

RECOMMENDATIONS

RECOMMENDATIONS

- Asthmatic patients should be fully assessed for the detection of other biomarkers which could affect the outcome of bronchial asthma and its response to treatment.
- Further studies of fibulin-1 as a biomarker in asthmatic patients in larger sample size are required.
- More studies of fibulin-1 as a biomarker in other respiratory diseases as COPD are required.
- In the light of these data, further studies concerning more ethnic population will contribute to a better understanding of the relation between fibulin-1 and disease severity.

REFERENCES

REFERENCES

1. Global Initiative for Asthma. Global strategy for asthma management and prevention. Issued January 1995 (NIH Publication No. 02-3659); updated 2010. Available at: <http://www.ginasthma.org>.
2. Mason RJ, Broaddus VC, Murray JF, Nadel JA. Murray and Nadel's textbook of respiratory medicine. 4thed. USA: Elsevier; 2005.
3. Yawn BP. Factors accounting for asthma variability: achieving optimal symptom control for individual patients. *Prim Care Respir J* 2008; 17(3):138-47.
4. Kumar V, Abbas AK, Fausto N, Aster J. Robbins and Cotran pathologic basis of disease. 8thed. Philadelphia: Saunders; 2010.
5. Martinez FD. Genes, environments, development and asthma: a reappraisal. *Eur Respir J* 2007; 29 (1): 179–84.
6. Lemanske RF, Busse WW. Asthma: clinical expression and molecular mechanisms. *J Allergy Clin Immunol* 2010; 125(2 Suppl 2): S95–102.
7. Fanta CH. Asthma. *N Engl J Med* 2009; 360(10): 1002–14.
8. World Health Organization (WHO). Fact Sheet Fact sheet No 307: Asthma. Geneva: WHO; 2009.
9. Braman SS. The global burden of asthma. *Chest* 2006; 130(Suppl): 4S–12S.
10. Lazarus SC. Clinical practice. Emergency treatment of asthma. *N Engl J Med* 2010; 363 (8): 755–64.
11. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC, The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998; 351 (9111): 1225–32.
12. Gold DR, Wright R. Population disparities in asthma. *Annu Rev Public Health* 2005; 26: 89–113.
13. World Health Organization. (WHO). Asthma. Geneva: WHO; 2007.
14. Anderson HR, Gupta R, Strachan DP, Limb ES. 50 years of asthma: UK trends from 1955 to 2004. *Thorax* 2007; 62(1): 85–90.
15. Getahun D, Demissie K, Rhoads GG. Recent trends in asthma hospitalization and mortality in the United States. *J Asthma* 2005; 42(5): 373–8.
16. Hayden M. Asthma Guide. Web Med [Cited On: (19 Sept, 2009)]. Available from: <http://www.webmd.com/asthma/guide/how-we-breathe>. [Accessed On: 12 Apr, 2014].
17. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med* 2010; 103 (3): 98–106.

References

18. Global Strategy for asthma management and prevention 2010 (update). Global Initiative for Asthma 2010. Available from: http://www.ginasthma.org/pdf/GINA_Report_2010.pdf. [Accessed On: 13 Mar, 2014].
19. Self T, Chrisman C, Finch C. Asthma. In: Koda-Kimble MA, Young LY, Kradjan WA, Guglielmo BJ, Alldredge BK, Corelli RL, et al (eds). *Applied therapeutics: the clinical use of drugs*. 9thed. Philadelphia: Lippincott Williams & Wilkins; 2009. 22.1-38.
20. Delacourt, C. Bronchial changes in untreated asthma. *Arch Pédiatr* 2004; 11 (Suppl 2): 71s–3s.
21. Schiffman G. chronic obstructive pulmonary disease. *MedicineNet* (Cited On: 18 Dec, 2009). Available from: http://www.medicinenet.com/chronic_obstructive_pulmonary_disease_copd/article.htm. [Accessed On: 2 Mar, 2014].
22. Barnes PJ. "Asthma". In Fauci AS, Braunwald E, Kasper DL. *Harrison's principles of internal medicine*. 17thed. New York: McGraw-Hill. 2008. 1596–607.
23. Dipper JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. *Pharmacotherapy: a pathophysiologic approach*. 7thed. New York: McGraw-Hill; 2008.
24. Weiler JM, Layton T, Hunt M. Asthma in United States olympic athletes who participated in the 1996 summer games. *J Allergy Clin Immunol* 1998; 102 (5): 722–6.
25. Helenius I, Haahtela T. Allergy and asthma in elite summer sport athletes. *J Allergy Clin Immunol* 2000; 106(3): 444–52.
26. National Institute for Occupational Safety and Health. Fatal and nonfatal injuries, and selected illnesses and conditions: respiratory diseases. *Worker Health Chartbook* [Cited On: Sept, 2004]. Available from; <http://www.cdc.gov/niosh/docs/2004-146/ch2/ch2-10.asp.htm>. [Accessed On: 17 Dec, 2008].
27. National Institute for Occupational Safety and Health. Asthma and allergies. NIOSH [Cited On: 22 Sept, 2008]. Available from: <http://www.cdc.gov/niosh/topics/asthma/>. [Accessed On: 23 Mar, 2014].
28. Choudhry S1, Seibold MA, Borrell LN, Tang H, Serebrisky D, Chapela R, et al. Dissecting complex diseases in complex populations: asthma in latino americans. *Proc Am Thorac Soc* 2007; 4(3): 226–33.
29. Miller RL, Ho SM. Environmental epigenetics and asthma: current concepts and call for studies. *Am J Respir Crit Care Med* 2008; 177(6): 567–73.
30. Salam MT, Islam T, Gilliland FD. Recent evidence for adverse effects of residential proximity to traffic sources on asthma. *Curr Opin Pulm Med* 2008; 14(1): 3–8.
31. Harju TH, Leinonen M, Nokso-Koivisto J, Korhonen T, Rätty R, He Q, et al. Pathogenic bacteria and viruses in induced sputum or pharyngeal secretions of adults with stable asthma. *Thorax* 2006; 61(7): 579–84.

References

32. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. *Brain Behave Immun* 2007; 21 (8): 993–9.
33. O'Rourke ST. Antianginal actions of beta-adrenoceptor antagonists. *Am J Pharm Educ* 2007; 71(5): 95.
34. Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. *Pediatrics* 2011; 127(6): 1125–38.
35. Droste JH, Wieringa MH, Weyler JJ, Nelen VJ. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease?. *Clin Exp Allergy* 2000; 30 (11): 1547–53.
36. Lehmann I, Rehwagen M, Diez U. Enhanced in vivo IgE production and T cell polarization toward the type 2 phenotype in association with indoor exposure to VOC: results of the LARS study. *Int J Hyg Environ Health* 2001; 204 (4): 211–21.
37. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. *Genes Immun* 2006; 7 (2): 95–100.
38. Baxi SN, Phipatanakul W. The role of allergen exposure and avoidance in asthma. *Adolesc Med State Art Rev* 2010; 21 (1): 57–71.
39. World Health Organization(WHO). Asthma. Geneva: WHO; 2010.
40. American Academy of Allergy Asthma & Immunology (AAAAI). Patient/public education: fast facts — asthma demographics/statistics. AAAAI 2006. Available from:
http://www.aaaai.org/patients/resources/fastfacts/asthma_demographics.stm.
[Accessed On: 2 Oct, 2014].
41. Environmental Protection Agency. Cockroaches and pests — indoor environmental asthma triggers. EPA 2009. Available from: <http://www.epa.gov/asthma/pests.html>.
[Accessed On: 23 Mar, 2014].
42. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J* 2009; 33 (4): 897–906.
43. Harrington JJ, Lee-Chiong T. Sleep and older patients. *Clin Chest Med* 2007; 28 (4): 673–84.
44. Tippets B, Guilbert TW. Managing asthma in children: part 1: making the diagnosis, assessing severity. *Consultant for Pediatricians* 2009; 8 (5): 168-174.
45. Maddox L, Schwartz DA. The pathophysiology of asthma. *Annu Rev Med* 2002; 53: 477–98.
46. Beckett PA, Howarth PH. Pharmacotherapy and airway remodelling in asthma. *Thorax* 2003; 58(2): 163–74.
47. Argraves WS, Dickerson K, Burgess WH, Ruoslahti E. Fibulin, novel protein that interacts with the fibronectin receptor β subunit cytoplasmic domain. *Cell* 1989; 58: 623–9.

References

48. Timpl R, Sasaki T, Kostka G, Chu ML. Fibulins: a versatile family of extracellular matrix proteins. *Nature Rev Mol Cell Biol* 2003; 4: 479–89.
49. Argraves WS, Tran H, Burgess WH, Dickerson K. Fibulin is an extracellular matrix and plasma glycoprotein with repeated domain structure. *J Cell Biol* 1990; 111(6 Pt 2):3155-64.
50. Kluge M, Mann K, Dziadek M, Timpl R. Characterization of a novel calcium-binding 90-kDa glycoprotein (BM-90) shared by basement membranes and serum. *Eur J Biochem* 1990; 193(3):651-9.
51. Pan TC, Sasaki T, Zhang RZ, Fassler R, Timpl R, Chu ML. Structure and expression of fibulin-2, a novel extracellular matrix protein with multiple EGF-like repeats and consensus motifs for calcium binding. *J Cell Biol* 1993; 123(5):1269-77.
52. Tran H, Mattei M, Godyna S, Argraves WS. Human fibulin-1D: molecular cloning, expression and similarity with S1-5 protein, a new member of the fibulin gene family. *Matrix Biol* 1997; 15(7):479-93.
53. Gallagher WM, Argentini M, Sierra V, Bracco L, Debussche L, Conseiller E. MBP1: a novel mutant p53-specific protein partner with oncogenic properties. *Oncogene* 1999; 18(24):3608-16.
54. Giltay R, Timpl R, Kostka G. Sequence, recombinant expression and tissue localization of two novel extracellular matrix proteins, fibulin-3 and fibulin-4. *Matrix Biol* 1999; 18(5):469-80.
55. Kowal RC, Richardson JA, Miano JM, Olson EN. EVEC, a novel epidermal growth factor-like repeat-containing protein upregulated in embryonic and diseased adult vasculature. *Circ Res* 1999; 84(10):1166-76.
56. Nakamura T, Ruiz-Lozano P, Lindner V, Yabe D, Taniwaki M, Furukawa Y, et al. DANCE, a novel secreted RGD protein expressed in developing, atherosclerotic, and balloon-injured arteries. *J Biol Chem* 1999; 274(32):22476-83.
57. Vogel BE, Hedgecock EM. Hemicentin, a conserved extracellular member of the immunoglobulin superfamily, organizes epithelial and other cell attachments into oriented line-shaped junctions. *Development* 2001; 128: 883–94.
58. Pan TC, Kluge M, Zhang RZ, Mayer U, Timpl R, Chu ML. Sequence of extracellular mouse protein BM-90/fibulin and its calcium-dependent binding to other basement-membrane ligands. *Eur J Biochem* 1993; 215(3):733-40.
59. Zhang RZ, Pan TC, Zhang ZY, Mattei MG, Timpl R, Chu ML. Fibulin-2 (FBLN2): human cDNA sequence, mRNA expression, and mapping of the gene on human and mouse chromosomes. *Genomics* 1994;22(2):425-30.
60. Sasaki T, Gohring W, Pan TC, Chu ML, Timpl R. Binding of mouse and human fibulin-2 to extracellular matrix ligands. *J Mol Biol* 1995;254(5):892-9.

References

61. Sasaki T, Mann K, Wiedemann H, Gohring W, Lustig A, Engel J, et al. Dimer model for the microfibrillar protein fibulin-2 and identification of the connecting disulfide bridge. *Embo J* 1997;16(11):3035-43.
62. Huber R, Scholze H, Paques EP, Deisenhofer J. Crystal structure analysis and molecular model of human C3a anaphylatoxin. *Hoppe Seylers Z Physiol Chem* 1980;361(9):1389-99.
63. Lecka-Czernik B, Lumpkin CK, Jr., Goldstein S. An overexpressed gene transcript in senescent and quiescent human fibroblasts encoding a novel protein in the epidermal growth factor-like repeat family stimulates DNA synthesis. *Mol Cell Biol* 1995;15(1):120-8.
64. Gallagher WM, Greene LM, Ryan MP, Sierra V, Berger A, Laurent-Puig P, et al. Human fibulin-4: analysis of its biosynthetic processing and mRNA expression in normal and tumour tissues. *FEBS Lett* 2001;489(1):59-66.
65. Downing AK, Knott V, Werner JM, Cardy CM, Campbell ID, Handford PA. Solution structure of a pair of calcium-binding epidermal growth factor-like domains: implications for the Marfan syndrome and other genetic disorders. *Cell* 1996;85(4):597-605.
66. Sasaki T, Mann K, Murphy G, Chu ML, Timpl R. Different susceptibilities of fibulin-1 and fibulin-2 to cleavage by matrix metalloproteinases and other tissue proteases. *Eur J Biochem* 1996;240(2):427-34.
67. Roark EF, Keene DR, Haudenschild CC, Godyna S, Little CD, Argraves WS. The association of human fibulin-1 with elastic fibers: an immunohistological, ultrastructural, and RNA study. *J Histochem Cytochem* 1995;43(4):401-11.
68. Nakamura T, Lozano PR, Ikeda Y, Iwanaga Y, Hinek A, Minamisawa S, et al. Fibulin-5/DANCE is essential for elastogenesis in vivo. *Nature* 2002;415(6868):171-5.
69. Yanagisawa H, Davis EC, Starcher BC, Ouchi T, Yanagisawa M, Richardson JA, et al. Fibulin-5 is an elastin-binding protein essential for elastic fibre development in vivo. *Nature* 2002;415(6868):168-71.
70. Kielty CM, Sherratt MJ, Shuttleworth CA. Elastic fibres. *J Cell Sci* 2002;115(Pt 14):2817-28.
71. Dietz HC, Mecham RP. Mouse models of genetic diseases resulting from mutations in elastic fiber proteins. *Matrix Biol* 2000;19(6):481-8.
72. Milewicz DM, Urban Z, Boyd C. Genetic disorders of the elastic fiber system. *Matrix Biol* 2000;19(6):471-80.
73. Spence SG, Argraves WS, Walters L, Hungerford JE, Little CD. Fibulin is localized at sites of epithelial-mesenchymal transitions in the early avian embryo. *Dev Biol* 1992;151(2):473-84.

References

74. Miosge N, Gotz W, Sasaki T, Chu ML, Timpl R, Herken R. The extracellular matrix proteins fibulin-1 and fibulin-2 in the early human embryo. *Histochem J* 1996;28(2):109-16.
75. Hungerford JE, Owens GK, Argraves WS, Little CD. Development of the aortic vessel wall as defined by vascular smooth muscle and extracellular matrix markers. *Dev Biol* 1996;178(2):375-92.
76. Bouchey D, Argraves WS, Little CD. Fibulin-1, vitronectin, and fibronectin expression during avian cardiac valve and septa development. *Anat Rec* 1996;244(4):540-51.
77. Zhang HY, Kluge M, Timpl R, Chu ML, Ekblom P. The extracellular matrix glycoproteins BM-90 and tenascin are expressed in the mesenchyme at sites of endothelial-mesenchymal conversion in the embryonic mouse heart. *Differentiation* 1993;52(3):211-20.
78. Zhang HY, Chu ML, Pan TC, Sasaki T, Timpl R, Ekblom P. Extracellular matrix protein fibulin-2 is expressed in the embryonic endocardial cushion tissue and is a prominent component of valves in adult heart. *Dev Biol* 1995;167(1):18-26.
79. Tsuda T, Wang H, Timpl R, Chu ML. Fibulin-2 expression marks transformed mesenchymal cells in developing cardiac valves, aortic arch vessels, and coronary vessels. *Dev Dyn* 2001;222(1):89-100.
80. Miosge N, Sasaki T, Chu ML, Herken R, Timpl R. Ultrastructural localization of microfibrillar fibulin-1 and fibulin-2 during heart development indicates a switch in molecular associations. *Cell Mol Life Sci* 1998;54(6):606-13.
81. Ohsawa I, Takamura C, Kohsaka S. Fibulin-1 binds the amino-terminal head of beta-amyloid precursor protein and modulates its physiological function. *J Neurochem* 2001;76(5):1411-20.
82. Reinhardt DP, Sasaki T, Dzamba BJ, Keene DR, Chu ML, Gohring W, et al. Fibrillin-1 and fibulin-2 interact and are colocalized in some tissues. *J Biol Chem* 1996;271(32):19489-96.
83. Sasaki T, Gohring W, Miosge N, Abrams WR, Rosenbloom J, Timpl R. Tropoelastin binding to fibulins, nidogen-2 and other extracellular matrix proteins. *FEBS Lett* 1999;460(2):280-4.
84. Sasaki T, Wiedemann H, Matzner M, Chu ML, Timpl R. Expression of fibulin-2 by fibroblasts and deposition with fibronectin into a fibrillar matrix. *J Cell Sci* 1996;109(Pt 12):2895-904.
85. Loveland K, Schlatt S, Sasaki T, Chu ML, Timpl R, Dziadek M. Developmental changes in the basement membrane of the normal and hypothyroid postnatal rat testis: segmental localization of fibulin-2 and fibronectin. *Biol Reprod* 1998;58(5):1123-30.

References

86. Raghunath M, Tschodrich-Rotter M, Sasaki T, Meuli M, Chu ML, Timpl R. Confocal laser scanning analysis of the association of fibulin-2 with fibrillin-1 and fibronectin define different stages of skin regeneration. *J Invest Dermatol* 1999;112(1):97-101.
87. Fassler R, Sasaki T, Timpl R, Chu ML, Werner S. Differential regulation of fibulin, tenascin-C, and nidogen expression during wound healing of normal and glucocorticoid-treated mice. *Exp Cell Res* 1996;222(1):111-6.
88. Hunzelmann N, Nischt R, Brenneisen P, Eickert A, Krieg T. Increased deposition of fibulin-2 in solar elastosis and its colocalization with elastic fibres. *Br J Dermatol* 2001;145(2):217-22.
89. Kusubata M, Hirota A, Ebihara T, Kuwaba K, Matsubara Y, Sasaki T, et al. Spatiotemporal changes of fibronectin, tenascin-C, fibulin-1, and fibulin-2 in the skin during the development of chronic contact dermatitis. *J Invest Dermatol* 1999;113(6):906-12.
90. Roger P, Pujol P, Lucas A, Baldet P, Rochefort H. Increased immunostaining of fibulin-1, an estrogen-regulated protein in the stroma of human ovarian epithelial tumors. *Am J Pathol* 1998;153(5):1579-88.
91. Clinton GM, Rougeot C, Derancourt J, Roger P, Defrenne A, Godyna S, et al. Estrogens increase the expression of fibulin-1, an extracellular matrix protein secreted by human ovarian cancer cells. *Proc Natl Acad Sci U S A* 1996;93(1):316-20.
92. Hayashido Y, Lucas A, Rougeot C, Godyna S, Argraves WS, Rochefort H. Estradiol and fibulin-1 inhibit motility of human ovarian- and breast-cancer cells induced by fibronectin. *Int J Cancer* 1998;75(4):654-8.
93. Ishibashi T, Takagi Y, Mori K, Naruse S, Nishino H, Yue BY, et al. cDNA microarray analysis of gene expression changes induced by dexamethasone in cultured human trabecular meshwork cells. *Invest Ophthalmol Vis Sci* 2002;43(12):3691-7.
94. Okada H, Nakajima T, Yoshimura T, Yasuda K, Kanzaki H. Microarray analysis of genes controlled by progesterone in human endometrial stromal cells in vitro. *Gynecol Endocrinol* 2003;17(4):271-80.
95. Gu YC, Talts JF, Gullberg D, Timpl R, Ekblom M. Glucocorticoids down-regulate the extracellular matrix proteins fibronectin, fibulin-1 and fibulin-2 in bone marrow stroma. *Eur J Haematol* 2001;67(3):176-84.
96. Hayashi SI, Eguchi H, Tanimoto K, Yoshida T, Omoto Y, Inoue A, et al. The expression and function of estrogen receptor alpha and beta in human breast cancer and its clinical application. *Endocr Relat Cancer* 2003;10(2):193-202.
97. Castoldi M, Chu ML. Structural and functional characterization of the human and mouse fibulin-1 gene promoters: role of Sp1 and Sp3. *Biochem J* 2002;362(Pt 1):41-50.

References

98. Grassel S, Sicot FX, Gotta S, Chu ML. Mouse fibulin-2 gene. Complete exon-intron organization and promoter characterization. *Eur J Biochem* 1999;263(2):471-7.
99. Anderson LM, Choe SE, Yukhananov RY, Hopfner RL, Church GM, Pratt RE, et al. Identification of a novel set of genes regulated by a unique liver X receptor-alpha-mediated transcription mechanism. *J Biol Chem* 2003;278(17):15252-60.
100. Balbona K, Tran H, Godyna S, Ingham KC, Strickland DK, Argraves WS. Fibulin binds to itself and to the carboxyl-terminal heparin-binding region of fibronectin. *J Biol Chem* 1992;267(28):20120-5.
101. Tran H, VanDusen WJ, Argraves WS. The self-association and fibronectin-binding sites of fibulin-1 map to calcium-binding epidermal growth factor-like domains. *J Biol Chem* 1997;272(36):22600-6.
102. Zhang HY, Timpl R, Sasaki T, Chu ML, Ekblom P. Fibulin-1 and fibulin-2 expression during organogenesis in the developing mouse embryo. *Dev Dyn* 1996;205(3):348-64.
103. Sasaki T, Kostka G, Gohring W, Wiedemann H, Mann K, Chu ML, et al. Structural characterization of two variants of fibulin-1 that differ in nidogen affinity. *J Mol Biol* 1995;245(3):241-50.
104. Ruoslahti E. Brain extracellular matrix. *Glycobiology* 1996; 6: 489-92.
105. Kostka G, Giltay R, Bloch W, Addicks K, Timpl R, Fassler R, et al. Perinatal lethality and endothelial cell abnormalities in several vessel compartments of fibulin-1-deficient mice. *Mol Cell Biol* 2001;21(20):7025-34.
106. Hungerford JE, Hoeffler JP, Bowers CW, Dahm LM, Falchetto R, Shabanowitz J, et al. Identification of a novel marker for primordial smooth muscle and its differential expression pattern in contractile vs noncontractile cells. *J Cell Biol* 1997;137(4):925-37.
107. Bell SE, Mavila A, Salazar R, Bayless KJ, Kanagala S, Maxwell SA, et al. Differential gene expression during capillary morphogenesis in 3D collagen matrices: regulated expression of genes involved in basement membrane matrix assembly, cell cycle progression, cellular differentiation and G-protein signaling. *J Cell Sci* 2001;114(Pt 15):2755-73.
108. Jean JC, Eruchalu I, Cao YX, Joyce-Brady M. DANCE in developing and injured lung. *Am J Physiol Lung Cell Mol Physiol* 2002;282(1):L75-82.
109. Qing J, Maher VM, Tran H, Argraves WS, Dunstan RW, McCormick JJ. Suppression of anchorage-independent growth and matrigel invasion and delayed tumor formation by elevated expression of fibulin-1D in human fibrosarcoma-derived cell lines. *Oncogene* 1997;15(18):2159-68.
110. Twal WO, Czihak A, Hegedus B, Knaak C, Chintalapudi MR, Okagawa H, et al. Fibulin-1 suppression of fibronectin-regulated cell adhesion and motility. *J Cell Sci* 2001;114(Pt 24):4587-98.

References

111. Du M, Fan X, Hong E, Chen JJ. Interaction of oncogenic papillomavirus E6 proteins with fibulin-1. *Biochem Biophys Res Commun* 2002;296(4):962-9.
112. Forti S, Scanlan MJ, Invernizzi A, Castiglioni F, Pupa S, Agresti R, et al. Identification of breast cancer-restricted antigens by antibody screening of SKBR3 cDNA library using a preselected patient's serum. *Breast Cancer Res Treat* 2002;73(3):245-56.
113. Greene LM, Twal WO, Duffy MJ, McDermott EW, Hill AD, O'Higgins NJ, et al. Elevated expression and altered processing of fibulin-1 protein in human breast cancer. *Br J Cancer* 2003;88(6):871-8.
114. Moll F, Katsaros D, Lazennec G, Hellio N, Roger P, Giacalone PL, et al. Estrogen induction and overexpression of fibulin-1C mRNA in ovarian cancer cells. *Oncogene* 2002;21(7):1097-107.
115. Creighton C, Hanash S. Expression of matrix metalloproteinase 9 (MMP-9/gelatinase B) in adenocarcinomas strongly correlated with expression of immune response genes. *In Silico Biol* 2003;3(3):301-11.
116. Ramaswamy S, Ross KN, Lander ES, Golub TR. A molecular signature of metastasis in primary solid tumors. *Nat Genet* 2003;33(1):49-54.
117. Schiemann WP, Blobel GC, Kalume DE, Pandey A, Lodish HF. Context-specific effects of fibulin-5 (DANCE/EVEC) on cell proliferation, motility, and invasion. Fibulin-5 is induced by transforming growth factor-beta and affects protein kinase cascades. *J Biol Chem* 2002;277(30):27367-77.
118. Redfern CH, Degtyarev MY, Kwa AT, Salomonis N, Cotte N, Nanevicz T, et al. Conditional expression of a Gi-coupled receptor causes ventricular conduction delay and a lethal cardiomyopathy. *Proc Natl Acad Sci U S A* 2000;97(9):4826-31.
119. Wada J, Zhang H, Tsuchiyama Y, Hiragushi K, Hida K, Shikata K, et al. Gene expression profile in streptozotocin-induced diabetic mice kidneys undergoing glomerulosclerosis. *Kidney Int* 2001;59(4):1363-73.
120. Lecka-Czernik B, Moerman EJ, Jones RA, Goldstein S. Identification of gene sequences overexpressed in senescent and Werner syndrome human fibroblasts. *Exp Gerontol* 1996;31(1-2):159-74.
121. Heine H, Delude RL, Monks BG, Espevik T, Golenbock DT. Bacterial lipopolysaccharide induces expression of the stress response genes hop and H411. *J Biol Chem* 1999;274(30):21049-55.
122. Kawata K, Tanaka A, Arai M, Argraves WS, Fukutake K. Alteration of plasma fibulin-1 concentrations in ischemic heart diseases. *Jpn J Thromb Hemostasis* 2001; 12: 126-32.
123. Tran H, Tanaka A, Litvinovich SV, Medved LV, Haudenschild CC, Argraves WS. The interaction of fibulin-1 with fibrinogen. A potential role in hemostasis and thrombosis. *J Biol Chem* 1995; 270: 19458-64.

References

124. Pfaff M, Sasaki T, Tangemann K, Chu ML, Timpl R. Integrin-binding and cell-adhesion studies of fibulins reveal a particular affinity for alpha IIb beta 3. *Exp Cell Res* 1995; 219(1):87-92.
125. \Perbal B, Martinerie C, Sainson R, Werner M, He B, Roizman B. The C-terminal domain of the regulatory protein NOVH is sufficient to promote interaction with fibulin 1C: a clue for a role of NOVH in cell-adhesion signaling. *Proc Natl Acad Sci U S A* 1999;96(3):869-74.
126. Hesselson D, Newman C, Kim KW, Kimble J. GON-1 and fibulin have antagonistic roles in control of organ shape. *Curr Biol* 2004; 14: 2005–10.
127. Ducros E, Berthaut A, Mirshahi P, Lemarchand S, Soria J. Expression of extracellular matrix proteins fibulin-1 and fibulin-2 by human corneal fibroblasts. *Curr Eye Res* 2007; 32: 481–90.
128. Laprise C, Sladek R, Ponton A, Bernier MC, Hudson TJ, Laviolette M. Functional classes of bronchial mucosa genes that are differentially expressed in asthma. *BMC Genomics* 2004; 5: 21.
129. Pan TC, Kostka G, Zhang RZ, Timpl R, Chu ML. Complete exon-intron organization of the mouse fibulin-1 gene and its comparison with the human fibulin-1 gene *FEBS Lett* 1999;444(1):38-42.
130. Godyna S, Diaz-Ricart M, Argraves WS. Fibulin-1 mediates platelet adhesion via a bridge of fibrinogen. *Blood* 1996;88(7):2569-77.
131. Ruoslahti E. The Walter Herbert Lecture: control of cell motility and tumour invasion by extracellular matrix interactions. *Br J Cancer* 1992; 66: 239- 42.
132. Sheetz MP, Felsenfeld DP, Galbraith CG. Cell migration: regulation of force on extracellular-matrix-integrin complexes. *Trends Cell Biol* 1998;8(2):51-4.
133. Lukashev ME, Werb Z. ECM signalling: orchestrating cell behaviour and misbehaviour. *Trends Cell Biol* 1998; 8: 437-41.
134. Duband JL, Dufour S, Thiery JP. The instructive role of fibronectins in cell migrations during embryonic development. *Ann N Y Acad Sci* 1990;588:273-80.
135. Davis LA, Ogle RC, Little CD. Embryonic heart mesenchymal cell migration in laminin. *Dev Biol* 1989; 133: 37-43.
136. Taraboletti G, Roberts DD, Liotta LA. Thrombospondin-induced tumor cell migration: haptotaxis and chemotaxis are mediated by different molecular domains. *J Cell Biol* 1987;105(5):2409-15.
137. Olivero DK, Furcht LT. Type IV collagen, laminin, and fibronectin promote the adhesion and migration of rabbit lens epithelial cells in vitro. *Invest Ophthalmol Vis Sci* 1993;34(10):2825-34.

References

138. Perris R, Krotoski D, Bronner-Fraser M. Collagens in avian neural crest development: distribution in vivo and migration-promoting ability in vitro. *Development* 1991; 113: 969-84.
139. Hasselaar P, Sage EH. SPARC antagonizes the effect of basic fibroblast growth factor on the migration of bovine aortic endothelial cells. *J Cell Biochem* 1992; 49: 272-83.
140. Landolt RM, Vaughan L, Winterhalter KH, Zimmermann DR. Versican is selectively expressed in embryonic tissues that act as barriers to neural crest cell migration and axon outgrowth. *Development* 1995; 121: 2303-12.
141. Perris R, Perissinotto D, Pettway Z, Bronner-Fraser M, Morgelin M, Kimata K. Inhibitory effects of PG-H/aggrecan and PG-M/versican on avian neural crest cell migration. *Faseb J* 1996;10(2):293-301.
142. Spring J, Beck K, Chiquet-Ehrismann R. Two contrary functions of tenascin: dissection of the active sites by recombinant tenascin fragments. *Cell* 1989; 59: 325-34.
143. Sasaki T, Fukai N, Mann K, Gohring W, Olsen BR, Timpl R. Structure, function and tissue forms of the C-terminal globular domain of collagen XVIII containing the angiogenesis inhibitor endostatin. *Embo J* 1998;17(15):4249-56.
144. Godyna S, Mann DM, Argraves WS. A quantitative analysis of the incorporation of fibulin-1 into extracellular matrix indicates that fibronectin assembly is required. *Matrix Biol* 1995;14(6):467-77.
145. Roman J, McDonald JA. Fibulin's organization into the extracellular matrix of fetal lung fibroblasts is dependent on fibronectin matrix assembly. *Am J Respir Cell Mol Biol* 1993;8(5):538-45.
146. Gu YC, Nilsson K, Eng H, Ekblom M. Association of extracellular matrix proteins fibulin-1 and fibulin-2 with fibronectin in bone marrow stroma. *Br J Haematol* 2000;109(2):305-13.
147. Bloom L, Ingham KC, Hynes RO. Fibronectin regulates assembly of actin filaments and focal contacts in cultured cells via the heparin-binding site in repeat III13. *Mol Biol Cell* 1999;10(5):1521-36.
148. Saoncella S, Echtermeyer F, Denhez F, Nowlen JK, Mosher DF, Robinson SD, et al. Syndecan-4 signals cooperatively with integrins in a Rho-dependent manner in the assembly of focal adhesions and actin stress fibers. *Proc Natl Acad Sci U S A* 1999;96(6):2805-10.
149. Woods A, Couchman JR, Johansson S, Hook M. Adhesion and cytoskeletal organisation of fibroblasts in response to fibronectin fragments. *EMBO J* 1986; 5: 665-70.

References

150. McCarthy JB, Hagen ST, Furcht LT. Human fibronectin contains distinct adhesion- and motility-promoting domains for metastatic melanoma cells. *J Cell Biol* 1986;102(1):179-88.
151. Mould AP, Humphries MJ. Identification of a novel recognition sequence for the integrin alpha 4 beta 1 in the COOH-terminal heparin-binding domain of fibronectin. *Embo j* 1991;10(13):4089-95.
152. Ruoslahti E. Fibronectin and its receptors. *Annu Rev Biochem* 1988; 57: 375-413.
153. Humphries MJ, Akiyama SK, Komoriya A, Olden K, Yamada KM. Identification of an alternatively spliced site in human plasma fibronectin that mediates cell type-specific adhesion. *J Cell Biol* 1986;103(6 Pt 2):2637-47.
154. Watanabe K, Takahashi H, Habu Y, Kamiya-Kubushiro N, Kamiya S, Nakamura H, et al. Interaction with heparin and matrix metalloproteinase 2 cleavage expose a cryptic anti-adhesive site of fibronectin. *Biochemistry* 2000;39(24):7138-44.
155. van Leeuwen FN, van Delft S, Kain HE, van der Kammen RA, Collard JG. Rac regulates phosphorylation of the myosin-II heavy chain, actinomyosin disassembly and cell spreading. *Nat Cell Biol* 1999;1(4):242-8.
156. Franklin RA, Atherfold PA, McCubrey JA. Calcium-induced ERK activation in human T lymphocytes occurs via p56(Lck) and CaM-kinase. *Mol Immunol* 2000; 37: 675-83.
157. Rosengart MR, Arbabi S, Garcia I, Maier RV. Interactions of calcium/calmodulin-dependent protein kinases (CaMK) and extracellular-regulated kinase (ERK) in monocyte adherence and TNFalpha production. *Shock* 2000; 13: 183-9.
158. Wu X, Davis GE, Meininger GA, Wilson E, Davis MJ. Regulation of the L-type calcium by alpha5beta1 integrin requires signaling between focal adhesion proteins. *J Biol Chem* 2001; 276: 30285-92.
159. Pupa SM, Argraves WS, Forti S, Casalini P, Berno V, Agresti R, et al. Immunological and pathobiological roles of fibulin-1 in breast cancer. *Oncogene* 2004; 23(12):2153-60.
160. Pupa SM, Forti S, Balsari A, Menard S. Humoral immune response for early diagnosis of breast carcinoma. *Ann Oncol* 2002;13(3):483.
161. Pupa SM, Giuffre S, Castiglioni F, Bertola L, Cantu M, Bongarzone I, et al. Regulation of breast cancer response to chemotherapy by fibulin-1 *Cancer Res* 2007; 67(9):4271-7.
162. Pan S, Cheng L, White JT, Lu W, Utleg AG, Yan X, et al. Quantitative proteomics analysis integrated with microarray data reveals that extracellular matrix proteins, catenins, and p53 binding protein 1 are important for chemotherapy response in ovarian cancers. *OMICS* 2009; 13(4):345-54.

References

163. Cheng YY, Jin H, Liu X, Siu JM, Wong YP, Ng EK, et al. Fibulin 1 is down regulated through promoter hypermethylation in gastric cancer. *Br J Cancer* 2008; 99(12):2083-7.
164. Wlazlinski A, Engers R, Hoffmann MJ, Hader C, Jung V, Muller M, et al. Down regulation of several fibulin genes in prostate cancer. *Prostate* 2007; 67(16):1770-80.
165. Kanda M, Nomoto S, Okamura Y, Hayashi M, Hishida M, Fujii T, et al. Promoter hypermethylation of fibulin 1 gene is associated with tumor progression in hepatocellular carcinoma. *Mol Carcinog* 2011; 50(8):571-9.
166. Kubista B, Klinglmueller F, Bilban M, Pfeiffer M, Lass R, Giurea A, et al. Microarray analysis identifies distinct gene expression profiles associated with histological subtype in human osteosarcoma. *Int Orthop* 2011 ; 35(3): 401-11.
167. Kischel P, Waltregny D, Greffe Y, Mazzucchelli G, De Pauw E, de Leval L, et al. Identification of stromal proteins overexpressed in nodular sclerosis Hodgkin lymphoma. *Proteome Sci* 2011; 9(1):63.
168. Debeer P, Schoenmakers EF, Twal WO, Argraves WS, De Smet L, Fryns JP, et al. The fibulin-1 gene (FBLN1) is disrupted in at(12;22) associated with a complex type of synpolydactyly. *J Med Genet* 2002; 39(2):98-104.
169. Lanza F. Bernard-Soulier syndrome (hemorrhagic thrombocytic dystrophy). *Orphanet J Rare Dis* 2006; 1:46.
170. Singh U, Sun T, Larsson T, Elliott RW, Kostka G, Fundele RH. Expression and functional analysis of fibulin-1 (Fbln1) during normal and abnormal placental development of the mouse. *Placenta* 2006; 27(9-10):1014-21.
171. Cooley MA, Kern CB, Fresco VM, Wessels A, Thompson RP, McQuinn TC, et al. Fibulin-1 is required for morphogenesis of neural crest-derived structures. *Dev Biol* 2008; 319(2):336-45.
172. Mohamed SA, Sievers HH, Hanke T, Richardt D, Schmidtke C, Charitos EI, et al. Pathway analysis of differentially expressed genes in patients with acute aortic dissection. *Biomark Insights* 2009; 4:81-90.
173. Argraves WS, Tanaka A, Smith EP, Twal WO, Argraves KM, Fan D, et al. Fibulin-1 and fibrinogen in human atherosclerotic lesions. *Histochem Cell Biol* 2009; 132(5): 559-65.
174. Cangemi C, Skov V, Poulsen MK, Funder J, Twal WO, Gall MA, et al. Fibulin-1 is a marker for arterial extracellular matrix alterations in type 2 diabetes. *Clin Chem* 2011; 57(11):1556-65.
175. Courtney HS, Li Y, Twal WO, Argraves WS. Serum opacity factor is a streptococcal receptor for the extracellular matrix protein fibulin-1. *J Biol Chem* 2009; 284(19): 12966-71.

References

176. Ebina M, Takahashi T, Chiba T, Motomiya M. Cellular hypertrophy and hyperplasia of airway smooth muscles underlying bronchial asthma. A 3-D morphometric study. *Am Rev Respir Dis* 1993; 148: 720–6.
177. Woodruff PG, Dolganov GM, Ferrando RE, Donnelly S, Hays SR. Hyperplasia of smooth muscle in mild to moderate asthma without changes in cell size or gene expression. *Am J Respir Crit Care Med* 2004; 169: 1001–6.
178. Johnson PR, Roth M, Tamm M, Hughes M, Ge Q. Airway smooth muscle cell proliferation is increased in asthma. *Am J Respir Crit Care Med* 2001; 164: 474–7.
179. Trian T, Benard G, Begueret H, Rossignol R, Girodet PO, Ghosh D, et al. Bronchial smooth muscle remodeling involves calcium-dependent enhanced mitochondrial biogenesis in asthma. *J Exp Med* 2007; 204: 3173–81.
180. Akiyama SK, Yamada SS, Chen WT, Yamada KM. Analysis of fibronectin receptor function with monoclonal antibodies: roles in cell adhesion, migration, matrix assembly, and cytoskeletal organization. *J Cell Biol* 1989; 109: 863–75.
181. Johnson PR, Burgess JK, Underwood PA, Au W, Poniris MH, Tamm M, et al. Extracellular matrix proteins modulate asthmatic airway smooth muscle cell proliferation via an autocrine mechanism. *J Allergy Clin Immunol* 2004; 113: 690–6.
182. Laitinen LA, Laitinen A. Inhaled corticosteroid treatment and extracellular matrix in the airways in asthma. *Int Arch Allergy Immunol* 1995; 107: 215–6.
183. Parameswaran K, Radford K, Zuo J, Janssen LJ, O'Byrne PM, Cox PG. Extracellular matrix regulates human airway smooth muscle cell migration. *Eur Respir J* 2004;24(4):545-51.
184. Redington AE, Madden J, Frew AJ, Djukanovic R, Roche WR, Holgate ST, et al. Transforming growth factor-beta 1 in asthma. Measurement in bronchoalveolar lavage fluid. *Am J Respir Crit Care Med* 1997;156(2 Pt 1):642-7.
185. Vignola AM, Chanez P, Chiappara G, Merendino A, Pace E. Transforming growth factor-beta expression in mucosal biopsies in asthma and chronic bronchitis. *Am J Respir Crit Care Med* 1997; 156: 591–9.
186. Romberger DJ, Beckmann JD, Claassen L, Ertl RF, Rennard SI. Modulation of fibronectin production of bovine bronchial epithelial cells by transforming growth factor-beta. *Am J Respir Cell Mol Biol* 1992; 7: 149–55.
187. Westergren-Thorsson G, Chakir J, Lafreniere-Allard MJ, Boulet LP, Tremblay GM. Correlation between airway responsiveness and proteoglycan production by bronchial fibroblasts from normal and asthmatic subjects. *Int J Biochem Cell Biol* 2002; 34: 1256–67.
188. Tran H, VanDusen WJ, Argraves WS. The self-association and fibronectin-binding sites of fibulin-1 map to calcium-binding epidermal growth factor-like domains. *J Biol Chem* 1997; 272: 22600–6.

References

189. Syed F, Panettieri RA, Jr., Tliba O, Huang C, Li K, Bracht M, et al. The effect of IL-13 and IL-13R130Q, a naturally occurring IL-13 polymorphism, on the gene expression of human airway smooth muscle cells. *Respir Res* 2005;6:9.
190. Zimmermann N, King NE, Laporte J, Yang M, Mishra A. Dissection of experimental asthma with DNA microarray analysis identifies arginase in asthma pathogenesis. *J Clin Invest* 2003; 111: 1863–74.
191. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; 31(1):143-78.
192. Wenzel SE, Szeffler SJ, Leung DYM, Sloan SI, Rex MD. Bronchoscopic evaluation of severe asthma. *Am J Respir Crit Care Med* 1997; 156:737-43.
193. Engvall E, Perlmann P. Enzyme-linked immunosorbent assay (ELISA). Quantitative assay of immunoglobulin G. *Immunochemistry* 1971;8(9):871-4.
194. Engvall E, Perlmann P. Enzyme-linked immunosorbent assay, Elisa. 3. Quantitation of specific antibodies by enzyme-labeled anti-immunoglobulin in antigen-coated tubes. *J Immunol* 1972;109(1):129-35.
195. Van Weemen BK, Schuurs AH. Immunoassay using antigen enzyme conjugates. *FEBS Letters* 1971; 15: 232.
196. de Boer WI, van Schadewijk A, Sont JK, Sharma HS, Stolk J, Sharma HS, et al. Transforming growth factor beta1 and recruitment of macrophages and mast cells in airways in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158: 1951–7.
197. Mak JC, Chan-Yeung MM, Ho SP, Chan KS, Choo K. Elevated plasma TGF-beta1 levels in patients with chronic obstructive pulmonary disease. *Respir Med* 2009; 103: 1083–9.
198. Khalil N, O'Connor RN, Unruh HW, Warren PW, Flanders KC, Kemp A, et al. Increased production and immunohistochemical localization of transforming growth factor-beta in idiopathic pulmonary fibrosis. *Am J Respir Cell Mol Biol* 1991; 5: 155–62.
199. Zhang K, Flanders KC, Phan SH. Cellular localization of transforming growth factor-beta expression in bleomycin-induced pulmonary fibrosis. *Am J Pathol* 1995; 147: 352–61.
200. Moir LM, Burgess JK, Black JL. Transforming growth factor beta 1 increases fibronectin deposition through integrin receptor alpha 5 beta 1 on human airway smooth muscle. *J Allergy Clin Immunol* 2008; 121: 1034–9.
201. Rosenbloom J, Castro SV, Jimenez SA. Narrative review: fibrotic diseases: cellular and molecular mechanisms and novel therapies. *Ann Intern Med* 2010; 152: 159–66.

References

202. Johnson PR, Burgess JK, Underwood PA, Au W, Poniris MH, Tamm M, et al. Extracellular matrix proteins modulate asthmatic airway smooth muscle cell proliferation via an autocrine mechanism. *J Allergy Clin Immunol* 2004; 113: 690–6.
203. Shull MM, Ormsby I, Kier AB, Pawlowski S, Diebold RJ, Yin M, et al. Targeted disruption of the mouse transforming growth factor- β 1 gene results in multifocal inflammatory disease. *Nature* 1992;359:693-9.
204. Kulkarni AB, Huh CG, Becker D, Geiser A, Lyght M, Flanders KC, et al. Transforming growth factor- β 1, null mutation in mice causes excessive inflammatory response and death. *Proc Natl Acad Sci USA* 1993;90:770-4.
205. Yamauchi K, Martinet Y, Basset P, Fells GA, Crystal RG. High levels of transforming growth factor- β 1 are present in the epithelial lining fluid of the normal human lower respiratory tract. *Am Rev Respir Dis* 1988;137:1360-3.
206. Assoian RK, Fleurdelys BE, Stevenson HC, Miller PJ, Madtes DK, Raines EW, et al. Expression and secretion of transforming growth factor- β 1 by activated human macrophages. *Proc Natl Acad Sci USA* 1987;84:6020-4.
207. Adolff CH, Golden JA, Kennedy PW, Goetzl EJ, Turck CW. Polymerase chain reaction amplification of messages for growth factors in cells from human bronchoalveolar lavage fluids. *Inflammation* 1991;15:259-68.
208. Pelton RW, Moses HL. The beta-type transforming growth factor: mediation of cell regulation in the lung. *Am Rev Respir Dis* 1990;142:S31-S35.
209. Border WA, Ruoslahti E. Transforming growth factor- β 1 in disease: the dark side of tissue repair. *J Clin Invest* 1992;90: 1-7.
210. Sacco O, Romberger D, Rizzino A, Beckmann JD, Rennard SI, Spurzem JR. Spontaneous production of transforming growth factor- β 1 by primary cultures of bronchial epithelial cells. Effects on cell behaviour in vitro. *J Clin Invest* 1992;90: 1379-85.
211. Gibbons GH, Pratt RE, Dzau VJ. Vascular smooth muscle cell hypertrophy vs. hyperplasia: autocrine transforming growth factor- β 1 expression determinates growth response to angiotensin II. *J Clin Invest* 1992;90:456-61.
212. Oswald IP, Gazinelli RT, Sher A, James SL. IL-10 synergizes with IL-4 and transforming growth factor- β 1 to inhibit macrophage cytotoxic activity. *J Immunol* 1992; 148:3578-82.
213. Nelson BJ, Ralph P, Green SJ, Nacy CA. Differential susceptibility of activated macrophage cytotoxic effector reactions to the suppressive effects of transforming growth factor- β 1. *J Immunol* 1991;146:1849-57.
214. Musso T, Espinosa-Delgado I, Pulkki K, Gusella GL, Longo DL, Vareso L. Transforming growth factor- β 1 downregulates interleukin-1 (IL-1)-induced IL-6 production by human monocytes. *Blood* 1990;76:2466-9.

References

215. Dubois CM, Ruscetti FW, Palaszynski EW, Falk LA, Oppenheim JJ, and Keller JR. Transforming growth factor- β 1 is a potent inhibitor of interleukin-1 (IL-1) receptor expression. *J Exp Med* 1990;72:737-44.
216. Tsunawaki S, Sporn M, Ding A, Nathan C. Deactivation of macrophages by transforming growth factor- β 1. *Nature* 1988;334:260-2.
217. Turner M, Chantry D, Katsikis P, Berger A, Brenmann FM, Felman M. Induction of the interleukin-1 receptor antagonist protein by transforming growth factor- β 1. *Eur J Immunol* 1991;21:1635-9.
218. Kehrl JH, Roberts AB, Wakefield LM, Jakolew S, Sporn MB, Fauci AS. Transforming growth factor- β 1 is an important immunomodulatory protein for human B lymphocytes. *J Immunol* 1986;137:3855-60.
219. Fargeas C, Wu CY, Nakajima T, Cox D, Nutman T, Delespesse G. Differential effects of transforming growth factor- β 1 on the synthesis of Th-1 and Th-2-like lymphokines by human T lymphocytes. *Eur J Immunol* 1992; 22:2173-6.
220. Meade R, Askenase PW, Geba GP, Neddermann K, Jacoby RO, Pasternak RD. Transforming growth factor- β 1 inhibits murine immediate and delayed type hypersensitivity. *J Immunol* 1992;149:521-8.
221. Swain SL, Huston G, Tonkonogy S, Weinberg A. Transforming growth factor- β 1 and IL-4 cause helper cells precursors to develop into distinct effector helper cells that differ in lymphokine secretion pattern and cell surface phenotype. *J Immunol* 1991;147:2991-3000.
222. Saltini C, Richaldi L, Holroyd KJ, du Bois RM, Crystal RG. Lymphocytes. In: Crystal RG, West JB, eds. *Lymphocytes in the lung: scientific foundations*. New York: Raven Press, 1991:459-81.
223. Van Vlasselaer P, Punnonen J, de Vries JE. Transforming growth factor- β 1 directs IgA switching in human B cells. *J Immunol* 1992;148:2062-7.
224. Daniele RP. Immunoglobulin secretion in the airways. *Annu Rev Physiol* 1990;52:177-95.
225. Masui T, Wakefield LM, Lechner JF, LaVaeck MA, Sporn MB, Harris CC. Type β transforming growth factor is the primary differentiation-inducing serum factor for normal human bronchial epithelial cells. *Proc Natl Acad Sci USA* 1986;83:2438-42.
226. Hirst SJ, Twort CH, Lee TH. Differential effects of extracellular matrix proteins on human airway smooth muscle cell proliferation and phenotype. *Am J Respir Cell Mol Biol* 2000; 23: 335-44.
227. Jeffery PK. Pathology of asthma. *Br Med Bull* 1992; 48: 23-39.
228. Kenyon NJ, Ward RW, McGrew G, Last JA. TGF- β 1 causes airway fibrosis and increased collagen I and III mRNA in mice. *Thorax* 2003; 58: 772-7.

References

229. Lau JY, Oliver BG, Baraket M, Beckett EL, Hansbro NG. Fibulin-1 Is Increased in Asthma – A Novel Mediator of Airway Remodeling?. PLoS ONE 2010; 5(10): e13360.
230. Chen L, Ge Q, Black JL, Deng L, Burgess JK, Oliver BG. Differential regulation of extracellular matrix and soluble fibulin-1 levels by TGF- β 1 in airway smooth muscle cells. PLoS ONE 2013; 8(6): e65544.

PROTOCOL

تمت الموافقة
على هذا البحث
2012/10/10

**THE STUDY OF FIBULIN-1 AS A NOVEL BIOMARKER IN
BRONCHIAL ASTHMA AND ITS ASSOCIATION WITH
DISEASE SEVERITY**

دراسة مستوى الفيبولين 1 كدليل بيولوجي لمرض الربو الشعبي وعلاقته بشدة
المرض

Dr. Elshor

Protocol of a thesis submitted
to the Faculty of Medicine
University of Alexandria
In partial fulfillment of the
requirements of the degree of
**Master of Clinical and Chemical
Pathology**

by

Mona Mustafa Abdellatif Mahmoud
MBBCh, Alex
Resident
Ministry of Health Hospitals
Department of Clinical and Chemical Pathology
Faculty of Medicine
University of Alexandria
2012

خطة بحث مقدمة
لكلية الطب
جامعة الإسكندرية
إيفاء جزئياً
لشروط الحصول على درجة
الماجستير في الباثولوجيا الإكلينيكية
والكيميائية

من

منى مصطفى عبد اللطيف محمود
بكالوريوس الطب والجراحة ، الإسكندرية
طبيب مقیم
مستشفيات وزارة الصحة
قسم الباثولوجيا الإكلينيكية والكيميائية
كلية الطب
جامعة الإسكندرية

٢٠١٢

١١٢٤٦١١٨
٢٠٢٣
١١/١٢/٢٠٢٣

SUPERVISORS

المشرفون

Prof. Dr. Dalal Abd Elglel El Giziry

Professor of Clinical and Chemical
Pathology,
Faculty of Medicine,
University of Alexandria.

أ.د. دلال عبد الجليل الجزيري

أستاذة الباثولوجيا الإكلينيكية

والكيميائية
كلية الطب

جامعة الإسكندرية

Dr. Nermine Hossam Eldin Zakaria

Assistant Professor of Clinical and Chemical
Pathology,
Faculty of Medicine,
University of Alexandria.

د. نيرمين حسام الدين زكريا

أستاذة مساعد الباثولوجيا الإكلينيكية

والكيميائية

كلية الطب

جامعة الإسكندرية

CO-SUPERVISOR

المشرف المشارك

Dr. Abeer Hassan Kassem

Lecturer of Chest Diseases,
Faculty of Medicine,
University of Alexandria.
For her experience in pulmonary function
tests and bronchoscope

د. عبير حسن قاسم

مدرس الأمراض الصدرية

كلية الطب

جامعة الإسكندرية

وذلك لخبرتها في مجال وظائف التنفس

ومناظير الجهاز التنفسي

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by variable and reversible airflow obstruction and airway hyper responsiveness (AHR). A key feature of asthmatic airways is remodeling which involves thickening of the airway wall, altered deposition of extracellular matrix (ECM) proteins and increased airway smooth muscle (ASM) mass.^(1,2)

These structural changes may result from an aberrant repair process in the lung, which includes increased proliferation of the ASM cells.^(3,4) The ECM maintains airway function and structure by providing mechanical support in addition to constituting a dynamic and complex network that influences cellular function.⁽⁵⁾

The ECM deposited by asthma derived ASM cells is altered such that increased amounts of collagen I and laminin,⁽⁶⁻⁸⁾ as well as fibronectin (FN) are produced which mediate a range of cellular interactions including migration, growth and differentiation.

Fibulin-1(FBLN), a secreted glycoprotein, assists in stabilizing the ECM. It associates with FN and a variety of other ECM proteins including laminin and fibrinogen.⁽⁹⁾ Many studies reported reduced FBLN-1D levels in asthma derived bronchial biopsies compared with those derived from non-asthmatics.⁽¹⁰⁾ Four isoforms of FBLN-1 have been identified to date in humans, designated FBLN-1A, 1B, 1C, and 1D.⁽¹¹⁾

These isoforms are splice variants which possess different C-terminal sequences. It was shown that the proliferation of ASM cells derived from



asthmatic individuals is enhanced compared with those from non-asthmatic individuals.^(4,12,13)

Using the recommendations for classification of asthma severity of the NHLBI/WHO Workshop on the Global Strategy for Asthma,⁽¹⁴⁾ asthmatic patients are classified into three categories: intermittent, mild to moderate persistent and severe persistent asthma.



AIM OF THE WORK

The objective of this work is to study the association of the fibulin-1 levels in asthmatic patients and its relation to asthma severity.

[Handwritten signatures and initials]

oboikeyanadl.com

PATIENTS

The study will be conducted on 2 groups recruited from the chest Department Alexandria University Hospital:

1. Thirty six asthmatic patients will be recruited and will be classified into three groups.⁽¹⁵⁾

Group I: Twelve asthmatic patients (mild stage).

Group II: Twelve asthmatic patients (moderate stage).

Group III: Twelve asthmatic patients (severe stage).

2. Eighteen normal healthy adults will be recruited as controls with matched age and sex.

Approval for the study will be obtained from the ethics committee of the Faculty of Medicine, Alexandria University. All patients signed a written informed consent to participate in this study.

Exclusion criteria: renal, hepatic, immunological diseases and smoking.



MATERIALS AND METHODS

All subjects included in the present study will be subjected to:

- Full history taking.
- Complete thorough clinical examination.
- Laboratory Investigation:
 - Complete blood picture (CBP).
 - Liver function tests: ALT, AST.
 - Kidney function tests: blood urea and serum creatinine.
- Chest X-ray: Standard poster-anterior (PA) chest radiographs.
- Pulmonary function test (PFT): including forced expiratory volume in one second (FEV₁%) predicted, forced expiratory volume in one second/Forced vital capacity (FEV₁/FVC %), peak expiratory flow rate (PEFR %) and reversibility test to confirm the diagnosis and to assess its severity.
- Bronchoscope and bronchoalveolar lavage (BAL).⁽¹⁶⁾

All asthmatic patients will be examined with fiberoptic bronchoscope and BAL will be taken for estimation of level of
- Fibulin-1.
 - Serum sample from all studied patients and controls will be taken for estimation of level of Fibulin-1.



RESULTS

The results of this study will be tabulated and analyzed with the use of appropriate statistical methods and appropriate figures and diagrams.

Handwritten signature and text in Urdu script.

Handwritten signature.

DISCUSSION

The results of the study will be discussed in view of the achievement of the aim of the work, their significance and their comparison with previous related published researches.



REFERENCES

1. Ebina M, Takahashi T, Chiba T, Motomiya M. Cellular hypertrophy and hyperplasia of airway smooth muscles underlying bronchial asthma. A 3-D morphometric study. *Am Rev Respir Dis* 1993; 148: 720-6.
2. Woodruff PG, Dolganov GM, Ferrando RE, Donnelly S, Hays SR. Hyperplasia of smooth muscle in mild to moderate asthma without changes in cell size or gene expression. *Am J Respir Crit Care Med* 2004; 169:1001-6.
3. Johnson PR, Roth M, Tamm M, Hughes M, Ge Q. Airway smooth muscle cell proliferation is increased in asthma. *Am J Respir Crit Care Med* 2001; 164: 474-7.
4. Trian T, Benard G, Begueret H, Rossignol R, Girodet PO. Bronchial smooth muscle remodeling involves calcium-dependent enhanced mitochondrial biogenesis in asthma. *J Exp Med* 2007; 204:3173-81.
5. Akiyama SK, Yamada SS, Chen WT, Yamada KM. Analysis of fibronectin receptor function with monoclonal antibodies: roles in cell adhesion, migration, matrix assembly, and cytoskeletal organization. *J Cell Biol* 1989; 109:863-75.
6. Johnson PR, Burgess JK, Underwood PA, Au W, Poniris MH. Extracellular matrix proteins modulate asthmatic airway smooth muscle cell proliferation via an autocrine mechanism. *J Allergy Clin Immunol* 2004; 113:690-6.

Handwritten signatures and initials in black ink, including a large signature on the left, initials 'JL' in the middle, and a signature 'Wahab' on the right.

7. Laitinen LA, Laitinen A. Inhaled corticosteroid treatment and extracellular matrix in the airways in asthma. *Int Arch Allergy Immunol* 1995; 107:215-6.
8. Parameswaran K, Radford K, Zuo J, Janssen LJ, O'Byrne PM. Extracellular matrix regulates human airway smooth muscle cell migration. *Eur Respir J* 2004; 24:545-51.
9. Tran H, Dusen WJ, Argraves WS. The self-association and fibronectin-binding sites of fibulin-1 map to calcium-binding epidermal growth factor-like domains. *J Biol Chem* 1997; 272: 22600-6.
10. Laprise C, Sladek R, Ponton A, Bernier MC, Hudson TJ. Functional classes of bronchial mucosa genes that are differentially expressed in asthma. *BMC Genomics* 2004; 5:21.
11. Roark EF, Keene DR, Haudenschild CC, Godyna S, Little CD. The association of human fibulin-1 with elastic fibers: an immunohistological, ultrastructural, and RNA study. *J Histochem Cytochem* 1995; 43:401-11.
12. Johnson PRA, Roth M, Tamm M, Hughes JM, Ge Q. Airway smooth muscle cell proliferation is increased in asthma. *Am J Respir Crit Care Med* 2001; 164:474-7.
13. Hassan M, Jo T, Risse PA, Tolloczko B, Lemiere C. Airway smooth muscle remodeling is a dynamic process in severe long-standing asthma. *J Allergy Clin Immunol* 2010; 125:1037-45.

Handwritten signatures and initials, including a large signature on the left, initials 'EJ' in the middle, and a signature 'Curtis' on the right.

14. NHLBI/WHO Workshop Report. Global strategy for asthma management and prevention. National Institutes of Health. National Heart, Lung, and Blood Institute, Bethesda, MD. Publication No 1995; 95-3659.
15. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; 31(1):143-78.
16. Wenzel SE, Szeffler SJ, Leung DYM, Sloan SI, Rex MD. Bronchoscopic evaluation of severe asthma. *Am J Respir Crit Care Med* 1997; 156:737-43.



ARBIC SUMMARY

المخلص العربي

الربو الشعبي هو مرض التهابي مزمن شائع في الشعب الهوائية و يتميز بالأعراض المتغيرة والمنكررة، انسداد تدفق الهواء وتشنج قصبي.

ويصنف الربو سريريا وفقا لتواتر الأعراض، وحجم الزفير القسري في ثانية واحدة ومعدل الزفير.

ومن السمات الرئيسية للربو الشعبي إعادة هيكلة مجرى الهواء وتتضمن زياده سماكة جدار مجرى الهواء وترسب بروتينات من المصفوفة خارج الخلية وزيادة كتلة العضلات الملساء في مجرى الهواء. هذه التغيرات الهيكلية قد تنجم عن عملية الإصلاح الشاذة في الرئة، والذي يتضمن زيادة انتشار خلايا العضلات الملساء.

عائلة الفيبيولين هي عائلة من البروتينات التي ترتبط مع الأغشية السفلي والألياف المرنة المصفوفة خارج الخلية.

يتم تحديد عائلة الفيبيولين بوجود سلسلة وحدات موازية من عامل نمو البشرة، تليها وحدة-كربوكسي الطرفية من نوع الفيبيولين.

وتعمل عائلة الفيبيولين كجسور لتحقيق الاستقرار في تنظيم هيكل الألياف المرنة والأغشية السفليه.

وقد كان فيبيولين-1 أول أفراد العائلة.

ويبدأ ظهور فيبيولين-1 في مراحل مبكرة من التطور الجنيني وهو أحد مكونات معظم الأغشية السفليه في جنين الطيور.

ويتواجد فيبيولين-1 في الألياف التي تحتوي على الفيبرونيكتين ويلعب دورا ابضا في التصاق وهجرة الخلايا على طول الياف البروتين داخل المصفوفه خارج الخلية له دورا ابضا في عمليات تنمويه عديده

وقد تم تحديد أربعة انواع من فيبيولين-1 حتى الآن في البشر.

وبقياس فيبيولين-1 في البشر فقد وجد بتركيزات عاليه نسبيا تصل الى (10-50 ميكروغرام / مل).

وافادت العديد من الدراسات ان فيبيولين-1 يزداد وجوده في مختلف الاورام التي تصيب الانسان ويشارك في عمليات غزو وحركة ونمو الخلايا السرطانيه في الجسم. وقد وجد ان فيبيولين-1 يمنع التصاق وحركة الخلايا السرطانيه.

اما بالنسبه لعلاقه فيبيولين-1 بمجري الهواء فإنه يساعد على تحقيق الاستقرار في المصفوفه خارج الخلية والتي تحافظ بدورها على وظيفة مجرى الهواء من خلال توفير الدعم الميكانيكي بالاضافه الي تشكيل شبكه 8 ديناميكيه معقده من دورها ان تؤثر على وظيفة الخلية.

ان هذه الدراسة تهدف إلى التحقيق في ارتباط مستوى الفيبيولين 1 كدليل بيولوجي لمرض الربو الشعبي وعلاقته بشدة المرض.

وقد أجريت هذه الدراسة على خمس واربعين من مرضى الربو الشعبي وثلاثين شخصا سليما .

وقد وجد أن فيبيولين-1 يزداد في مصل الدم لمرضى الربو ولكن دون علاقة بشدة الربو ويزداد أيضا في سائل غسل الشعب الهوائية في الحالات الشديده للربو عن الحالات البسيطة والمتوسطه .

الملخص العربي

لجنة الإشراف

موافقون

أ.د/ دلال عبد الجليل الجزيرى

أستاذ الباثولوجيا الاكلينيكية والكيميائية
قسم الباثولوجيا الاكلينيكية والكيميائية
كلية الطب
جامعة الإسكندرية

أ.م.د/ نيرمين حسام الدين زكريا

أستاذ مساعد الباثولوجيا الاكلينيكية والكيميائية
قسم الباثولوجيا الاكلينيكية والكيميائية
كلية الطب
جامعة الإسكندرية

المشرف المساعد

أ.م.د/ عبير حسن قاسم

أستاذ مساعد الأمراض الصدرية
قسم الأمراض الصدرية
كلية الطب
جامعة الإسكندرية



جامعة الإسكندرية
كلية الطب
قسم الباثولوجيا الاكلينيكية والكيميائية

دراسة مستوى الفيبيولين اكدليل بيولوجي لمرض الربو الشعبي وعلاقته
بشدة المرض

رسالة مقدمة من

منى مصطفى عبد اللطيف محمود

للحصول على درجة

الماجستير

فى

الباثولوجيا الاكلينيكية والكيميائية

التوقيع

.....

لجنة المناقشة والحكم على الرسالة

أ.د/ أمل عبد الفتاح كامل

أستاذ الباثولوجيا الكيميائية

قسم الباثولوجيا الكيميائية

معهد البحوث الطبية

جامعة الإسكندرية

.....

أ.م.د/ نيرمين حسام الدين زكريا

أستاذ مساعد الباثولوجيا الاكلينيكية والكيميائية

قسم الباثولوجيا الاكلينيكية والكيميائية

كلية الطب

جامعة الإسكندرية

.....

أ.م.د/ دعاء إبراهيم حشاد

أستاذ مساعد الباثولوجيا الاكلينيكية والكيميائية

قسم الباثولوجيا الاكلينيكية والكيميائية

كلية الطب

جامعة الإسكندرية



جامعة الإسكندرية
كلية الطب
قسم الباثولوجيا الاكلينيكية والكيميائية

دراسة مستوى الفيبيولين اكدليل بيولوجي لمرض الربو الشعبي وعلاقته بشدة المرض

رسالة مقدمة

لقسم الباثولوجيا الاكلينيكية والكيميائية - كلية الطب - جامعة الإسكندرية
ضمن متطلبات درجة

الماجستير

فى

الباثولوجيا الاكلينيكية والكيميائية

من

منى مصطفى عبد اللطيف محمود
بكالوريوس الطب والجراحة العامه
كلية الطب، جامعة الإسكندرية

[٢٠١٤ / ١٠]