

46. Dooley TP, Curto EV, Reddy SP, Davis RL, Lambert GW, Wilborn TW, Elson CO. Regulation of gene expression in inflammatory bowel disease and correlation with IBD drugs: screening by DNA microarrays. Inflamm Bowel Dis. 2004;10:1-14.

47. Fang M, Yuan J, Peng C, Li Y. Collagen as a double-edged sword in tumor progression. Tumor Biol. 2014;35:2871-82. doi: 10.1007/s13277-013-1511-7.

48. Schmalbach CE, Chepeha DB, Giordano TJ, Rubin MA, Teknos TN, Bradford CR, Wolf GT, Kuick R, Misek DE, Trask DK, Hanash S. Molecular profiling and the identification of genes associated with metastatic oral cavity/pharynx squamous cell carcinoma. Arch Otolaryngol Head Neck Surg. 2004;130:295-302.

49. Sok JC, Kuriakose MA, Mahajan VB, Pearlman AN, DeLacure MD, Chen FA. Tissue-specific gene expression of head and neck squamous cell carcinoma in vivo by complementary DNA microarray analysis. Arch Otolaryngol Head Neck Surg. 2003;129:760-70.

50. Sok JC, Lee JA, Dasari S, Joyce S, Contrucci SC, Egloff AM, Trevelline BK, Joshi R, Kumari N, Grandis JR, Thomas SM. Collagen type XI α1 facilitates head and neck squamous cell cancer growth and invasion. Br J Cancer 2013; 109:3049-56. doi: 10.1038/bjc.2013.624.

51. Fuentes-Martínez N. Colágeno 11: Nuevo marcador en el cáncer de mama. PhD thesis. Universidad de Oviedo, Surgery and Medical Surgical Specialities Department; 2009.

52. Pavlides S, Tsirigos A, Vera I, Flomenberg N, Frank PG, Casimiro MC, Wang C, Pestell RG, Martinez-Outschoorn UE, Howell A, Sotgia F, Lisanti MP. Transcriptional evidence for the "Reverse Warburg Effect" in human breast cancer tumor stroma and metastasis: similarities with oxidative stress, inflammation, Alzheimer's disease, and "Neuron-Glia Metabolic Coupling". Aging (Albany NY) 2010;2:185-99.

53. Planche A, Bacac M, Provero P, Fusco C, Delorenzi M, Stehle JC, Stamenkovic I. Identification of prognostic molecular features in the reactive stroma of human breast and prostate cancer. PLoS One 2011;6:e18640. doi: 10.1371/journal.pone.0018640.

54. García-Ocaña M, Vázquez F, García-Pravia C, Fuentes-Martínez N, Menéndez-Rodríguez P, Fresno-Forcelledo F, Barneo-Serra L, Del Amo-Iribarren J, Simón-Buela L, De Los Toyos JR. Characterization of a novel mouse monoclonal antibody, clone 1E8.33, highly specific for human procollagen 11A1, a tumor-associated stromal component. Int J Oncol. 2012;40:1447-54. doi: 10.3892/ijo.2012.1360.

55. Freire J, Domínguez-Hormaetxe S, Pereda S, De Juan A, Vega A, Simón L, Gómez-Román J. Collagen, type XI, alpha 1: An accurate marker for differential diagnosis of breast carcinoma invasiveness in core needle biopsies. Pathol Res Pract. 2014; pii: S0344-0338(14)00225-8. doi: 10.1016/j.prp.2014.07.012.

56. Wang KK, Liu N, Radulovich N, Wigle DA, Johnston MR, Shepherd FA, Minden MD. Tsao MS. Novel candidate tumor marker genes for lung adenocarcinoma. Oncogene 2002;21:7598-604.

57. Chong IW, Chang MY, Chang HC, Yu YP, Sheu CC, Tsai JR, Hung JY, Chou SH, Tsai MS, Hwang JJ, Lin SR. Great potential of a panel of multiple hMTH1, SPD, ITGA11 and COL11A1 markers for diagnosis of patients with non-small cell lung cancer. Oncol Rep. 2006;16:981-8.

58. Fuentes N, Pravia CG, Rodriguez, PM, De los Toyos JR, Ocana, MG, Del Amo J, Simon L, Barneo L, Fresno M. Anticol11a1 a marker of infiltration in bronchioloalveolar lung carcinoma. Virchows Arch. 2010; 457:230.

59. Sun Y, Wang L, Jiang M, Huang J, Liu Z, Wolfl S. Secreted phosphoprotein 1 upstream invasive network construction and analysis of lung adenocarcinoma compared with human normal adjacent tissues by integrative biocomputation. Cell Biochem Biophys. 2010;56:59-71. doi: 10.1007/s12013-009-9071-6.

60. Navab R, Strumpf D, Bandarchi B, Zhu CQ, Pintilie M, Ramnarine VR, Ibrahimov E, Radulovich N, Leung L, Barczyk M, Panchal D, To C, Yun JJ, Der S, Shepherd FA, Jurisica I, Tsao MS. Prognostic gene-expression signature of carcinoma-associated fibroblasts in non-small cell lung cancer. Proc Natl Acad Sci U S A 2011;108:7160-5. doi: 10.1073/pnas.1014506108.

61. Xu SH, Qian LJ, Mou HZ, Zhu CH, Zhou XM, Liu XL, Chen Y, Bao WY. Difference of gene expression profiles between esophageal carcinoma and its pericancerous epithelium by gene chip. World J Gastroenterol. 2003;9:417-22.

62. Vecchi M, Nuciforo P, Romagnoli S, Confalonieri S, Pellegrini C, Serio G, Quarto M, Capra M, Roviaro GC, Contessini Avesani E, Corsi C, Coggi G, Di

Fiore PP, Bosari S. Gene expression of early and advanced gastric cancer. Oncogene 2007;26:4284-94.

63. Zhao Y, Zhou T, Li A, Yao H, He F, Wang L, Si J. A potential role of collagens expression in distinguishing between premalignant and malignant lesions in stomach. Anat Rec. 2009;292:692-700.

64. Barneo L, del Amo J, García-Pravia C, de los Toyos JR, Pérez-Basterrechea M, González-Pinto I, Vazquez L, Miyar A, Simón L. Identification of specific genes by microarrays, validation and use of polyclonal antibodies in pancreatic cancer: preliminary results. In: Brigitte Vollmar, editor. 41st Congress of the European Society for Surgical Research-ESSR 2006. Bologna: Medimond, International Proceedings; 2006. Pp. 27-35.

65. del Amo-Iribarren J. Identificación de marcadores para diagnóstico diferencial y potenciales dianas terapéuticas en adenocarcinoma ductal de páncreas mediante herramientas genómicas. PhD thesis. Universidad del País Vasco, Genetics, Physical Anthropology and Animal Physiology Department; 2006.

66. García-Pravia C, Galván JA, Gutiérrez-Corral N, Solar-García L, García-Pérez E, García-Ocaña M, Del Amo-Iribarren J, Menéndez-Rodríguez P, García-García J, de los Toyos JR, Simón-Buela L, Barneo L. Overexpression of COL11A1 by cancer-associated fibroblasts: Clinical relevance of a stromal marker in pancreatic cancer. PLoS One 2013;8:e78327. doi:10.1371/journal.pone.0078327.

67. Fischer H, Stenling R, Rubio C, Lindblom A. Colorectal carcinogenesis is associated with stromal expression of COL11A1 and COL5A2. Carcinogenesis 2001;22:875–8. doi: 10.1093/carcin/22.6.875.

68. Croner RS, Foertsch T, Brueckl WM, Guenther K, Siebenhaar R, Stremmel C, Matzel KE, Papadopoulos T, Kirchner T, Behrens J, Klein-Hitpass L, Stuerzl M, Hohenberger W, Reingruber B. Common denominator genes that distinguish colorectal carcinoma from normal mucosa. Int J Colorectal Dis. 2005;20:353-62.

69. Lascorz J, Hemminki K, Försti A. Systematic enrichment analysis of gene expression profiling studies identifies consensus pathways implicated in colorectal cancer development. J Carcinog. 2011;10:7. doi: 10.4103/1477-3163.78268.

70. Cueva-Cayetano R, Galvan-Hernandez JÁ, Suarez-Fernandez L, Menendez-Rodriguez MP , Garcia-Pravia C , Barneo L. Preliminary analysis of collagen, type XI, alpha 1 (COL11A1), inhibin alpha (INHBA) and secreted protein acidic and rich in cysteine (SPARC, osteonectin) as potential markers of colon cancer [abstract]. Brit J Surg. 2013, 100 (Suppl. 1): 7.

71. Galván JA, García-Martínez J, Vázquez-Villa F, García-Ocaña M, García-Pravia C, Menéndez-Rodríguez P, González-del Rey C, Barneo-Serra L, de los Toyos JR. Validation of *COL11A1*/procollagen 11A1 expression in TGF-β1-activated immortalised human mesenchymal cells and in stromal cells of human colon adenocarcinoma. BMC Cancer 2014; 14:867 doi:10.1186/1471-2407-14-867.

72. Cheon DJ, Tong Y, Sim MS, Dering J, Berel D, Cui X, Lester J, Beach JA, Tighiouart M, Walts AE, Karlan BY, Orsulic S. A collagen-remodeling gene signature regulated by TGF-β signaling is associated with metastasis and poor survival in serous ovarian cancer. Clin Cancer Res. 2014;20:711-23. doi: 10.1158/1078-0432.CCR-13-1256.

73. Schuetz CS, Bonin M, Clare SE, Nieselt K, Sotlar K, Walter M, Fehm T, Solomayer E, Riess O, Wallwiener D, Kurek R, Neubauer HJ. Progression-

specific genes identified by expression profiling of matched ductal carcinomas in situ and invasive breast tumors, combining laser capture microdissection and oligonucleotide microarray analysis. Cancer Res. 2006;66:5278-86.

74. Ma XJ, Dahiya S, Richardson E, Erlander M, Sgroi DC. Gene expression profiling of the tumor microenvironment during breast cancer progression. Breast Cancer Res. 2009;11:R7. doi: 10.1186/bcr2222.

75. Lee S, Stewart S, Nagtegaal I, Luo J, Wu Y, Colditz G, Medina D, Allred DC. Differentially expressed genes regulating the progression of ductal carcinoma in situ to invasive breast cancer. Cancer Res. 2012;72:4574-86. doi: 10.1158/0008-5472.CAN-12-0636.

76. Castellana B, Escuin D, Peiró G, Garcia-Valdecasas B, Vázquez T, Pons C, Pérez-Olabarria M, Barnadas A, Lerma E. ASPN and GJB2 are implicated in the mechanisms of invasion of ductal breast carcinomas. J Cancer 2012;3:175-83. doi: 10.7150/jca.4120.

77. Vargas AC, McCart Reed AE, Waddell N, Lane A, Reid LE, Smart CE, Cocciardi S, da Silva L, Song S, Chenevix-Trench G, Simpson PT, Lakhani SR. Gene expression profiling of tumour epithelial and stromal compartments during breast cancer progression. Breast Cancer Res Treat. 2012;135:153-65. doi: 10.1007/s10549-012-2123-4.

78. Zhu TX, Lan B, Meng LY, Yang YL, Li RX, Li EM, Zheng SY, Xu LY. ECM-related gene expression profile in vascular smooth muscle cells from human saphenous vein and internal thoracic artery. J Cardiothorac Surg. 2013;8:155. doi: 10.1186/1749-8090-8-155.

79. Buckanovich RJ, Sasaroli D, O'Brien-Jenkins A, Botbyl J, Hammond R, Katsaros D, Sandaltzopoulos R, Liotta LA, Gimotty PA, Coukos G. Tumor

vascular proteins as biomarkers in ovarian cancer. J Clin Oncol. 2007;25:852-61.

80. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest. 2009;119:1420–8. doi:10.1172/JCI39104.

81. Zeisberg M, Neilson EG. Biomarkers for epithelial-mesenchymal transitions. J Clin Invest. 2009;119: 1429–37. doi:10.1172/JCI36183.

82. Moreno-Bueno G, Peinado H, Molina P, Olmeda D, Cubillo E, Santos V, Palacios J, Portillo F, Cano A. The morphological and molecular features of the epithelial-to-mesenchymal transition. Nat Protoc. 2009;4:1591-613.

83. Badea L, Herlea V, Dima SO, Dumitrascu T, Popescu I. Combined gene expression analysis of whole-tissue and microdissected pancreatic ductal adenocarcinoma identifies genes specifically overexpressed in tumor epithelia. Hepatogastroenterology 2008;55:2016-27.

84. Anastassiou D, Rumjantseva V, Cheng W, Huang J, Canoll PD, Yamashiro DJ, Kandel JJ. Human cancer cells express Slug-based epithelial-mesenchymal transition gene expression signature obtained in vivo. BMC Cancer 2011; 11:529. http://www.biomedcentral.com/1471-2407/11/529.

85. Xu Z, Vonlaufen A, Phillips PA, Fiala-Beer E, Zhang X, Yang L, Biankin AV, Goldstein D, Pirola RC, Wilson JS, Apte MV. Role of pancreatic stellate cells in pancreatic cancer metastasis. Am J Pathol. 2010;177:2585-96. doi: 10.2353/ajpath.2010.090899.

86. Pishvaian MJ, Feltes CM, Thompson P, Bussemakers MJ, Schalken JA, Byers SW. Cadherin-11 is expressed in invasive breast cancer cell lines. Cancer Res. 1999;59:947-52.

87. Chu K, Cheng CJ, Ye X, Lee YC, Zurita AJ, Chen DT, Yu-Lee LY, Zhang S, Yeh ET, Hu MC, Logothetis CJ, Lin SH. Cadherin-11 promotes the metastasis of prostate cancer cells to bone. Mol Cancer Res. 2008;6:1259-67.

88. Huang CF, Lira C, Chu K, Bilen MA, Lee YC, Ye X, Kim SM, Ortiz A, Wu FL, Logothetis CJ, Yu-Lee LY, Lin SH. Cadherin-11 increases migration and invasion of prostate cancer cells and enhances their interaction with osteoblasts. Cancer Res. 2010;70:4580-9.

89. Armstrong AJ, Marengo MS, Oltean S, Kemeny G, Bitting RL, Turnbull JD, Herold CI, Marcom PK, George DJ, Garcia-Blanco MA. Circulating tumor cells from patients with advanced prostate and breast cancer display both epithelial and mesenchymal markers. Mol Cancer Res. 2011;9:997-1007.

90. Kim H, Watkinson J, Varadan V, Anastassiou D. Multi-cancer computational analysis reveals invasion-associated variant of desmoplastic reaction involving INHBA, THBS2 and COL11A1. BMC Med Genomics 2010;3:51. http://www.biomedcentral.com/1755-8794/3/51.

91. Suzuki M, Tarin D. Gene expression profiling of human lymph node metastases and matched primary breast carcinomas: clinical implications. Mol Oncol. 2007;1:172-80. doi: 0.1016/j.molonc.2007.03.005.

92. Feng Y, Sun B, Li X, Zhang L, Niu Y, Xiao C, Ning L, Fang Z, Wang Y, Zhang L, Cheng J, Zhang W, Hao X. Differentially expressed genes between primary cancer and paired lymph node metastases predict clinical outcome of node-positive breast cancer patients. Breast Cancer Res Treat. 2007;103:319-29.

93. Ellsworth RE, Seebach J, Field LA, Heckman C, Kane J, Hooke JA, Love B, Shriver CD. A gene expression signature that defines breast cancer metastases. Clin Exp Metastasis 2009;26:205-13. doi: 10.1007/s10585-008-9232-9.

94. Yuzugullu H, Benhaj K, Ozturk N, Senturk S, Celik E, Toylu A, Tasdemir N, Yilmaz M, Erdal E, Akcali KC, Atabey N, Ozturk M. Canonical Wnt signaling is antagonized by noncanonical Wnt5a in hepatocellular carcinoma cells. Mol Cancer 2009; 8:90. doi: 10.1186/1476-4598-8-90.

95. López-Lago MA, Thodima VJ, Guttapalli A, Chan T, Heguy A, Molina AM, Reuter VE, Motzer RJ, Chaganti RS. Genomic deregulation during metastasis of renal cell carcinoma implements a myofibroblast-like program of gene expression. Cancer Res. 2010;70:9682-92. doi: 10.1158/0008-5472.CAN-10-2279.

96. ArrayExpress Experiment E-MTAB-37. Transcription profiling of human multiple cancer cell lines (950 samples). http://www-test.ebi.ac.uk/gxa/experiment/E-MTAB-37/ENSG00000060718?ef=cell_line. Accessed 23 Dec 2014.

97. Raglow Z, Thomas SM. Tumor matrix protein collagen XIα1 in cancer. Cancer Lett. 2015; 357:448–53. doi: 10.1016/j.canlet.2014.12.011.

Fig. 1 Schematic drawing of collagen fibrillogenesis by fibroblasts (adapted from [1] and [2], with permission of *BiomedCentral* and *The Company of Biologists Ltd*). Procollagen polypeptides are individually synthesized and then they form trimers in the cytoplasm. Once secreted, the terminal propeptides are excised, remaining the typical triple helix of the mature collagen molecule which conserves short telopeptides at both ends. Covalent cross-links through these telopeptides and specific Triple-helical Telopeptide-Binding Regions allow mature collagen molecules self-assemble into fibrils.

Fig. 2 Summarized representation of *COL11A1*/(pro)collagen 11A1 expression in normal healthy tissues and in tumours. A reference to the putative expression of *COL11A1*/(pro)collagen 11A1 in neoplastic epithelial cells at the front of invasive carcinomas has been made.

Fig. 3 Representative immunostainings with the anti-human procollagen 11A1 DTMX1/1E8.33 mAb (cell line cultures, original magnification x400; tissue samples, original magnification x200). A) Negative staining of a human pancreatic adenocarcinoma CAPAN-1 cell line culture; B) Pancreatic ductal adenocarcinoma; C) Negative staining of a human alveolar lung carcinoma A549 cell line culture; D) Lung adenocarcinoma; E) Very positive staining of a human large cell lung carcinoma NCI-H661 cell line culture; F) Head and neck squamous cell carcinoma. In tissue samples, only peritumoral stromal cells show a strong intracytoplasmatic staining.

Table 1
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Table 1 Up-regulated *COL11A1*/(pro)collagen 11A1 expression in human tumours

Cancer type	Cell type	Study	Up-regulation associated to	References
Soft tissue (rhabdomyosarcoma, chondrosarcoma, fibrosarcoma, osteosarcoma, Ewing´s sarcoma, solitary fibrous tumours)	Mesenchymal-type, fibroblastic	cDNA microarray, protein	Malignancy	[24-26, 54, 84]
Glioma/ glioblastoma	Mesenchymal-type	cDNA microarray, protein	High grade	[27-30]
Keloid	Mesenchymal-type, fibroblastic	cDNA microarray	Excessive extracellular matrix	[31-33]
Carcinoma				
Oral cavity/pharynx	Not determined	cDNA microarray	Lymph node metastasis	[48]
Head and neck	Tumour –derived fibroblasts, transformed epithelial cell lines	cDNA microarray, RT-PCR, siRNA	Tumour proliferation, migration and invasion	[49-50]
Breast	Stromal cells, invading neoplastic epithelial cells	cDNA microarray, Q-RT-PCR, protein	Progression from ductal carcinoma *in situ* (DCIS) to invasive ductal carcinoma (IDC)	[43, 51-55, 73-77, 90-93]
Lung	Carcinoma-associated fibroblasts	cDNA microarray, Q-RT-PCR, protein	Tumour size, stage, invasion, lymph node metastasis, poor prognosis	[56-60]
Esophagus	Not determined	cDNA microarray	Malignancy	[61]

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Stomach	Stromal cells	cDNA microarray, Q-RT-PCR	Progression from premalignant to malignant lesions	[62-63]
Pancreas	Carcinoma-associated fibroblasts, pancreatic stellate cells	cDNA microarray, Q-RT-PCR, protein	Progression to ductal adenocarcinoma	[44, 64-66]
Colon	Carcinoma-associated stromal cells	cDNA microarray, Q-RT-PCR, protein	Stage, lymph node metastasis	[20, 67-71]
Ovary	Tumour epithelial cell lines, carcinoma-associated stromal cells, rare foci of tumour epithelial cells	cDNA microarray, Q-RT-PCR, protein	Tumour progression, lymph node metastasis, poor prognosis	[14, 72]

Figure 1
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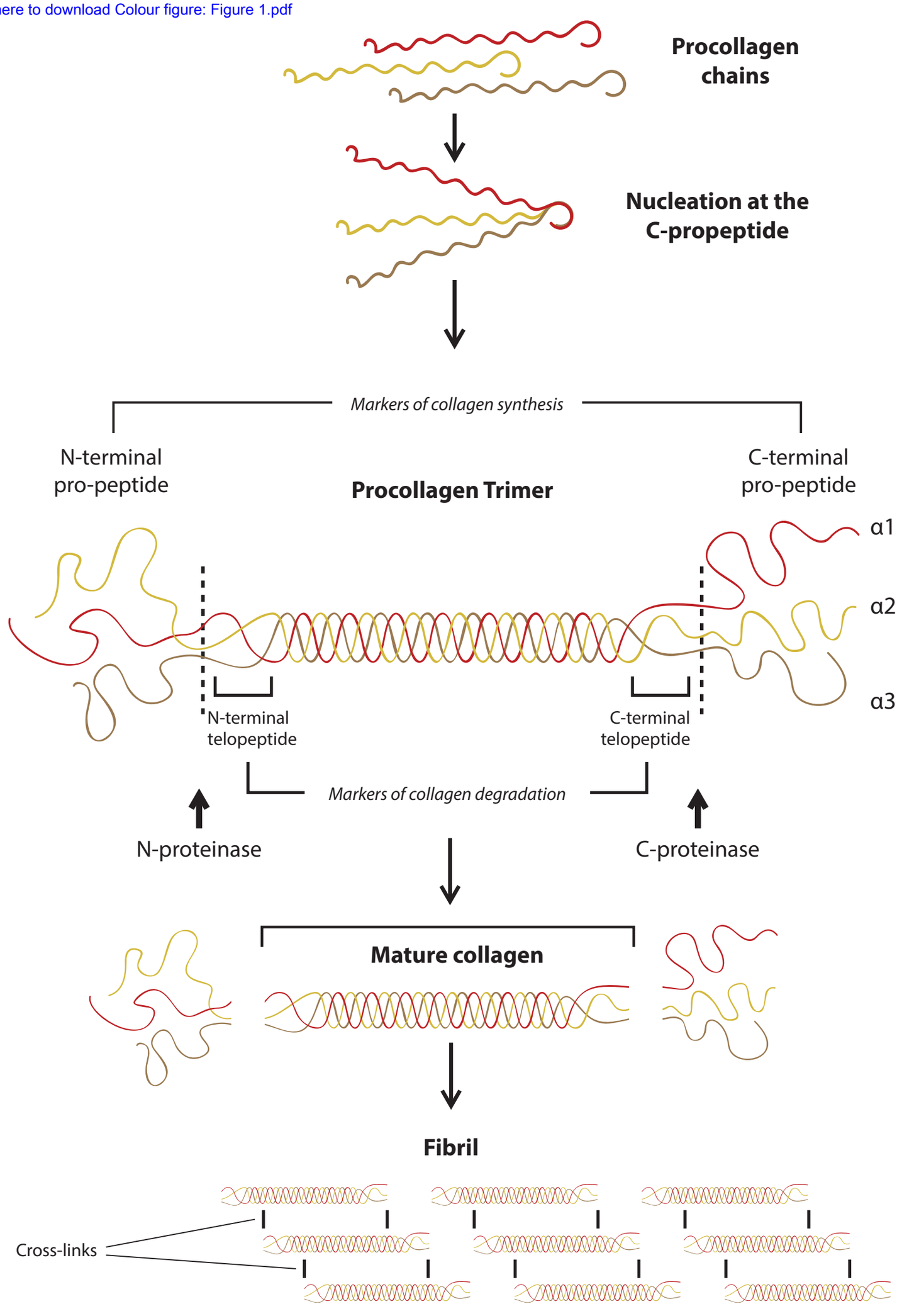

Figure 2

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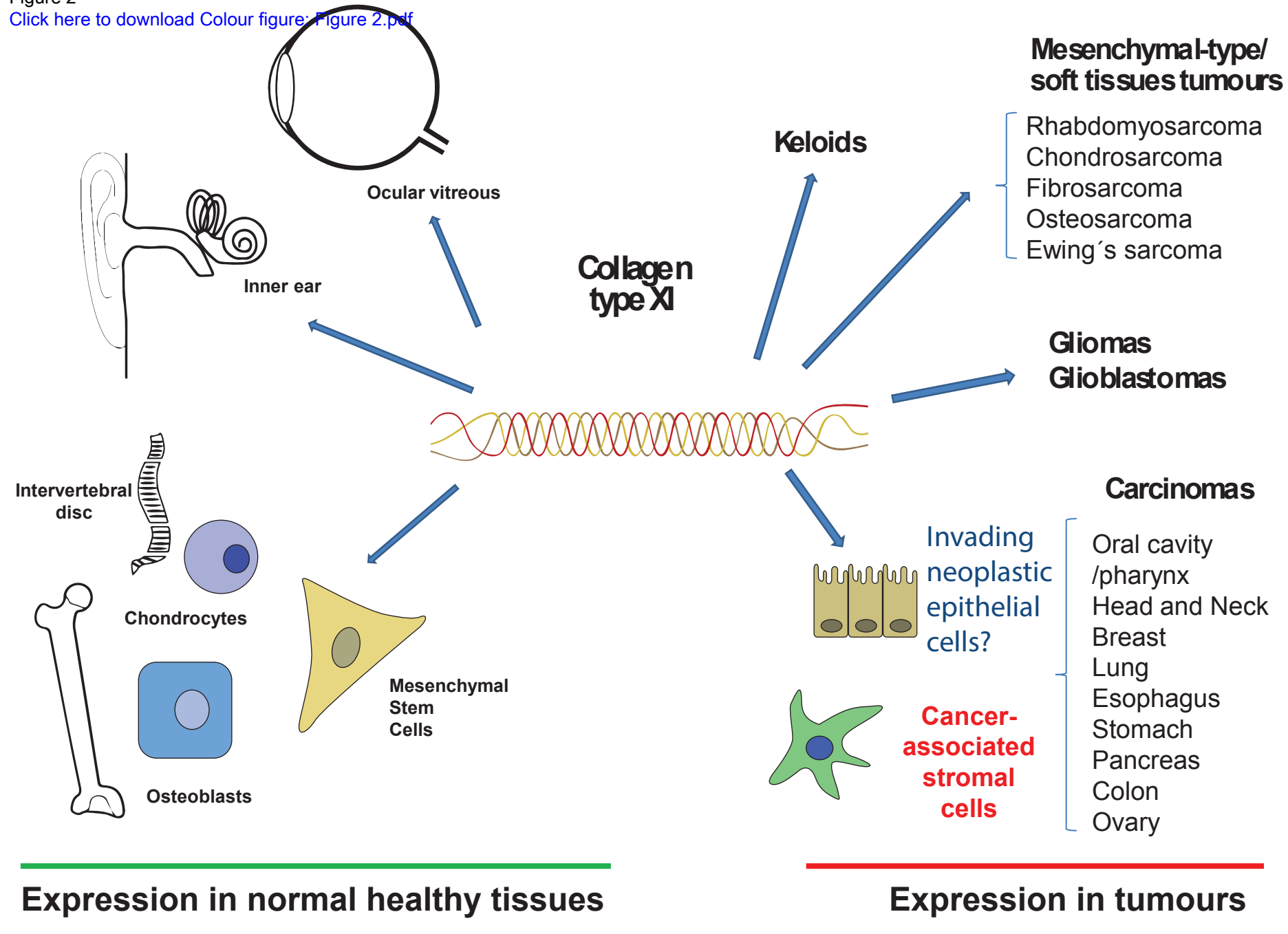

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