Longmate WM. Keeping a Secretome: Emerging Roles for Epithelial Integrins in Controlling a Stroma-Supportive Secretome. J Dermatol & Skin Sci. 2020;2(2):13-20

Journal of Dermatology and Skin Science

Mini Review Article

Open Access

Keeping a Secretome: Emerging Roles for Epithelial Integrins in Controlling a Stroma-Supportive Secretome

Whitney M. Longmate*

Department of Surgery, Albany Medical College, Albany, NY 12208, USA

Article Info

Article Notes
Received: July 16, 2020
Accepted: August 28, 2020

***Correspondence:**
*Dr. Whitney M. Longmate, Department of Surgery, Albany Medical College, Albany, NY 12208, USA;
Email: LongmaW@amc.edu.

Keywords
Integrins
Secretome
Stroma
Tumor microenvironment
Extracellular matrix
Wound-healing

Abstract

As transmembrane receptors that mediate physical linkage of the intracellular cytoskeleton with the extracellular matrix, integrins are poised to mediate epithelial cell response to the microenvironment. However, it is becoming increasingly appreciated that epithelial integrins take an active role in regulating their microenvironment through secreted factors, known as a secretome. During tissue remodeling, the epithelial integrin-regulated secretome may impact locally by contributing matrix components or by promoting matrix remodeling via proteases. Additionally, this regulation can extend to distinct cell compartments, whereby the epithelial-derived secretome can support stromal constituents. In this review, emerging roles for integrins on epithelial cells in regulation of the secretome will be examined, with a focus on roles for integrin α3β1 in epidermal keratinocytes. I will discuss how the integrin-regulated secretome can both impact matrix composition and mediate supportive crosstalk to stromal cells, particularly during instances of tissue remodeling including cancer progression and wound healing.

The Integrin Family of Cell Adhesion Receptors

Integrins are the major cell surface receptors for adhesion to extracellular matrix (ECM)[1]. Members of the integrin family are obligate heterodimers composed of an α and a β subunit, each with a cytoplasmic domain, a single-pass transmembrane domain and a large extracellular domain. Integrin monomers include 18 α subunits and 8 β subunits which can dimerize in limited combinations to form 24 different integrins with distinct and overlapping ligand-binding specificities. Integrins bind a variety of ECM proteins and they are often classified by their ability to recognize the tripeptide RGD (Arg, Gly, Asp) sequence present in some ligands (i.e., RGD-binding integrins versus non-RGD-binging integrins). Fibronectin, vitronectin, and tenascin, for example, contain accessible RGD motifs while collagen and laminin do not[1]. Non-RGD-binging integrins are among the most highly and constitutively expressed in skin keratinocytes, as integrins α3β1 and α6β4 are laminin receptors and integrin α2β1 is a collagen receptor[2]. The remaining epidermal integrins, including α9β1, α5β1, αvβ5, and αvβ6 are RGD-binding integrins[2].

Integrins bind to ligands via their extracellular domains, whilst simultaneously interacting with cytoskeletal proteins via their cytoplasmic domains[1]. These interactions form a physical linkage of the ECM to the cytoskeleton, which is essential for regulating cell shape, adhesion, polarization, and motility[1, 3-6]. Integrins are also known to interact directly and indirectly with a variety of signaling effectors. This function as a signaling conduit allows integrins to

act as bidirectional signal transducers[1, 3, 7, 8], capable of "outside-in" signaling (e.g., an extracellular cue such as ECM binding promotes intracellular pathway modulation) and "inside-out" signaling (e.g., a cytoplasmic interaction promotes modulation of the activation state of an integrin to alter its affinity for extracellular ligands)[1, 7, 9]. This integrin-mediated signal transduction regulates many cell functions that are critical for normal as well as pathological processes, including survival, migration, proliferation, ECM remodeling, and gene expression[1, 4, 7].

Within tissues, integrins are expressed on the surface of epithelial *and* stromal cells. Indeed, integrins are well-known to regulate many autonomous functions of both epithelial cells and stromal cells. However, this review will examine emerging roles for epithelial integrins in regulation of secreted factors into the microenvironment (i.e., the secretome). In particular, the focus will be on integrin-dependent, epithelial-derived proteins of the secretome that support distinct cells within the stroma, principally in the contexts of tumor progression and wound healing.

Regulation of the Secretome by Epithelial Integrins

While integrins were first described as cell adhesion receptors, recent studies have expanded the role of integrins to include a variety of functions, both cell-autonomous and paracrine. These so-called 'paracrine' functions of epithelial integrins are thought to occur through the regulation of secreted factors (Table 1), which can impact matrix composition/remodeling (see below) and may modulate crosstalk to distinct cell types within the stroma (see section 3.0). Mechanistically, the regulation of secreted factors by epithelial integrins may occur at the level of transcription, secretion, or via integrin-mediated cell surface recruitment as reviewed elsewhere[10]. Furthermore, it is possible that epithelial integrins mediate the exocytic process or cargo within exosomes. Indeed, integrin-dependent signaling has been demonstrated to coordinate exocytic machinery during the process of neurite sprouting in neurons[11], although it remains to be seen whether this is a general mechanism of secretome regulation by integrins in other contexts. Interestingly, integrins themselves are often found in exosome cargo, and exosome-derived integrins have been found to promote cancer progression, as reviewed elsewhere[12].

Matrix proteins, proteases, and growth factors

It is well-appreciated that alterations in matrix composition can act upstream of integrins, activating intracellular signaling pathways through ligation. However, several integrins have long been known to alter the ECM at the levels of expression and assembly. For instance, integrin α2β1 has been shown to regulate type-1 collagen gene expression[13], while integrin α1β1 inhibits collagen synthesis in the dermis[14]. Also, it has been demonstrated that fibronectin-binding integrins support fibronectin matrix assembly and fibrillogenesis[15].

Importantly, extracellular proteases also contribute to the state of the ECM by mediating matrix degradation and remodeling[16]. Matrix metalloproteases (MMPs), for example, are involved in all stages of cancer progression and wound resolution[17, 18]. Additionally, proteases allow for the release of growth factors from the cell surface or matrix reservoirs[17, 19]. The integrin-mediated regulation of proteases that impact ECM remodeling is reviewed elsewhere[10]. Examples of epithelial integrins regulating

Table 1. Examples of secreted factors regulated by epithelial integrins, and their known function in regulating matrix remodeling/composition or crosstalk to stromal cells.

Integrin	Known Cell Type(s)	Secreted factor	Class	Known Function
α9β1	Breast cancer cells	Osteopontin	Matricellular	ECM component
α6β4	Breast cancer cells	VEGF	Growth Factor	Pro-angiogenic
α5β1	Keratinocytes	MMP-9	Protease	ECM remodeling
	Keratinocytes	MMP-3	Protease	ECM remodeling
αvβ6	Squamous carcinoma cells	MMP-9	Protease	ECM remodeling
	Squamous carcinoma cells	MMP-3	Protease	ECM remodeling
	Ovarian cancer cells	uPA	Protease	ECM remodeling
α3β1	Keratinocytes, Breast cancer cells	MMP-9	Protease	Pro-angiogenic
	Keratinocytes	BMP-1	Protease	ECM remodeling
	Keratinocytes	uPA	Protease	ECM remodeling
	Keratinocytes	MRP-3	Growth Factor	Pro-angiogenic
	Keratinocytes	Fibulin-2	Matricellular	ECM component
	Transformed hair bulge keratinocytes	CCN2	Growth Factor	Enhanced colony formation, growth
	Keratinocytes, Epidermal tumor cells	CSF1	Cytokine	Immune cell homing
	Keratinocytes, Wound keratinocytes	IL-1α	Cytokine	Suppressed fibroblast differentiation
	Lung, Colonic epithelial cells	MCP-1	Cytokine	Immune cell homing

See text for expanded discussions, supporting literature, and abbreviations.

proteases include α5β1-mediated regulation of MMP-9 and MMP-3[20], and α3β1-mediated induction of MMP-9, bone morphogenetic protein-1 (BMP-1), or urokinase-type plasminogen activator (uPA) in keratinocytes[21-23]. Furthermore, integrin αvβ6 has been shown to mediate the regulation of several proteases in the cancer setting, contributing to invasive behavior. Examples include integrin αvβ6-mediated induction of MMP-9[24] and MMP-3[25] in squamous carcinoma cells, and uPA in epithelial ovarian cancer cells[26].

While protease-mediated remodeling can allow for the release of cell surface or matrix-bound growth factors, there are also instances of direct regulation of growth factors by epithelial integrins. For example, integrin αvβ6 can activate the ECM-bound pool of latent transforming growth factor β (TGFβ)[27], and integrin α6β4 has been shown to enhance vascular endothelial growth factor (VEGF) translation in breast cancer cells[28]. Additionally, keratinocyte integrin α3β1 has been shown to enhance the growth factors mitogen-regulated protein-3 (MRP-3)[29] and connective tissue growth factor (CCN2)[30], as discussed in more detail below. Overall, it seems likely that the differential regulation of growth factors and proteases by integrins during instances of tissue remodeling reflects the change in expression of the integrins themselves, or a change in the expression/availability of ligand.

Integrin α3β1 as a regulator of the secretome

Recent studies using mass spectrometry (MS)-based proteomics on conditioned medium from cultured cells have allowed for large-scale analyses of epithelial integrin α3β1-regulated secreted factors, confirming that α3β1 is an important regulator of the secretome[31, 32]. A study from the Has group profiled secreted proteins from keratinocytes of patients with inherited mutations in the ITGA3 gene, which encodes the α3 integrin subunit. These patients therefore lack integrin α3β1, resulting in a condition known as interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa (ILNEB). MS analysis revealed that ILNEB keratinocytes alter the microenvironment in part by upregulating the deposition of fibronectin-rich matrix as well as the expression of fibronectin-binding integrins[31].

Previous studies have identified integrin α3β1-dependent regulation of several genes in keratinocyte cell lines that encode matrix proteins or proteases with known roles in regulating the microenvironment, such as MMP-9, MRP-3 and fibulin-2[21, 29, 33, 34]. More recently, we utilized MS analysis to precisely identify the integrin α3β1-dependent secretome in cultured keratinocytes. Indeed, several other growth factors, ECM/matricellular proteins, or extracellular proteases with known roles in modulating the microenvironment of tumors or wounds were determined to be part of the integrin α3β1-dependent secretome, as well as cytokines interleukin 1α (IL-1α) and colony stimulating factor 1 (CSF1) (Table 1; discussed in more detail in sections 3.1 and 3.2)[32]. Furthermore, genetic ablation of epithelial integrin α3 in established skin tumors caused their rapid regression and concomitant alteration of the tumor stroma, including increased stromal cell apoptosis, indicating that epithelial integrin α3β1 is essential to maintain tumor growth and to promote a supportive secretome[32]. Moving forward, it would be informative to use MS-based proteomics to determine the extent to which other epithelial integrins regulate the secretome in normal and pathological settings, and to confirm these findings using *in vivo* models which have the benefit of a fully-intact microenvironment. Further work may include delineating which factors are secreted directly versus as exosome cargo.

The Integrin-Regulated Secretome Supports Stromal Cells During Tissue Remodeling

Within adult tissue, integrins play especially important roles during instances of tissue remodeling such as cancer progression or wound healing, where they are expressed on the surfaces of both tumor cells/wound keratinocytes and all other cell types present in their respective stroma. Indeed, integrins have critical regulatory roles autonomously for the cells on which they are expressed. However, it is evident that integrins on epithelial cells, through regulation of the secretome, can provide support to distinct cell types within the stroma, including fibroblasts, immune cells, and endothelial cells, which may be particularly critical during cutaneous wound healing and epithelial tumor progression, such as skin tumorigenesis. The following sections will discuss how, in a paracrine fashion, the secretome regulated by epithelial integrins supports the stromal cells within the context of tissue remodeling, beginning with the tumor microenvironment (section 3.1; summarized in Figure 1A), and followed by the cutaneous wound stroma (section 3.2; summarized in Fig. 1B).

Supporting cells of the tumor microenvironment

It is now accepted that transformed epithelial cells alone are not sufficient for carcinoma progression, but there is also a requirement for a permissive tumor microenvironment (TME), wherein non-tumor stromal cells can act as drivers of cancer progression [for reviews on this topic, see[35-37]]. The tumor cell-derived secretome is a major way through which transformed epithelial cells can crosstalk to stromal cells in order to bolster their support of tumorigenesis. The following subsections will review emerging roles for the integrin-regulated, tumor cell-derived secretome in support of stromal cell populations including tumor-associated fibroblasts (TAFs; section 3.1.1), tumor-associated macrophages (TAMs; section

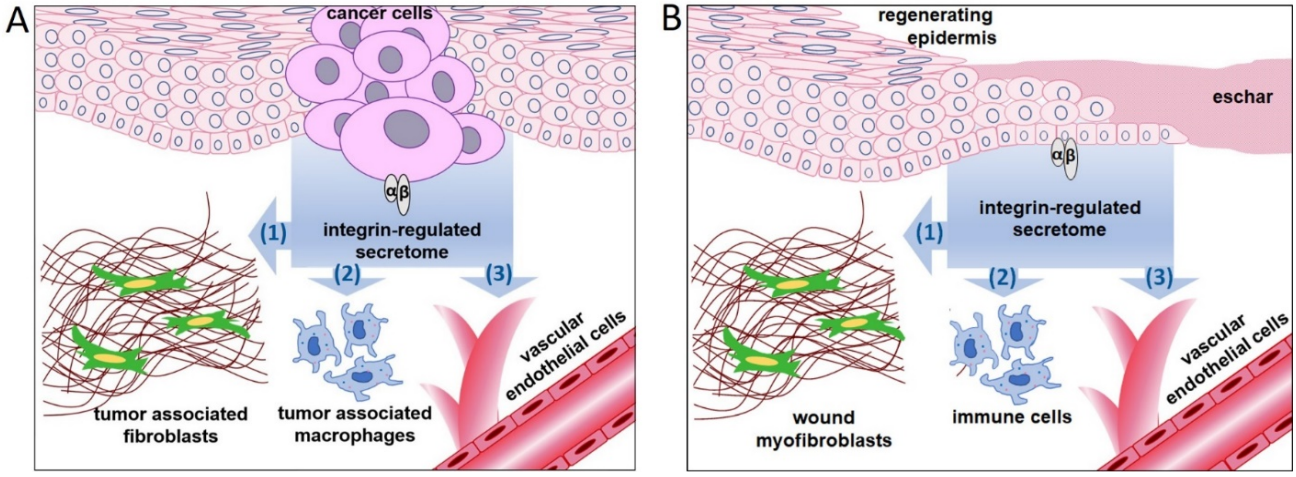

Figure 1. Epithelial integrins regulate a secretome (i.e., secreted factors) supportive of stromal cells during tissue remodeling. (A) The integrin-regulated secretome contributed by epithelial cancer cells supports stromal cells critical to the process of cancer progression. Arrows indicate support to stromal cells of the tumor microenvironment including, but not limited to, (1) tumor-associated fibroblasts, (2) tumor-associated macrophages and (3) vascular endothelial cells. (B) Similarly, the integrin-regulated secretome contributed by wound keratinocytes of the regenerating epidermis supports stromal cells critical to the process of cutaneous wound healing. Arrows indicate support to stromal cells of the cutaneous wound microenvironment including, but not limited to, (1) wound myofibroblasts, (2) immune cells and (3) vascular endothelial cells. (A, B) Secreted factors that make up the epithelial integrin-regulated secretome include growth factors, cytokines, ECM/matricellular proteins, and extracellular proteases, which may directly or indirectly provide support to cell populations within the stroma during (A) epithelial cancer progression and (B) cutaneous wound healing (see Table 1 for examples of integrin-dependent secreted factors and text for detailed discussion and supporting references).

3.1.2) and vascular endothelial cells (ECs; section 3.1.3) to promote cancer progression (Figure 1A).

Tumor-associated fibroblasts

In a recent study from the Sonnenberg group, RNA sequencing was performed on hair bulge stem cells from mice that underwent two-step chemical carcinogenesis treatment[30]. Gene expression profiling found 15 protein-coding genes that were significantly differentially expressed, 4 of which are known to be secreted proteins. The work went on to demonstrate that keratinocyte integrin α3β1 promotes the expression of growth factor CCN2[30]. In this study, CCN2 was confirmed *in vitro* to promote colony formation and 3D growth of transformed keratinocytes[30]. Presumably, integrin α3β1-dependent CCN2 expression provides a growth advantage during skin tumorigenesis. As CCN2 is a factor that is well-known to promote myofibroblast transdifferentiation[38], it will be of interest to determine whether tumor-derived, integrin α3β1-dependent CCN2 production drives tumor progression *in vivo*, at least in part through mediating TAF function.

Furthermore, tumor cell integrin α9β1 on breast cancer cells was demonstrated to promote the recruitment of TAFs and production of matricellular protein osteopontin, contributing to tumor growth and lymphatic metastasis[39]. Additionally, tumor cell integrins may in some cases interact more directly with stromal cells to aid in tumor progression. For instance, interaction of integrin α6β1 on pancreatic cancer cells with uPA receptor on fibroblasts was shown to induce a MMP-2-activating proteolytic cascade in the latter cells, aiding in tumor progression[40].

Tumor-associated macrophages

A recent study from the Cheresh group has shown that tumor cell expression of integrin αvβ3 was associated with accumulation of TAMs in several epithelial human and mouse tumors[41]. Moreover, our latest study demonstrated a role for tumor cell integrin α3β1 in supporting the TAM population in skin papillomas[32]. As previously mentioned (section 2.2), we used MS analysis to evaluate the keratinocyte secretome, and several integrin α3β1-dependent proteins in the secretome have known roles in crosstalk to TAMs, including colony stimulating factors. Consistent with this finding, TAMs were reduced in the stroma following deletion of the integrin α3 subunit from epidermal tumor cells, as was CSF1 mRNA expression within tumor cells[32].

Vascular endothelial cells

Several studies in breast cancer models have demonstrated that tumor cell integrins generate pro-angiogenic signals that crosstalk to ECs. As mentioned previously, integrin α6β4 on breast carcinoma cells has been shown to promote the expression of VEGF, enhancing angiogenesis as well as tumor cell survival[28]. Additionally, integrin α3β1 in breast cancer cells can stimulate the expression of angiogenic factors MMP-9[42]

and cyclooxygenase-2 (Cox-2)[43]. In an interesting paradox, expression of the above-mentioned integrins α6 or α3 on vascular ECs has been associated with suppression of pathological angiogenesis[44,45], demonstrating the important point that roles for specific integrins may depend on the type of cell on which the integrin is expressed, and that certain roles may not be consistent across all cell types.

Supporting Cells of the Cutaneous Wound Stroma

It is perhaps not surprising that the integrin-regulated keratinocyte secretome can offer support to cells of the stroma during cutaneous wound healing (Fig. 1B), as aspects of this tissue remodeling process have long been known to mirror tumorigenesis[46]. For instance, as discussed above, our own group has demonstrated a pro-angiogenic role for epithelial integrin α3β1 in the tumor setting (section 3.1.3). Moreover, integrin α3β1 in wound epidermis induces paracrine stimulation of angiogenesis, at least in part through secretion of the pro-angiogenic growth factor, MRP-3[29]. Additionally, another study from our group has demonstrated that integrin α9β1 in the epidermis can inhibit integrin α3β1-dependent, paracrine stimulation of wound angiogenesis in order to aid in vascular regression as wound healing resolves[47]. Interestingly, it has been shown that ablation of integrin α2β1 in α2-null mice (albeit in all cell types) enhances neovasculature in wounds, suggesting an anti-angiogenic role for this integrin[48]. Together, these findings indicate a role for epidermal integrins in mediating keratinocyte-to-EC crosstalk during wound angiogenesis, and that different integrins must function in a coordinated fashion for proper outcome.

A recent study from the Van De Water group identified a role for keratinocyte integrin α3β1 in crosstalk to dermal fibroblasts, regulating the wound myofibroblast phenotype[49]. Specifically, integrin α3β1-dependent production of cytokine IL-1α by keratinocytes stimulated Cox-2 expression/prostaglandin E_2 (PGE_2) signaling to regulate TGFβ-induced fibroblast differentiation[49]. Consistently, a separate study previously showed that epidermal expression of a β1 integrin transgene enhances IL-1α secretion[50]. As myofibroblasts in a wound are akin to TAFs[51], it is perhaps not surprising that tumor-cell associated IL-1α has been demonstrated to regulate the paracrine stimulation of TAFs in a model of pancreatic ductal adenocarcinoma[52], similar to regulation of the wound myofibroblasts phenotype by keratinocyte-derived IL-1α discussed above.

Finally, roles for epidermal integrins in paracrine signaling to immune cells during wound healing have not been extensively explored. However, treatment of epithelial cells with an antibody against integrin α3β1 has been shown to inhibit the induction of macrophage chemoattractant protein 1 (MCP-1) and other immune cell-homing interleukins[53], consistent with our findings in a skin papilloma model (section 3.1.2)[32].

Conclusion

The multilayered nature of integrin biology is more and more evident as studies continue to reveal the wide range of roles that epithelial integrins play during tissue remodeling, both in normal (i.e., wound healing) and in pathological (i.e., tumor growth/metastasis) processes. Indeed, the ability of epithelial integrins to contribute to a stromal-supportive secretome is likely gained or heightened within these contexts of tissue remodeling compared to homeostasis, and more work needs to be done to identify the precise mechanisms through which the integrin-regulated, epithelial-derived secretome supports distinct stromal cell populations. It is likely that the integrin-dependent epithelial cell secretome differs contextually between normal and pathological processes. Further work needs to be done to identify similarities and differences in this regard. Additionally, it is important to consider that stromal cells, expressing their own repertoire of integrins, are likely to participate dynamically in cellular crosstalk within the stroma, as well as to epithelial cells in a reciprocal manner[54,55].

Future Direction: Exploiting integrins as targets of therapy

It is intriguing to consider epithelial integrins as therapy targets in the treatment of cancer or chronic wounds, since the pleiotropic effect of such targeting would extend to the secretome, thereby impacting the stromal cells and microenvironment in a potentially powerful way. The general concept of targeting integrin function for therapy has been established (i.e., vedolizumab, an antibody against integrin α4β7, is used clinically to inhibit the trafficking of lymphocytes to the gut mucosa for the treatment of Crohn's disease and ulcerative colitis, both potential precursors to gastrointestinal malignancies[56,57]). With regard to the cancer clinic, success of the integrin-blocking agent Cilengitide, an RGD mimetic, was limited[58,59]. Interestingly, Cilengitide was thought to inhibit tumor angiogenesis by targeting RGD-binding integrins on ECs. However, this approach may be complicated by expression of these integrins on other cell types within the TME. For instance, a study in a model of glioblastoma multiforme indicated that treatment with an RGD peptide also inhibits integrin αvβ3 on TAMs, resulting in their inhibited recruitment[60]. Thus, moving forward it is critically important to consider the potential effects of integrin-targeting agents on the distinct cell types within the entire milieu, including the paracrine crosstalk that occurs between them.

Additionally, RGD mimetics only block integrins that bind RGD-containing ligands and fail to inhibit other potentially important integrins that bind non-RGD ligands,

such as laminins. As discussed throughout the review, abundant preclinical evidence contributed by our group and others have indicated an important role for laminin binding integrins, like α3β1, in mediating critical paracrine functions in wound healing and tumor progression. Indeed, targeting epithelial integrins that perform cell-autonomous functions *and* contribute a stoma-supportive secretome may be especially impactful in the treatment of cancer or aberrant wound healing, although this hypothesis remains to be tested clinically.

Abbreviations

ECM = extracellular matrix

RGD = arginine, glycine, aspartic acid tripeptide sequence

MMP = matrix metalloprotease

BMP-1 = bone morphogenetic protein-1

uPA = urokinase-type plasminogen activator

TGFβ = transforming growth factor β

VEGF = vascular endothelial growth factor

MRP-3 = mitogen-regulated protein-3

CCN2 = connective tissue growth factor

MS = mass spectrometry

ILNEB = interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa

IL-1α = interleukin 1α

CSF1 = colony stimulating factor 1

TME = tumor microenvironment

TAF = tumor-associated fibroblast

TAM = tumor-associated macrophage

EC = endothelial cell

Cox-2 = cyclooxygenase-2

PGE_2 = prostaglandin E_2

MCP-1 = macrophage chemoattractant protein 1

Conflict of Interest Statement

The author declares no conflicts of interest.

Acknowledgements

The author is an Assistant Professor at Albany Medical College. Dr. Longmate's work is supported by NIH grants from NCI to C. M. DiPersio (R01CA129637) and from NIAMS to L. Van De Water and C. M. DiPersio (R01AR063778). The author is grateful to Dr. DiPersio for critical reading of the manuscript, and for important insight provided by colleagues at Albany Medical College. Many thanks to the researchers whose valuable contributions to the field could not be cited owing to space constraints.

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