A

Anti-integrins

Shaker A. Mousa[1] and Paul J. Davis[2]
[1]The Pharmaceutical Research Institute, Albany College of Pharmacy and Health Sciences, Albany, NY, USA
[2]The Pharmaceutical Research Institute, Albany College of Pharmacy and Health Sciences, and Albany Medical College, Albany, NY, USA

Definition of Integrin

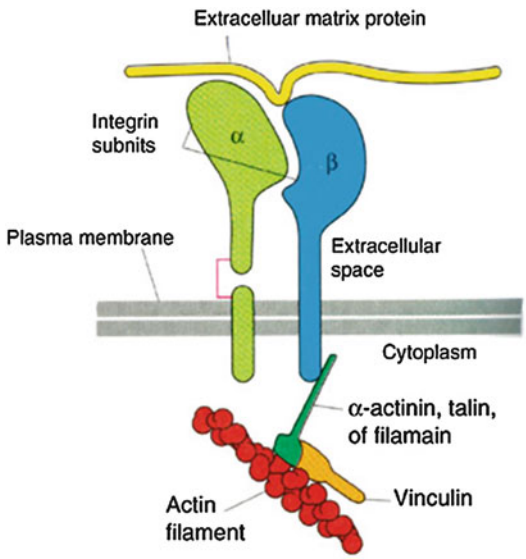
Integrins are heterodimeric proteins of the plasma membrane that are critical to cell-cell interactions and to interactions of the cell with extracellular matrix (ECM) proteins. These physical interactions are critical to individual cell migration paths and multicellular tissue structure. There are 24 or more integrins, each composed of one of 18 monomeric alpha subunits and one of 8 beta subunits (Seguin et al. 2015). Each heterodimeric integrin binds to at least one ECM protein. Such interactions result in a conformational change in the integrin ("activation") (Arnout 2002; Arnaout et al. 2007; Ginsberg 2014). The physical changes in the extracellular integrin component generate intracellular signals via induced changes in the cytoplasmic components ("feet") of the integrins (Fig. 1). These cytoplasmic extensions in cancer cells of the integrin change their physical relationships with components of signal transduction pathways to regulate downstream functions such as the cell cycle and mechanisms of apoptosis (Davis et al. 2016). Specific integrins may act on blood vessel cells to modulate angiogenesis (Eliceiri and Cheresh 1998).

Alterations in the conformation of the large extracellular component of the integrin expose (or obscure) receptor sites for other large molecule ligands in the extracellular space or, as is now known, of extracellular small molecule ligands. As discussed below, such ligands include thyroid hormone analogues (Bergh et al. 2005; Davis et al. 2016) or steroid or steroid-like molecules (Lin et al. 2009).

Anti-integrin

The concept that the substantial extracellular domain of integrins may be manipulated by naturally occurring factors such as ECM proteins – for example, fibronectin, vitronectin, and von Willebrand factor – prompted investigators to search for pharmacologic ligands that might alter normal cell function or the functions of cancer and endothelial cells. Such protein ligands are designated **anti-integrins**. Protein ligands of integrins may contain similar short amino acid sequences, for example, Arg-Gly-Asp (RGD), and such short peptides can serve as anti-integrins (Danhier et al. 2012; Reardon et al. 2008). Another category of anti-integrins is antibodies developed to bind to specific regions of an integrin to modify its function, for example, interactions with the adjacent plasma membrane

S. Offermanns, W. Rosenthal (eds.), *Encyclopedia of Molecular Pharmacology*,
https://doi.org/10.1007/978-3-030-21573-6_81-1



Anti-integrins, Fig. 1 Diagrammatic representation of integrin inside-out signaling and integrin activation, which require conformational switch from bent-closed or extended-closed to extended-open confirmation

proteins (Byron et al. 2009). The interactions targeted by anti-integrins may be between integrins and extracellular matrix proteins or between integrins and cell surface proteins of adjacent cells (cell-cell interactions). Finally, anti-integrins may be small molecule integrin ligands, such as thyroid hormone analogues, that block the activity of the specific thyroid hormone (L-thyroxine, T4) at its discrete cell surface receptor on integrin αvβ3 (Cheng et al. 2010). In contrast, RGD peptides may bind to multiple integrins at sites of different overall structure that recognize the RGD sequence. Integrin antagonists demonstrated a wide range of therapeutic applications in thrombosis, vascular restenosis, cancer, asthma, allergy, and inflammatory diseases (Desgrosellier and Cheresh 2010; Dotan et al. 2020; Raab-Westphal et al. 2017).

In addition to affecting functions of integrins, anti-integrins may also serve as drug delivery tools (Li et al. 2016; Sudha et al. 2017a; Sun et al. 2017) or as imaging agents (Danhier et al. 2012) for cancers or inflamed tissues expressing integrins.

Basic Characteristics of Anti-integrins and Mechanisms of Anti-integrin Action

The protein-ligands of integrins, such as ECM proteins, often contain the RGD sequence, and RGD peptides have anti-integrin activity. Another strategic approach to the identification of anti-integrin ligands has been to determine whether naturally occurring small molecules, such as nonpeptide hormone analogues (Davis et al. 2013), might bind to specific sites on specific integrins under physiological circumstances to modify integrin-based cell functions. An example of the use of this strategy was the description of the pro-angiogenic action of thyroid hormone, T4 (Mousa et al. 2014; Davis et al. 2015), initiated at a previously unrecognized hormone receptor on integrin αvβ3. Removal of a single iodine from T4 occurs in vivo to yield tetraiodothyroacetic acid (tetrac) and resulted in an anti-angiogenic molecule that eradicated the pro-angiogenic activity of T4 in endothelial cells (Mousa et al. 2014; Stryker et al. 2019). This topic is reviewed in more detail in the specific anti-integrin section below on αvβ3.

Anti-integrin products may be directed at specific integrin monomers or at an intact heterodimer. The RGD peptide model and the thyroid hormone analogue and resveratrol anti-integrin molecules require heterodimeric integrin structure to construct the discrete receptor sites that may be formed at conjunctions of the specific monomers in a heterodimer. Antibody anti-integrins may be directed at specific facets of monomers.

As this chapter describes in more detail below, integrin αvβ3 also contains discrete sites that specifically bind dihydrotestosterone (DHT) and resveratrol that are unrelated to the thyroid hormone analogue receptor. DHT may act via its receptor on the integrin to stimulate the proliferation of breast cancer cells (Lin et al. 2009) and thus is not anti-integrin. In contrast, resveratrol is an anti-integrin, blocking the proliferation of a wide variety of cancer cells. Among the qualities of resveratrol in tumor cells is interference with the PD1/PD-L1 immune checkpoint (Lin et al. 2019).

In addition to αvβ3, several other integrins have been the foci of anti-integrin development. Integrin-focused drug development has been

substantial for possible application to inflammatory states, such as inflammatory bowel disease (Dotan et al. 2020; Park and Jeen 2018; Sabino et al. 2019; Shah et al. 2017). Integrins other than αvβ3 have also been linked to cancer (Seguin et al. 2015; Desgrosellier and Cheresh 2010; Raab-Westphal et al. 2017). Certain integrins have been implicated in ophthalmologic diseases and have been considered targets for anti-integrins (Gonzalez-Salinas et al. 2018). Finally, there are thrombotic conditions in which anti-integrins have been mentioned as possible therapeutic interventions (Mousa et al. 2010; Davis et al. 2018a; Mousa et al. 2018; Davis et al. 2018b). Because normal platelets bear αvβ3 that originated in the plasma membrane of the megakaryocyte, thyroid hormone action on platelet aggregation via αvβ3 might be a source of hypercoaguability (Mousa et al. 2010). Anti-integrin treatment might be a strategy in such patients.

Activity of anti-integrins may be modified by the state of the activation (conformation) of the highly plastic heterodimeric integrin (Ginsberg 2014). That is, activation state/conformation change may alter the accessibility of binding sites for ligands on the extracellular domain of integrins. Small molecules such as thyroid hormone analogues alter activation state (Leith et al. 2017) and physical factors may also modify the conformation of integrins. X-irradiation is an example of a factor that may rapidly activate integrin αvβ3 (Leith et al. 2018). Thyroid hormone analogues that interact with the same integrin will also affect the interactions of the integrin with ECM proteins, such as vitronectin (Davis et al. 2015) and thus change the motility of cells that anti-integrins may be designed to affect.

Therapeutic Potential of Anti-integrins

Integrins are involved in and modulate cell-cell interactions, interactions of ECM proteins and cells, motility of a large variety of cells, tissue structure, and the state of the cytoskeleton. Pharmaceutics directed at integrins are under study in a wide variety of clinical states. These include inflammation (Arnaout 2016; Kourtzelis et al. 2017) – such as that of the intestinal tract (Catalan-Serra and Brenna 2018), in the vascular system (Huang and Frangogiannis 2018; Edwards and Bix 2019) and joints (Morshed et al. 2019) – cancer biology (Lavergne et al. 2017; Raab-Westphal et al. 2017; Leith et al. 2018; Mousa et al. 2018; Davis et al. 2019) and angiogenesis (Mousa et al. 2014; Davis et al. 2015; Duro-Castano et al. 2017; Guerrero and McCarty 2018).

We have pointed out above that chemical modification of anti-integrin molecules to enable the transporting of anti-cancer drugs allows the anti-integrin, when bound to cancer cell integrin, to unload specific chemotherapeutic agents at the cancer site (Sudha et al. 2017a, b; Sun et al. 2017).

Against this background, it is understandable that a preclinical and limited clinical anti-integrin literature has emerged. The most substantial literature involves application of anti-integrins to inflammatory bowel disease, neuronal disorders, thrombosis, cancer, and cancer-associated complications, as discussed below.

Specific Anti-integrins

Alpha Integrins

Alpha 1 Beta 1 Integrin

Short chain disintegrin obustatin demonstrated high affinity and specificity for the α1 β1 Integrin with potent anti-angiogenesis activity (Marcinkiewicz et al. 2003).

Alpha 2 Beta 1 Integrin (Very Late Activating Antigen 2, VLA2)

A key role for α2β1 integrin in cell adhesion, cell motility, angiogenesis, stemness, and immune/blood cell regulations and its implication in cancer has been demonstrated (Adorno-Cruz and Liu 2018).

Alpha 3 Beta 1 Integrin

The α3β1 integrin expressed in human breast cancer cells and its participation in the

degradation and phagocytosis of the extracellular matrix has been shown (Coopman et al. 1996).

Alpha 4 Beta 1 Integrin (Very Late Activating Antigen 4, VLA4)

The α4 integrin-dependent leukocyte trafficking promotes cognitive impairment in multiple sclerosis (MS), Alzheimer's disease (AD), and other neuropathological disorders, which suggests that blocking α4 integrins might offer a new therapeutic strategy in MS, AD, and other neuronal diseases. The FDA-approved humanized monoclonal antibody against the cell adhesion molecule α4-integrin, namely natalizumab, is indicated for the improvement of disability and reduction of relapse rate in MS patients (Mazdeh et al. 2018; Engelhardt and Kappos 2008; Li et al. 2018; Manocha et al. 2018; Dattoli et al. 2018; Pietronigro et al. 2019).

Alpha 4 Beta 1/Beta 7 Integrin

Natalizumab is also FDA approved for inflammatory bowel disease (IBD), namely Crohn's disease, but has limited risk. In contrast, vedolizumab α4β7 integrin antagonist is approved for IBD with fewer systemic adverse effects versus natalizumab (Park and Jeen 2018).

Alpha 5 Beta 1 Integrin

Integrin subunit α5 (ITGA5) often combines with ITGB1 to form integrin α5β1, which serves as a receptor for cell differentiation, cell development, migration, angiogenesis, and invasion of cancer cells or bacteria (Kim et al. 2000; Cue et al. 2000; Mostafavi-Pour et al. 2018; Ren et al. 2009). The emergence of integrin α5β1 expression was found to be associated with tumor progression in lung cancer and other cancers (Rivera et al. 2017).

Beta 2-Integrin

Beta2-integrins are complex leukocyte-specific adhesion molecules, which are essential for leukocyte trafficking and immunological processes such as neutrophil phagocytosis, T cell activation, and ROS production and are implicated in various inflammatory and immune diseases (Fagerholm et al. 2019).

Beta 3 Anti-integrins

Alpha IIb/β3 Integrin – Integrin αIIbβ3, Glycoprotein IIb/IIIa (GPIIb/IIIa)

Platelet integrin αIIbβ3 (GPIIb-IIIa) binds to fibrinogen and fibrin, and novel antagonists were developed and evaluated as effective anti-thrombotic in various settings (Hantgan et al. 2007; Mousa et al. 1996; Mousa et al. 1998, 1999; Mousa and Ahmad 2007). There are already three FDA approved intravenous GPIIb/IIIa receptor inhibitors including eptifibatide, tirofiban, and abciximab used in patients with acute coronary syndrome undergoing percutaneous coronary intervention (Capodanno et al. 2019; Podolnikova et al. 2014). Eptifibatide and tirofiban are specific GPIIb/IIIa inhibitors, while abciximab cross-reacts with αvβ3 and α2β1 integrins. Hence, abciximab might reduce restenosis, myocardial infarct size, inhibit adhesion of monocytes, and impact the inflammatory response. In that regard, potent small molecule high affinity αvβ3 integrin antagonists demonstrated anti-restenosis efficacy in various preclinical models (Bishop et al. 2001; Srivatsa et al. 1997). Additionally, anti-angiogenesis efficacy was demonstrated in a retinal neovascularization model with small molecule αvβ3 antagonists (Luna et al. 1996; Santulli et al. 2008).

Alpha v Beta 3 Integrin

Tetrac blocks the actions of vascular growth factors, such as fibroblast growth factor (FGF2), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) (Mousa et al. 2014). Thus, tetrac can be designated a naturally occurring anti-integrin with anti-angiogenic properties.

Tetrac and chemically modified tetrac also have anti-cancer properties (Bharali et al. 2013; Mousa et al. 2018; Rajabi et al. 2019), but the growth of noncancer cells appears to be unaffected by tetrac (Davis et al. 2016). This reflects the generous expression of integrin αvβ3 by cancer cells compared with nonmalignant cells (except for endothelial cells). High affinity and specific αvβ3 antagonists were developed and evaluated in various settings (Helluin et al. 2000;

Kerr et al. 2000, 2001, 2002; Mousa 2005; Mousa and Mohamed 2005).

Alpha v Beta 6 Integrin

Integrin αvβ6 is exclusively expressed in epithelial cells and it activates transforming growth factor-β1 (TGF-β1) to modulate innate immune surveillance in lungs, skin, and gastrointestinal tract to maintain epithelial stem cell quiescence. The expression of αvβ6 integrin and its activation of TGF-β1 are associated with organ fibrosis and cancer. Therefore, αvβ6 integrin might serve as an attractive target for cancer therapy, imaging, and fibrosis (Koivisto et al. 2018). Additionally, β6 expression activates multiple systems involved in tumor lesions and cancer metastasis and its overexpression correlated with reduced patient survival in renal carcinoma and perhaps other cancer (Cantor et al. 2015).

Neurotransmitter Receptors and Integrin

Endothelial cells, as key cells for the angiogenesis process, express several nonneuronal nicotinic acetylcholine receptors (AChRs). In endothelial cells, alpha7 AChR stimulation indirectly triggers the activation of the integrin αvβ3 receptor and an intracellular MAP kinase (ERK) pathway that mediates angiogenesis. The intracellular mechanisms by which alpha7 AChR activation mediates angiogenesis were examined by our group (Arias et al. 2009).

Future directions should focus on these different interfaces between neurotransmitter receptors as well as hormones and integrins function, which might serve as novel therapeutics as highlighted in this brief overview.

References

Adorno-Cruz V, Liu H (2018) Regulation and functions of integrin α2 in cell adhesion and disease. Genes Dis 6(1):16–24

Arias HR, Richards VE, Ng D, Ghafoori ME, Le V, Mousa SA (2009) Role of non-neuronal nicotinic acetylcholine receptors in angiogenesis. Int J Biochem Cell Biol 41(7):1441–1451

Arnaout MA (2002) Integrin structure: new twists and turns in dynamic cell adhesion. Immunol Rev 186:125–140

Arnaout MA (2016) Biology and structure of leukocyte β (2) integrins and their role in inflammation. F1000Research. 5:F1000 Faculty Rev-2433

Arnaout MA, Goodman SL, Xiong J-P (2007) Structure and mechanics of integrin-based cell adhesion. Curr Opin Cell Biol 19(5):495–507

Bergh JJ, Lin HY, Lansing L et al (2005) Integrin αVβ3 contains a cell surface receptor site for thyroid hormone that is linked to activation of mitogen-activated protein kinase and induction of angiogenesis. Endocrinology 146(7):2864–2871

Bharali DJ, Yalcin M, Davis PJ, Mousa SA (2013) Tetraiodothyroacetic acid-conjugated PLGA nanoparticles: a nanomedicine approach to treat drug-resistant breast cancer. Nanomedicine (Lond) 8(12):1943–1954

Bishop GG, McPherson JA, Sanders JM et al (2001) Selective $\alpha_v\beta_3$-receptor blockade reduces macrophage infiltration and restenosis after balloon angioplasty in the atherosclerotic rabbit. Circulation 103 (14):1906–1911

Byron A, Humphries JD, Askari JA, Craig SE, Mould AP, Humphries MJ (2009) Anti-integrin monoclonal antibodies. J Cell Sci 122(Pt 22):4009–4011

Cantor DI, Cheruku HR, Nice EC, Baker MS (2015) Integrin αvβ6 sets the stage for colorectal cancer metastasis. Cancer Metastasis Rev 34(4):715–734

Capodanno D, Milluzzo RP, Angiolillo DJ (2019) Intravenous antiplatelet therapies (glycoprotein IIb/IIIa receptor inhibitors and cangrelor) in percutaneous coronary intervention: from pharmacology to indications for clinical use. Ther Adv Cardiovasc Dis 13:1753944719893274–1753944719893274

Catalan-Serra I, Brenna Ø (2018) Immunotherapy in inflammatory bowel disease: Novel and emerging treatments. Hum Vaccin Immunother 14(11):2597–2611

Cheng SY, Leonard JL, Davis PJ (2010) Molecular aspects of thyroid hormone actions. Endocr Rev 31(2):139–170

Coopman PJ, Thomas DM, Gehlsen KR, Mueller SC (1996) Integrin alpha 3 beta 1 participates in the phagocytosis of extracellular matrix molecules by human breast cancer cells. Mol Biol Cell 7(11):1789–1804

Cue D, Southern SO, Southern PJ et al (2000) A nonpeptide integrin antagonist can inhibit epithelial cell ingestion of Streptococcus pyogenes by blocking formation of integrin α5β1-fibronectin-M1 protein complexes. Proc Natl Acad Sci U S A 97(6):2858–2863

Danhier F, Le Breton A, Préat V (2012) RGD-based strategies to target alpha(v) beta(3) integrin in cancer therapy and diagnosis. Mol Pharm 9(11):2961–2973

Dattoli SD, Baiula M, De Marco R, et al (2018) DS-70, a novel and potent α(4) integrin antagonist, is an effective treatment for experimental allergic conjunctivitis in guinea pigs. Br J Pharmacol 175(20):3891–3910

Davis PJ, Mousa SA, Cody V, Tang HY, Lin HY (2013) Small molecule hormone or hormone-like ligands of integrin alphaVbeta3: implications for cancer cell behavior. Horm Cancer 4(6):335–342

Davis PJ, Sudha T, Lin HY, Mousa SA (2015) Thyroid hormone, hormone analogs, and angiogenesis. Compr Physiol 6(1):353–362

Davis PJ, Goglia F, Leonard JL (2016) Nongenomic actions of thyroid hormone. Nat Rev Endocrinol 12 (2):111–121

Davis PJ, Tang HY, Hercbergs A, Lin HY, Keating KA, Mousa SA (2018a) Bioactivity of thyroid hormone analogs at cancer cells. Front Endocrinol 9:739

Davis PJ, Mousa SA, Schechter GP (2018b) New interfaces of thyroid hormone actions with blood coagulation and thrombosis. Clin Appl Thromb Hemost 24 (7):1014–1019

Davis PJ, Ashur-Fabian O, Incerpi S, Mousa SA (2019) Editorial: non genomic actions of thyroid hormones in cancer. Front Endocrinol 10(847)

Desgrosellier JS, Cheresh DA (2010) Integrins in cancer: biological implications and therapeutic opportunities. Nat Rev Cancer 10(1):9–22

Dotan I, Allez M, Danese S, Keir M, Tole S, McBride J (2020) The role of integrins in the pathogenesis of inflammatory bowel disease: approved and investigational anti-integrin therapies. Med Res Rev 40(1):245–262

Duro-Castano A, Gallon E, Decker C, Vicent MJ (2017) Modulating angiogenesis with integrin-targeted nanomedicines. Adv Drug Deliv Rev 119:101–119

Edwards DN, Bix GJ (2019) The inflammatory response after ischemic stroke: targeting β(2) and β(1) integrins. Front Neurosci 13:540

Eliceiri BP, Cheresh DA (1998) The role of alphav integrins during angiogenesis. Mol Med 4(12):741–750

Engelhardt B, Kappos L (2008) Natalizumab: targeting a4-integrins in multiple sclerosis. Neurodegener Dis 5 (1):16–22

Fagerholm SC, Guenther C, Llort Asens M, Savinko T, Uotila LM (2019) Beta2-integrins and interacting proteins in leukocyte trafficking, immune suppression, and immunodeficiency disease. Front Immunol 10:254

Ginsberg MH (2014) Integrin activation. BMB Rep 47 (12):655–659

Gonzalez-Salinas R, Hernández-Zimbrón LF, Gulias-Cañizo R, et al (2018) Current anti-integrin therapy for ocular disease. Semin Ophthalmol 33(5):634–642

Guerrero PA, McCarty JH (2018) Integrins in vascular development and pathology. Adv Pharmacol 81:129–153

Hantgan RR, Stahle MC, Connor JH, Connor RF, Mousa SA (2007) αIIbβ3 priming and clustering by orally active and intravenous integrin antagonists. J Thromb Haemost 5(3):542–550

Helluin O, Chan C, Vilaire G, Mousa S, DeGrado WF, Bennett JS (2000) The activation state of $\alpha_v\beta_3$ regulates platelet and lymphocyte adhesion to intact and thrombin-cleaved osteopontin. J Biol Chem 275 (24):18337–18343

Huang S, Frangogiannis NG (2018) Anti-inflammatory therapies in myocardial infarction: failures, hopes and challenges. Br J Pharmacol 175(9):1377–1400

Kerr JS, Slee AM, Mousa SA (2000) Small molecule αv integrin antagonists: novel anticancer agents. Expert Opin Investig Drugs 9(6):1271–1279

Kerr JS, Mousa SA, Slee AM (2001) αvβ3 integrin in angiogenesis and restenosis. Drug News Perspect 14 (3):143–150

Kerr JS, Slee AM, Mousa SA (2002) The αv integrin antagonists as novel anticancer agents: an update. Expert Opin Investig Drugs 11(12):1765–1774

Kim S, Bell K, Mousa SA, Varner JA (2000) Regulation of angiogenesis in vivo by ligation of integrin α5β1 with the central cell-binding domain of fibronectin. Am J Pathol 156(4):1345–1362

Koivisto L, Bi J, Häkkinen L, Larjava H (2018) Integrin αvβ6: structure, function and role in health and disease. Int J Biochem Cell Biol 99:186–196

Kourtzelis I, Mitroulis I, von Renesse J, Hajishengallis G, Chavakis T (2017) From leukocyte recruitment to resolution of inflammation: the cardinal role of integrins. J Leukoc Biol 102(3):677–683

Lavergne M, Janus-Bell E, Schaff M, Gachet C, Mangin PH (2017) Platelet integrins in tumor metastasis: do they represent a therapeutic target? Cancers 9(10):133

Leith JT, Davis PJ, Mousa SA, Hercbergs AA (2017) In vitro effects of tetraiodothyroacetic acid combined with X-irradiation on basal cell carcinoma cells. Cell Cycle 16(4):367–373

Leith JT, Mousa SA, Hercbergs A, Lin HY, Davis PJ (2018) Radioresistance of cancer cells, integrin αvβ3 and thyroid hormone. Oncotarget 9(97):37069–37075

Li XY, Wu MY, Pan LM, Shi JL (2016) Tumor vascular-targeted co-delivery of anti-angiogenesis and chemotherapeutic agents by mesoporous silica nanoparticle-based drug delivery system for synergetic therapy of tumor. Int J Nanomed 11:93–105

Li H, Shi F-H, Huang S-Y, Zhang S-G, Chen M-L (2018) A review on clinical pharmacokinetics, pharmacodynamics, and pharmacogenomics of natalizumab: a humanized anti-α4 iIntegrin monoclonal antibody. Curr Drug Metab 19(14):1213–1223

Lin HY, Sun M, Lin C et al (2009) Androgen-induced human breast cancer cell proliferation is mediated by discrete mechanisms in estrogen receptor-alpha-positive and -negative breast cancer cells. J Steroid Biochem Mol Biol 113(3–5):182–188

Lin C-C, Chin Y-T, Shih Y-J, et al (2019) Resveratrol antagonizes thyroid hormone-induced expression of checkpoint and proliferative genes in oral cancer cells. J Dent Sci 14(3):255–262

Luna J, Tobe T, Mousa SA, Reilly TM, Campochiaro PA (1996) Antagonists of integrin alpha v beta 3 inhibit retinal neovascularization in a murine model. Lab Investig 75(4):563–573

Manocha G, Ghatak A, Puig K, Combs C (2018) Anti-α 4β1 integrin antibodies attenuated brain inflammatory

changes in a mouse model of alzheimer's disease. Curr Alzheimer Res 15(12):1123–1135

Marcinkiewicz C, Weinreb PH, Calvete JJ et al (2003) Obtustatin: a potent selective inhibitor of α1β1 integrin in vitro and angiogenesis in vivo. Cancer Res 63 (9):2020–2023

Mazdeh M, Hosseini S, Taheri M, Ghafouri-Fard S (2018) The effect of natalizumab on disability score and relapse rate of multiple sclerosis patients: a prospective cohort study. Clin Transl Med 7(1):38

Morshed A, Abbas AB, Hu J, Xu H (2019) Shedding new light on the role of αvβ3 and α5β1 integrins in rheumatoid arthritis. Molecules 24(8):1537

Mostafavi-Pour Z, Ashrafi MR, Talaei-Khozani T (2018) Down regulation of ITGA4 and ITGA5 genes after formation of 3D spherules by human Wharton's jelly stem cells (hWJSCs). Mol Biol Rep 45(3):245–252

Mousa SA (2005) αv integrin affinity/specificity and anti-angiogenesis effect of a novel tetraaza cyclic peptide derivative, SU015, in various species. J Cardiovasc Pharmacol 45(5):462–467

Mousa SA, Mohamed S (2005) Human αvβ3 integrin potency and specificity of TA138 and its DOTA conjugated form (89)Y-TA138. J Cardiovasc Pharmacol 45 (2):109–113

Mousa SA, Ahmad S (2007) Platelet GPIIb/IIIa antagonist, XV459, in heparin-induced thrombocytopenia. Am J Hematol 82(4):276–282

Mousa SA, DeGrado WF, Mu DX, Kapil RP, Lucchesi BR, Reilly TM (1996) Oral antiplatelet, antithrombotic efficacy of DMP 728, a novel platelet GPIIb/IIIa antagonist. Circulation 93(3):537–543

Mousa SA, Bozarth JM, Lorelli W, et al (1998) Antiplatelet efficacy of XV459, a novel nonpeptide platelet GPIIb/IIIa antagonist: comparative platelet binding profiles with c7E3. J Pharmacol Exp Ther 286 (3):1277–1284

Mousa SA, Kapil R, Mu DX (1999) Intravenous and oral antithrombotic efficacy of the novel platelet GPIIb/IIIa antagonist roxifiban (DMP754) and its free acid form, XV459. Arterioscler Thromb Vasc Biol 19(10):2535–2541

Mousa SS, Davis FB, Davis PJ, Mousa SA (2010) Human platelet aggregation and degranulation is induced in vitro by L-thyroxine, but not by 3,5,3′-triiodo-L-thyronine or diiodothyropropionic acid (DITPA). Clin Appl Thromb Hemost 16(3):288–293

Mousa SA, Lin HY, Tang HY, Hercbergs A, Luidens MK, Davis PJ (2014) Modulation of angiogenesis by thyroid hormone and hormone analogues: implications for cancer management. Angiogenesis 17(3):463–469

Mousa SA, Glinsky GV, Lin HY, et al (2018) Contributions of thyroid hormone to cancer metastasis. Biomedicines 6(3)

Park SC, Jeen YT (2018) Anti-integrin therapy for inflammatory bowel disease. World J Gastroenterol. 24 (17):1868–1880

Pietronigro E, Zenaro E, Bianca VD, et al (2019) Blockade of α4 integrins reduces leukocyte-endothelial interactions in cerebral vessels and improves memory in a mouse model of Alzheimer's disease. Sci Rep 9 (1):12055–12055

Podolnikova NP, Yakovlev S, Yakubenko VP, Wang X, Gorkun OV, Ugarova TP (2014) The interaction of integrin αIIbβ3 with fibrin occurs through multiple binding sites in the αIIb β-propeller domain. J Biol Chem 289(4):2371–2383

Raab-Westphal S, Marshall JF, Goodman SL (2017) Integrins as therapeutic targets: successes and cancers. Cancers 9(9):110

Rajabi M, Godugu K, Sudha T, Bharali DJ, Mousa SA (2019) Triazole modified tetraiodothyroacetic acid conjugated to polyethylene glycol: high affinity thyrointegrin alphavbeta3 antagonist with potent anticancer activities in glioblastoma multiforme. Bioconjug Chem 30(12):3087–3097

Reardon DA, Nabors LB, Stupp R, Mikkelsen T (2008) Cilengitide: an integrin-targeting arginine-glycine-aspartic acid peptide with promising activity for glioblastoma multiforme. Expert Opin Investig Drugs 17 (8):1225–1235

Ren JS, Kamangar F, Qiao YL, et al (2009) Serum pepsinogens and risk of gastric and oesophageal cancers in the General Population Nutrition Intervention Trial cohort. Gut 58(5):636–642

Rivera C, Oliveira AK, Costa RAP, De Rossi T, Paes Leme AF (2017) Prognostic biomarkers in oral squamous cell carcinoma: a systematic review. Oral Oncol 72:38–47

Sabino J, Verstockt B, Vermeire S, Ferrante M (2019) New biologics and small molecules in inflammatory bowel disease: an update. Therap Adv Gastroenterol 12:1756284819853208–1756284819853208

Santulli RJ, Kinney WA, Ghosh S, et al (2008) Studies with an orally bioavailable av integrin antagonist in animal models of ocular vasculopathy: retinal neovascularization in mice and retinal vascular permeability in diabetic rats. J Pharmacol Exp Ther 324(3):894–901

Seguin L, Desgrosellier JS, Weis SM, Cheresh DA (2015) Integrins and cancer: regulators of cancer stemness, metastasis, and drug resistance. Trends Cell Biol 25 (4):234–240

Shah ED, Farida JP, Siegel CA, Chong K, Melmed GY (2017) Risk for overall infection with anti-TNF and anti-integrin agents used in IBD: a systematic review and meta-analysis. Inflamm Bowel Dis 23 (4):570–577

Srivatsa SS, Fitzpatrick LA, Tsao PW, et al (1997) Selective αvβ3 integrin blockade potently limits neointimal hyperplasia and lumen stenosis following deep

coronary arterial stent injury: evidence for the functional importance of integrin αvβ3 and osteopontin expression during neointima formation. Cardiovasc Res 36(3):408–428

Stryker ZI, Rajabi M, Davis PJ, Mousa SA (2019) Evaluation of angiogenesis assays. Biomedicines 7(2):37

Sudha T, Bharali DJ, Yalcin M et al (2017a) Targeted delivery of paclitaxel and doxorubicin to cancer xenografts via the nanoparticle of nano-diamino-tetrac. Int J Nanomedicine 12:1305–1315

Sudha T, Bharali DJ, Yalcin M et al (2017b) Targeted delivery of cisplatin to tumor xenografts via the nanoparticle component of nano-diamino-tetrac. Nanomedicine (Lond) 12(3):195–205

Sun Y, Kang C, Liu F, Zhou Y, Luo L, Qiao H (2017) RGD peptide-based target drug delivery of doxorubicin nanomedicine. Drug Dev Res 78(6):283–291