The secretome of skeletal muscle cells : A systematic review

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BACKGROUND. Proteomic studies of the secretome of skeletal muscle cells will help to understand the processes that govern the synthesis and organization of skeletal muscle. In this systematic review, we have summarized recent mass-spectrometry based proteomics discoveries of the secretome of skeletal muscle cells in response to disease, exercise or metabolic stress.

METHODS. A literature search was performed according to the PRISMA guidelines in the Medline/Ovid and Scopus electronic databases and manual searching of relevant literature was also carried out. Only papers published in English from 2000 and reporting the analysis of the secretome of isolated skeletal muscle myoblasts or of skeletal muscle explants of all species by mass spectrometry were included.

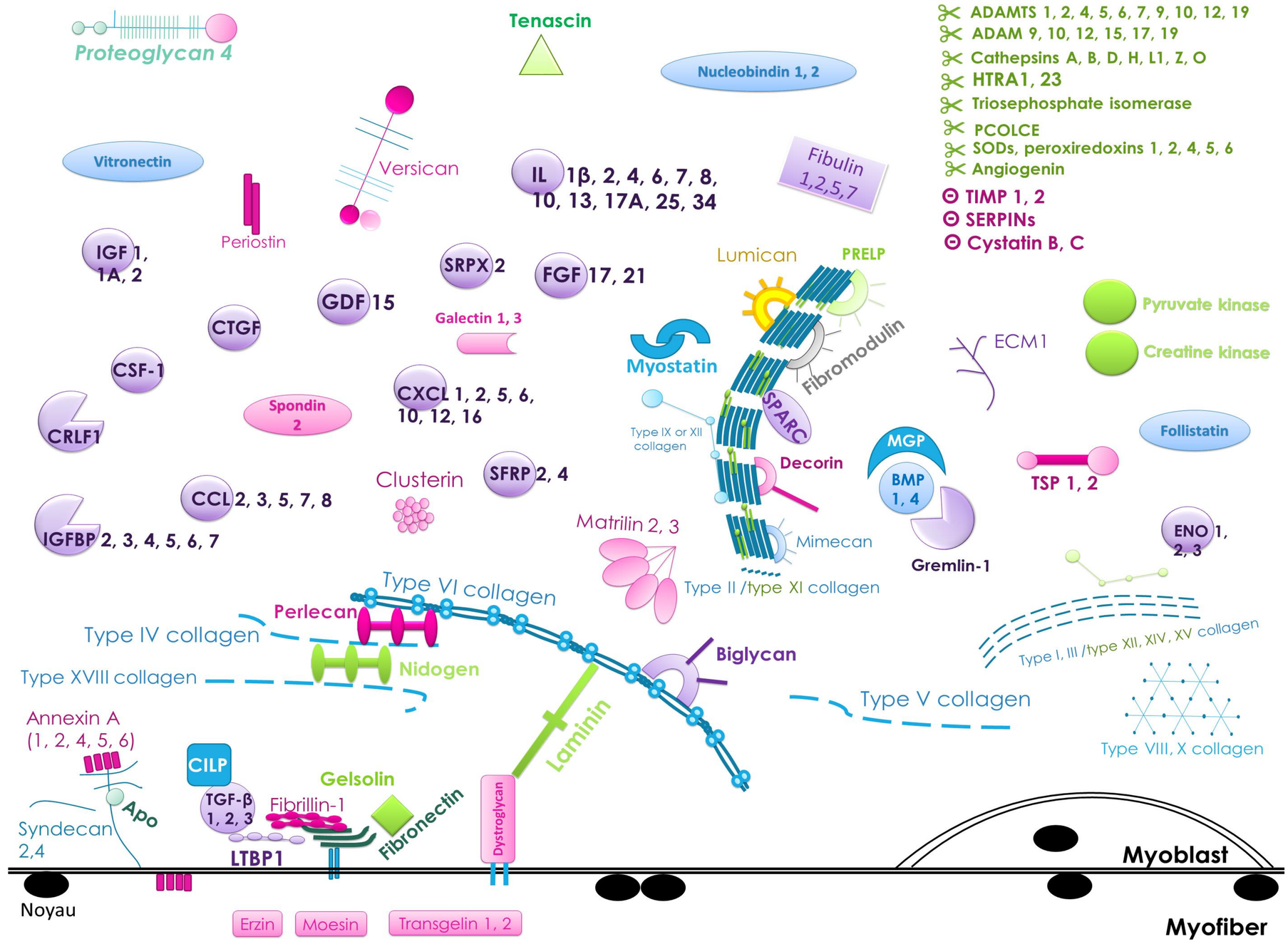


Figure 1,
Schematic representation of the skeletal muscle secretome, based on data from mass spectrometry studies.

Table 1.
Summary of recent mass spectrometry-based studies carried out on skeletal muscle cells to identify secretome components.

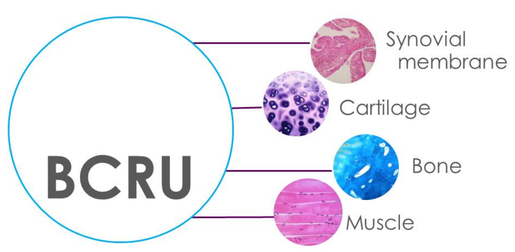
ECM Proteins	*Function*	*Secretion*	*Exercise*	*Myogenesis*	*Insulin stimulation*	*Insulin resistant cells*
Collagen I(α1, α2), II(α1), III(α1), IV(α1,α2,α3), V(α1,α2,α3), VI(α1,α2,α3), VII(α1), VIII(α1), IX(α3), XI(α1,α2), XII(α1), XIII(α1), XIV(α1), XV(α1), XVIII(α1)	Cell adhesion	Classical		I(α1), II(α1) , V(α1, α3) VI(α1), XI(α1) ↑ III(α1), XVIII(α1) ↓	VI(α1)↑ III(α1), V(α2)↓	I(α1, α2), III(α1), IV(α1, α2), V(α1,α2), VI(α1,α2), VIII(α1,α2), XI(α1), XII(α1), XV(α1)↓
Fibronectin	Cell adhesion, cell shape	Classical				↓
Fibulin 1, 2, 5, 7	Cell-cell interaction, cell migration, ECM remodeling, calcium-binding	Classical		1 (isoform C) ↓ 1 (isoform D), 2 (isoform B), 5↑		1, 2, 5 ↓
Glypican 1, 6	Developmental morphogenesis	Classical		1↑		1↓
Latent-transforming growth factor beta-binding protein 1(S, L), 2, 3, 4	Growth factor binding, membrane transport protein	Classical		3↑		1, 2, 3, 4↓
Mimecan	Induces bone formation in conjunction with TGF-β	Classical		↓		↓
Periostin	Cell adhesion, attachment and spreading	Classical		↑		↓
Secreted protein acidic and rich in cysteine (SPARC)	Regulates cell growth, binds calcium and copper	Classical				↓
Cytokines and growth factors	*Function*	*Secretion*	*Exercise*	*Myogenesis*	*Insulin stimulation*	*Insulin resistant cells*
Anamorsin (Ciapin 1)	Apoptosis	Non-classical		↑		
Bone morphogenetic protein 1, 4	Growth factor, cell differentiation	Classical			1 ↓	1 ↓
C-C motif chemokine 2, 3, 5, 7, 8, 9	Immunoregulatory and inflammatory processes	Classical		2, 7, 8↑		2↑ 9↓
C-X-C motif chemokine (CXCL) 1, 2, 5, 6, 10, 12, 16	Cytokine	Classical				1, 5↑
Follistatin-related protein 1, 3	Modulate action of some growth factors	Classical		1 ↓, 3 ↑	1↓	1↓
Granulins	Cytokine, role in inflammation and tissue remodeling	Classical				↓
Growth/differentiation factor 8 (myostatin), 11, 15	Role in development	Classical				11↓
Insulin-like growth factor 1, 1A, 2	Growth factor	Classical		1,2↑	2↓	1↓
Insulin-like growth factor binding protein(IGFBP) 2, 3, 4, 5, 6, 7	Growth factor binding	Classical		2 ↓ 4↑	6↓	2, 4, 5, 6, 7↓
Transforming growth factor ß (1, 2, 3)	Multifunctional cytokine	Classical		1, 2, 3↑		2↓
Enzymes	Function	Secretion	Exercise	Myogenesis	Insulin stimulation	Insulin resistant cells
A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) 1, 2, 4, 5, 6, 7, 9, 10, 12, 19	Protease	Classical		1↑		1, 2, 5, 7, 12↓
Matrix metalloproteinase 2, 9, 14, 19	Regulation of cell migration, protease, breakdown of ECM	Classical			2↑	2, 9, 19↓
Protein/nucleic acid deglycase DJ-1	Chaperone, hydrolase, protease	Non-classical				↓
Enzymatic inhibitors	Function	Secretion	Exercise	Myogenesis	Insulin stimulation	Insulin resistant cells
Metalloproteinase inhibitor (TIMP) 1, 2	Protease inhibitor	Classical		1, 2↑	2↓	2↓
Serpin E1 (Plasminogen activator inhibitor 1), E2	Protease inhibitor	Classical		E1↑	E1↑	E1↑ E2↓
Cytoskeletal proteins	Function	Secretion	Exercise	Myogenesis	Insulin stimulation	Insulin resistant cells
Actin, α skeletal muscle	Cell motility		↑			
Desmin	Maintains sarcomere structure	Non-classical	↑			
Miscellaneous	Function	Secretion	Exercise	Myogenesis	Insulin stimulation	Insulin resistant cells
Semaphorin 3(A ,B, C, D, E), 4(B, C), 5A, 6(A, B), 7A	Role in development	Classical		3A, 3D, 3E, 6A ↑		3(A, B), 4B, 4C, 6A↓

RESULTS. According to the preliminary results, a total of 17 papers met the inclusion criteria for this review. Published research included comparative analysis of differentially expressed proteins between healthy and unhealthy (Duchenne muscular dystrophy and insulin-resistant cells) muscle cells and comparison of the secretome of skeletal muscle cells during myogenesis and after insulin stimulation or exercising. The proteins were separated into several categories (extracellular matrix, growth factors and cytokines, enzymes, enzymatic inhibitors, cytoskeletal and miscellaneous proteins) and their differential secretion was compared and important differences were highlighted. In total, 644 proteins were listed in this systematic review as being present in the secretome of muscle cells. Among them, 11 proteins were differentially regulated by physical exercise (all up-regulated), 130 during myogenesis (90 up- and 40 down-regulated), 27 by insulin stimulation (14 up- and 13 down-regulated) and finally 174 proteins secreted by insulin-resistant muscle cells (26 up- and 148 down-regulated).

- MMP 2,9,14, 19
- ADAMTS 1, 2, 4, 5, 6, 7, 9, 10, 12, 19
- ADAM 9, 10, 12, 15, 17, 19
- Cathepsins A, B, D, H, L1, Z, O
- HTRA1, 23
- Triosephosphate isomerase
- PCOLCE
- SODs, peroxiredoxins 1, 2, 4, 5, 6
- Angiogenin
- ⊖ TIMP 1, 2
- ⊖ SERPINs
- ⊖ Cystatin B, C

- Pyruvate kinase
- Creatine kinase
- ECM1

CONCLUSIONS. This systematic review of the secretome of skeletal muscle cells in health and diseases provides a comprehensive overview of the most regulated proteins in pathological or physiological conditions. These proteins may be therapeutic targets or biochemical markers of muscle diseases.



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