Review Article

Alpha-Fetoprotein-derived Segments as Integrin Peptidomimetics for Potential Cancer Cell Targeting and Therapy: A Review and Commentary

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Abstract

Integrins constitute a group of dimeric polypeptide chains that function as natural agonists of cell surface receptor-dependent cell activities. The integrins themselves comprise a superfamily of hetero-dimeric (alpha and beta chains) transmembrane cell surface receptors whose functions include cell adhesion, growth, migration, and angiogenesis. In comparison, the integrin-like peptides (ILP) comprise groups of protein derived segments, namely, short peptides derived from naturally occurring proteins from intrinsic subdomain fragments or short motifs present on larger proteins or enzymes. Certain ILPs can bind or compete for amino acid sequence sites located on integrin beta-1 and beta-3 chains of heterocomplex receptors. Binding at major sites or allosteric minor sites can inhibit or block cell migration, angiogenesis, metastasis, and platelet aggregation. Recently, a small integrin-like peptide derived from naturally occurring alpha-fetoprotein (AFP), similar to a disintegrin, has been reported to inhibit growth and adhesion functions associated with integrin-dependent cell activities. The present report describes an example of an AFP integrin-like peptide and lends credence to support its proposed use in adjunct cancer therapies.

Introduction

A) General

Integrins comprise a superfamily of hetero-dimeric (alpha and beta chain) transmembrane receptors present on multiple cell types including tumor cells [1]. The numerous functions that integrins mediate include cell-to-cell and cell-to-extracellular matrix (ECM) adhesion, cell growth, migration and spreading, metastases, angiogenesis, cytoskeletal-induced locomotion, and platelet aggregation [2,3]. Naturally occurring antagonists of the integrin receptor are termed disintegrins (DTs) which block or inhibit integrin cell functions [4,5]. While the integrins comprise 23 or more different alpha and beta chain combinations, the DTs constitute families of only two types of molecules [6,7]. Integrin-like peptides function in a similar manner to the disintegrins which are derived from metalloproteinases. It has been demonstrated in previous publications, that small peptides, derived from naturally occurring serum-related proteins, can mimic portions of the integrin polypeptide chains [8,9]. Such an action could interfere, compete, interrupt, or block signal transduction in the integrin receptors. Thus, small integrin-like peptides (ILP) are being proposed that can inhibit or compete with adhesion functions associated with metastasis, cell migration, cell-to-cell contact, and cell spreading. Since integrins show promise as potential molecular targets for cancer, the integrin-like peptides could possibly serve as formidable anticancer therapeutic agents for cell migration and metastatic targets.

B) Objectives and Aims

The objectives in the present report comprise several in number. First, the integrin biologic functions and activities are described. Second, the types and family members of the heterodimeric cell-adhesion integrin molecules are discussed on an overview fashion. Third, naturally occurring peptides derived from "mother" proteins will be addressed as integrin-like peptidomimetics. Finally, a prime example of an integrin-like non-toxic peptide mimetic is described which displays activities such as inhibition of platelet aggregation, suppression of cell-to-matrix adhesion, cell migration/spreading, and cell-to-cell contact activities.

C) The Integrin Cell Surface Receptors

The integrin superfamily of cell surface receptors consists of hetero-dimeric (alpha and beta chains) transmembrane glycoproteins that mediate cell-to-extracellular matrix (ECM), adhesion, and cell-to-cell contact interactions [10,11]. The integrins are integral cell surface single pass-transmembrane receptors consisting of two paired chains of non-covalently linked alpha and beta polypeptide chains. Both integrins and the ECM molecules play important roles in ontogenetic development, maintenance of adult cell physiology, tissue repair, hyperplastic growth, hemostasis, and tumor oncogenesis [12-14]. The dimeric hetero-complexed integrins further serve as cell membrane receptors capable of forming focal adhesion contact linkages to the cytoskeleton; such links are located on the inner

layer of cell membranes. Integrins can further bind to multiple ECM ligand proteins such as: fibronectin, laminin, vitronectin, collagen, thrombospondin, entactin, fibrinogen, talin, the intracellular adhesion molecule (ICAM), and the vascular cell adhesion molecular (VCAM) [15-17]. Studies have further linked integrin signaling to cytoplasmic cytoskeletal filament-associated proteins such as vinculin, talin, α-actinin, paxillin, and divalent cation-dependent proteins such as calreticulin [18,19]. The integrins further play a major role in cell adhesion activities in the immune system [20-22].

Each integrin subfamily is characterized by a combination of a small number of β-chains associated with a large number of α-chains. To date, eight different β-chains and 14 different α-chains have been described, accounting for at least 20 combinatorial variations of the two heterodimeric receptors [9]. Both the α- and β- subunits are integral membrane glycoproteins containing variable long-lengths of extracellular domain chains linked to short intracellular chains [10]. The α-chains exhibit four repeat amino acid segments which bind calcium (Ca^{++}) and other divalent cations such as Mg^{++} and Mn^{++} [18,19]. The β-subunits display at least four cysteine-rich repeats in linear juxtaposition; these repeats stabilize the chains of the extracellular amino terminal loops [9,20]. In overview, both chains contribute to the formation of an interface which forms the ligand binding pocket. In contrast to their extracellular domains, the intracellular domains of both the α- and β- chain constitute short amino acid segments capable of binding to cytoskeletal-associated proteins that can link the integrins to G-proteins, actin, and calreticulin, a Ca^{++} influx regulator involved in cell migration [12,13].

D) The Integrins-ECM Interaction and Signal Transduction

Studies of ECM interaction with cells via their integrin receptors have shown that integrins function as bidirectional transducers of extra- and intracellular signals. The two-way (bidirectional) signaling can occur from "outside-to-inside" and from "inside-to-outside" the cell [21,22]. The regulation of cell proliferation, differentiation, survival, and immediate gene expression is influenced by integrin mediation of cell interaction associated with the ECM. The disruption of epithelial and endothelial cell interactions with the ECM can induce programmed cell death, while fibroblast-integrin adhesion can affect cell cycle activities by influencing cyclin-A and D expressions [23,24]. In addition to signal transduction with the actin cytoskeleton, the cytoplasmic domains of the integrins interact in a cascade fashion with protein kinases, calcium-binding proteins, focal adhesion kinases, Na^+/H^+ antiporters, tyrosine MAP kinases, and transcription nuclear factors such as NFkB and AP1 [25-27].

The integrins must be activated in order to undergo adhesion and binding to the ECM. Activation of integrins occurs through local soluble mediators such as hormones, cytokines, growth factors, or by interfaces with the ECM. Thus, cell activation is known to involve adhesion to clusters of stimulated integrins which culminate in signals triggered by local events in the cellular environment, such as thrombogenic agonists, antigen stimulation/processing, and T-cell activities [20,28,29]. In contrast, integrin activation can be blocked by ILP and/or disintegrins to disallow cell adhesion and ECM binding at inopportune times and locations. Untimely adhesions can lead to

unwanted thrombosis and inflammation, while already adhered cells may need to detach in order to undergo mitosis and cell migration [21,27]. As previously reported, both the disintegrins and ILPs can effectively contribute to blocking, inhibiting, reducing, and dysregulation of integrin function.

Protein-Encrypted Peptides; Growth Inhibitory Peptide (GIP)

The inclusion of a class of growth regulatory factors, extracellular ligands, and angiogenic peptide fragments encrypted within a polypeptide chain of a full-length protein is known but is not widely recognized [30]. However, some of the most potent growth inhibitors are derived from short peptide fragments (segments) already existent in naturally occurring mammalian full length proteins. Such intrinsic segments themselves can affect cell growth and proliferation in an opposite function from that of the "mother" protein [31,32]. This less recognized concept of a protein-derived body reserve containing peptide growth inhibitor fragments is becoming a recurring theme in the field of growth regulation, intracellular signaling, and crosstalk among and between signal transduction pathways. Classical examples of such occult (cryptic) peptides derived from proteins include the following examples,

1) Tenacin binding peptide derived from fibronectin;

2) Angiostatin from plasmin;

3) Endostatin from type XVIII collagen;

4) Vasostatin from calreticulin; and

5) Constatin from type IV collagen.

Such cryptic hidden peptide sites can be exposed following a conformational change on a protein or can be revealed following proteolytic cleavage from a larger protein [33,34]. Such peptides can also be chemically synthesized as single fragments of 20-45 amino acids. A well-published example of a peptide site revealed following a conformational transition change on a full-length protein is an encrypted "growth inhibitory" site on the alpha-fetoprotein (AFP) molecule [35]. The AFP protein is normally a growth promoting molecule, but can be temporarily converted to a growth inhibitory molecule.

The encrypted peptide segment on AFP, termed the growth inhibitory peptide (GIP), is a 34 amino acid segment concealed in a hydrophobic cleft of the tertiary folded AFP molecule. The GIP-34 site is revealed following protein unfolding in chemical environments consisting of high ligand concentrations of estrogens, fatty acids, and growth factors [32,35]. The exposed transitory GIP site converts the usually growth-enhancing AFP molecule into a temporary growth-inhibiting molecule. This conversion occurs via protein unfolding via a conformational change resulting in a denatured intermediate state that reflects a molten globular form (MGF) of the AFP protein [36]. Since the MGF of AFP is a transitory intermediate form, AFP can refold back to its native tertiary fold following removal of excess ligands (agents) in the microenvironment [37]. Because the AFP-MGF form is unstable, the GIP-34 amino acid segment alone has been

synthesized, purified, and characterized as a free and distinct 34-mer synthetic peptide segment [33-35]. Thus, 34-mer GIP fragment can inhibit growth factor, fatty acid, and estrogen-induced growth in a concentration-dependent manner in addition to blocking metastatic and cell migration-associated activities.

GIP-34 Physicochemical Properties

GIP-34 has been synthesized by classical F-MOC (9-fluronylemethoxy-carbonxyl)- protected solid phase synthesis, as previously described [38]. Following peptide syntheses, the lyophilized peptide was purified by reverse-phase high-performance liquid chromatography (HPLC), producing a peptide whose major peak displayed a molecular mass of 3573 (34-mer) as determined by electrospray ionization mass spectroscopy. Cyclization of GIP-34-mer can be accomplished by addition of reducing agents to form a disulfide bridge construct at the time of the linear peptide synthesis. Circular dichroism (CD) analyzed in the UV wavelength for GIP-34 displayed a negative maximum at approximately 201nm. Computer modeling and analysis of the GIP-34 CD spectrum revealed a secondary structure comprising 45% β-sheets and turns, 45% random coli (disordered), and 10% α-helix structure [35].

Amino Acid Sequence Matches

The GIP-34 AA sequence was subjected to a FASTA search in the Genbank (GCG Wisconsin Program) database, as described [32,33,35]. The GCG search found identity/similarity sequence matches to receptor-binding proteins, such as the fibroblast growth factor (FGF) receptor, insulin growth factor II receptor (IGFIIR), transforming growth factor-β (TGF-β), and the dopamine (DOPA) receptor [39]. Other Genbank matches revealed transcription-associated proteins, including homeodomain proteins and FTZ-F1 (the AFP transcription factor), which have been previously reported [40-42]. These AA matches provide evidence that the GIP fragments contain short recognition

cassettes for multiple and varied receptor involvement and interactions. Matches with cell-adhesion related proteins were also found; these included collagen XIII, collagen IV, laminin, fibrinogen, and fibronectin [41,42], (Table 1). Finally, identities/similarities were identified with transcription-associated factors, such as Hox, c-myc, forkhead, and Pax. GIP-34 matches were further found with integrin-associated proteins, the ECM proteins, cell mitosis proteins, and other adhesion proteins (Tables 1 and 3). Further identities were found with the integrin α/β chain proteins such as $\alpha_{11b}\beta_3$, $\alpha_1\beta_3$, and $\alpha_v\beta_1$. Such integrins can serve as receptors for ECM proteins and are known to participate in cell-to-cell activities such as cell adhesion and migration (spreading) activities. Finally, matches were also made with ECM-associated proteins, such as the Von-Willebrand Factor, VLA-1, and PG-IIIa proteins, which are involved in cell adhesion, aggregation, and the action of metalloproteinases (i.e., the Adams Family) (Table 3). Thus, GIP-34 shows an identity/similarity matches to integrins, basement membrane proteins, and ECM proteins, all of which are involved in cell-to-cell and cell-to-ECM interactions. A comparison of the properties and traits of integrins versus GIP are displayed on Table 2.

Cell Adhesion Assays with the AFP-derived Peptide

AFP-derived GIP has been subjected to cell adhesion studies involving many of the ECM ligand proteins known in the literature and discussed herein [32,33]. Various ECM proteins were coated on microtiter plates to serve as solid attachment surfaces for two breast cancer cell types: the human MCF-7 and the murine mammary 6WI-1 cell culture lines (Table 1). The adhesion of MCF-1 and 6WI-1 tumor cells either in the presence of AFP peptide or in peptide-free medium were assayed on ECM-coated microtiter plates with soluble GIP used as a competitive inhibitor. GIP-34 was capable of inhibiting cell adhesion of the ECM ligand proteins in both tumor cell lines which spanned inhibition of 30-50%. Inhibition of the mouse and human tumor cell adhesion was roughly equivalent on microtiter plates coated

Table 1: Growth Inhibitory Peptide (GIP) Amino Acid Sequences * were matched in the Genbank to Various Integrin Alpha/Beta Chain Complexes and the Compared to their Extracellular Matrix (ECM) Adhesion Inhibition by GIP. Note that many of the Integrins are expressed on a variety of tumor cells.

Integrin Subunits	*GIP Amino Acid Sequence	AA Identity%		ECM Binding Ligand	Tumor to ECM Adhesion% Inhibition	Cell/Tissue and Tumor Distribution
		α	β			
$\alpha_V\beta_{3A}$	LSEDKLLACGEGAAD, SEDKLLACG	100(9)	47(15)	FIB, VTN, FBN, TSP	40-50	Melanomas and angiogenic cell
$\alpha_M\beta_2$ (Mac)	SEDKLLACG, LACGEGAADI	66.7(9)	43(10)	FBN, C3bi, I CAM	50	Immune, Inflammatory cells
$\alpha_V\beta_6$	SEDKLLA	100(7)	50(12)	FBN	50	Carcinoma cells virus associated fusion
$\alpha_6\beta_1$	GEGAADIII	78(9)	75(8)	LAM-1	10-45	NSCL carcinoma
$\alpha_V\beta_1$	SEDKLLA-CGEG	100(7)	75(4)	VTN, FBN	40-50	Analytic tumors
$\alpha_1\beta_1$	CGEGAADIIIGH	43(12)	75(8)	LAM COLL	10-45	Breast carcinoma
$\alpha_1\beta_2$ (LFA-1)	CGEGAADIIIG	80(11)	43(10)	FBN, C3i	50	Myeloid cells, Leucocytes
$\alpha_4\beta_7$	GEGAADIII MTPVNPGV	78(9)	56(9)	FBN, VCAM MADCAM	50	Endothelial mucosal cells
$\alpha_3\beta_1$	DKLLACGEGAADIIICGEG	43(14)	75(4)	FBN, COLL LAM	30-55	Many tumor cells
$\alpha_V\beta_8$	IRHEMTPVNPG	67(12)	50(12)	Not reported	not done	Reproductive tissues
$\alpha_V\beta_5$	CGEGAADIIIGHLCIRHEM-TPBNPGVGQ	67(12)	80(25)	VTN, FBN	45-50	Epithelium carcinoma cells
$\alpha_6\beta_4$	IRHEMTPVPVNPGV	78(8)	50(12)	LAM-1, LAM-2	10-45	Keratinocyte malignancy
$\alpha_2\beta_1$	IIGHLCIRHE MTPVNPGV	53(17)	75(8)	COLL, LAM	10-55	Epithelium, endothelium leucocytes

Table 2: Comparison of properties shared by integrin-related components and the AFP-derived Growth Inhibitory Peptide (GIP).

Activity and/or Property	Integrin-related Properties	GIP Peptide Related Properties
Cell Toxicity	Non-toxic	Non-toxic (cytostatic)
Working Range	Nanogram concentrations	Nanogram concentrations
Platelet Physiology	Activate platelets for aggregation	Inhibits platelet aggregation
Cell Type Localization	Most body cells, platelets, uterus, breast cancer cells	Platelet, uterus, breast cancer cells
Ligand Binding	Extra-cellular matrix proteins. (fibromectin, virtomectin, etc.)	Extra-cellular matrix protein interaction
Protein Homology	C3b complement & C2 component, Factor B Von Willebrand factor, Mac-1	Von Willebrand factor, fibronectin precursor
Aggregation	Form dimers, receptor aggregation (clustering)	Forms dimers, trimers & oligomers
Adhesion	Cell-to-cell, cell-to-ECM	Cell-to-cell &cell-to ECM
Cellular Internalization	Soluble ligand/integrin internalization	Apparent cellular internalization
Secondary Structure	Beta sheets & turns in extracellular subunits	Mainly beta sheets & turns in soluble peptide
Distinctive Amino Acid Presence	Cysteine relative to aspartic acid spacing	Display 2 cysteine with aspartic acid spacing
Ligand Binding Region	N-terminal half of α and β subunits	Short sequence homologies to α chain component
Cellular Localization	Cell surface transmembrane peptides extending into cytoplasm	Fluorescence localization at cell surface and intercytoplasmic sites
Ligand Recognition Specificity	Controlled by the α subunit	AFP-peptide more homologous to α chain subunit
Influence of Estradial	Estradiol suppresses integrin ligand regulation of α_2 subunit	Peptide suppresses estrogen-sensitive growth
Integrin α (I-domain) Homology	Similar to collagen binding domain of Von Willebrand Factor	Similar to collagen binding domain of Von Willebrand Factor

Table 3: Integrin-associated Protein (IAP) amino acid sequences (left column) are matched to Growth Inhibitory Peptide (GIP) amino acid sequence stretches (middle column). Numbers to the left of the single letter amino acid code of GIP signify the amino acid number located on the full-length alpha-fetoprotein polypeptide.

I. Mitosis-associated Proteins

Protein (IAP) Name	Growth Inhibitory Peptide Amino Acid Sequences	Biological Activity or Function Affected by GIP
Contactin-associated Proteins	481 IGHLCIRH	Cell adhesion
Neurotropic Tyrosine Kinase Receptor-3	461 CCQLSEDK	Cell migration and invasion
Matrix metalloproteinase-13	497 ADIIIGHL 485 CIRHEMTP	Collagenases (ADAM-13)
ADAM-22, Integrin $\alpha_2\beta_1$	481 IGHLCIRH	Cell-to-Cell contact, cell migration, cell adhesion
Integrin α_6 (IGAG) linked to Beta chain (VLA-6)	485 CIRHEMTP	Cell-to-cell contact, cell migration, cell adhesion

II. Extracellular Matrix Proteins

Protein Name	Alpha-fetoprotein Growth Inhibitory Peptide Sequence Matches	Biological Analysis or Function Affected by GIP
Receptor for Peptin-54 (G-coupled receptor)	481 IGHCIRH	G-coupled receptor for signal transduction
Fibroblast Growth Factor receptor-4	497 ADIIIGHL	Regulates growth and proliferation, blood vessel angiogenesis
Ephrin Receptor 2B	481 IGHCIRH	Regulates bidirectional signaling related to tumor growth/metastasis
Met Oncogene Hepatocyte Factor Receptor (C-Met)	481 IGHCIRH	Tyrosine Kinase Receptor, axon guidance, cell segmentation, angiogeneis

III. Growth Factor Associated Proteins

Protein Name	Alpha-fetoprotein Growth Inhibitory Peptide Sequence Matches	Biological Activity or Function Affected by GIP
Vascular Endothelial Growth Factor	477 ADIIIGHL	Stimulates vascular permeability
P53 Protein Cell Tumor Antigen	477 ADIIIGHL	Prevents cancer growth, a tumor suppressor
Tyrosine Phosphate Non-Receptor-7	477 ADIIIGHL	Tyrosine kinase related
Cell Growth Regulator	477 ADIIIGHL	Enzyme that regulates cell growth/proliferation
NF-KB Signal Factor	477 ADIIIGHL	Signal transduction factor regulating phosphorylation

with either collagen IV, fibrinogen, fibronectin, or thrombospondin and slightly less for laminin, collagen-I, and vitronectin in the two cell types. Human MCF-7 breast cancer cells, in the presence of GIP-34, further displayed substantial inhibition of vitronectin-induced adhesion, while mouse 6WI-1 cells demonstrated similar peptide inhibition of laminin coated adhesion [34,35]. Overall, the AFP peptide was found to competitively inhibit both MCF-7 and 6WI-1 cell-to-ligand attachments which ranged from 40-60%. Finally, it was found that rabbit anti-GIP antibodies could also block the ligand adhesion inhibition effects, similar to the GIP fragment itself.

Inhibition of Cell Migration Spreading and Metastasis by GIP

Cell adhesion receptors and their ligands (i.e., ECM proteins), provide the traction and stimulus for the migration and spreading of tumor cells [28,41,43] (Table 3). In general, most cells including tumor cells, use adhesion molecules to execute cell migration, which is termed cell spreading in cell culture. The integrins initiate migration of adherent cells such as fibroblasts, epithelial cells, and tumor cells upon the ECM surfaces. Cell migration requires multivalent binding of integrins to matrix bound ligands such as collagen, laminin, and fibronectin [15,16,27]. Analysis of coverslip cell migration assays revealed that the GIP inhibited more than 60% of the MCF-7 cancer cells' spreading and migration on the surface of coverslips [34,35]. The MCF-7 cells that exhibited migration displayed distorted morphology such as star-shaped configurations, cytoplasmic spiking, surface spiny spheres, membrane ruffling, and extensions of cytoplasmic processes, all coupled with low cell viability. In cancer movements, it is noteworthy that cell migration and spreading constitute the initial steps in the metastatic process; furthermore, GIP has been reported to inhibit metastases *in vivo* in animal models [32,33,36].

Tumor Cell Adhesion to the Extracellular Matrix

Tumor cell adhesion to the ECM is an essential step in the tumor cell migration and metastases process, providing a means for migrating cancer cells to transiently attach to the connective tissue substratum while spreading [41]. A tumor cell adhesion ECM assay was utilized to assess whether the AFP derived GIP-34 could influence or modify tumor cell attachment to a protein substratum or matrix [38]. Various ECM proteins were absorbed to the walls of microtiter plates and screen for their ability to serve as a substratum for enhanced tumor cell adhesion, as compared to non-ECM protein-coated microtiter plates [32,33]. Using 6WI-1 mouse mammary tumor cells, substantial cell attachment was observed with vitronectin, laminin, fibrinogen, fibronectin, and collagens I and IV after 2.0 hours of incubation at 37°C. GIP-34 was then tested for its ability to compete with tumor cell adhesion to the ECM substratum. GIP-34 was capable of inhibiting many of the ECM proteins spanning from 40% to 60% [32,33,43,45].

Cross-talk signaling between the ECM and the tumor cell membrane is known to occur. Overall, GIP-34 was capable of inhibiting both the attachment of tumor cells to the substratum and the subsequent growth of remaining tumor cells on that particular ECM substratum. Based on the ECM adhesion data, tables of integrin-association inhibition with GIP fragments are presently presented, which exemplify integrin α- and β- chain to ECM interactions (Tables 1 and 3, and above references).

Additional Activities of Integrin-like Peptides (GIP)

It is germane to this discourse that additional insight and perspectives be addressed regarding the use of integrin-like peptides (ILPs) in cancer therapies. For example, short ILPs can be structurally altered and modified to produce more potent forms of such inhibitors. Recombinant and chimeric forms of ILPs and AFP subdomains have been synthesized for use in studies of integrin inhibition/

competition of tumor growth, proliferation, adhesion, migration, and angiogenesis of cancers such as liver, breast, lung, melanoma, and others [32,33,46,47]. In addition, ILPs such as GIP have been reported to induce apoptosis in radio-sensitized cultured lymphocytes [33]. Moreover, it has been reported that ADAM-22, a disintegrin-like metalloproteinase, is an active participant in the development of breast cancer resistance during endocrine hormone therapy in women [48-50]. With regard to this report, GIP administered to cultured MCF-7 human breast cancer cells was shown to down-regulate the expression of ADAM-22 by 30-fold as determined by a global RNA microarray analysis [44]. These data would suggest that GIP treatment not only could down-regulate the expression of ADAM-22, but could also block the development of hormone-resistance in breast cancer. In a further study, GIP was reported to further suppress the growth of MCF-7 human breast cancer cells *in vitro* and *in vivo* [51].

Concluding Remarks

It now seems plausible that interference with integrin signaling could provide a rational basis for the development of aids in the therapeutic treatments for cancer growth, progression, and metastases. Anti-integrin antibodies, disintegrins and ILPs all predict promise in future anti-cancer therapy studies. Integrin interruption of the adhesive interaction of tumor-to-tumor cells and platelets to tumor cells should be capable of serving to arrest or impede cancer cell migration and metastasis [41,45]. The observations that different integrins are expressed on various tumor types and are differentially expressed during tumor transformation, progression, and metastasis suggest that integrins might also serve as prognostic biomarkers [10]. Integrin-like mimetic agents that block or interfere with the initial attachment of integrins to ECM components, can also blunt signal transduction events thus inhibiting proliferation, cell migration/invasion, and platelet aggregation. Such agents could constitute a formidable armamentarium of non-toxic anti-cancer agents. Such anti-adhesive agents might further find potential application in the treatment of the five major classes of human disorders, namely; neoplasia, inflammation, trauma, wound healing, and infection.

Since integrin dysfunction frequently results in cancer pathology, integrins represent an appealing array of targets for anti-tumor therapy. Because ILPs specifically bind or compete with integrins, they serve to interfere with and/or block functions such as cancer cell growth and proliferation, and the migration activities described herein. All such activities described above suggest that integrins might have the potential to serve as prominent candidates for molecular cancer targets and as such, make integrin-like peptides promising non-toxic therapeutic adjunct agents to treat cancers.

Acknowledgment

Abbreviations

Coll: Collagen; FBG: Fibrinogen; FIB: Fibrin; LAM: Laminin; TSP: Thrombospondin; VTN: Vitronectin; VWF: Von Willebrand

Factor; *: Amino Acid Single Letter Code; C3i: Complement Factor-3 inhibited. Integrin data obtained from References 34 and 35.

ECM: Extracellular Matrix; C: Complement Protein; C3b: Complement Subunit; AFP: Alpha-Fetoprotein; GIP: Growth Inhibitory Peptide-34.

Disclosures

Financial

None; no U.S. federal grants were used in the preparation of this paper.

Interest

The author declares that there are no known conflicts of interest in the preparation of this manuscript.

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