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Every step of the way: integrins in cancer progression and metastasis

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Table 1. Clinical observations of integrin expression patterns in different cancer types and at different stages of disease. This table is not an exhaustive list and is used only to highlight the relevance of integrins in many cancers.

integrin		cancer type	Aetiopathological relevance in human cancer
β1	β1	MM	- expressed throughout development of primary and metastatic disease [1] - proposed marker of lymphatic metastases [2] - expression of conflicting prognostic value: reportedly associated with both improved DFS and OS and decreased OS [3, 4]
	α2β1	BrCa	- tropism for bone invasion and metastasis [5, 6] - paclitaxel and vincristine chemotherapeutic resistance [5, 7] - loss of expression associated with poor differentiation, correlating with ER expression [8] - weak expression observed in primary and metastatic sites [9]
		CRC	- tropism for hepatic invasion and metastasis [5, 10-13] - promotion of SC-like phenotype
		GaCa	- EMT induction [5, 14] - peritoneal and hepatic metastases [5, 15-17]
		HISC	- neoplastic transformation and disease progression [5, 18]
		LC	- EGFR inhibitor chemotherapeutic resistance [5, 19]
			- promotion of angiogenesis facilitating tumour growth and radio/chemotherapeutic resistance in SCLC [20-22]
		MM	- increased expression in malignant over benign tumours; promotes angiogenesis facilitating tumour growth [5, 23-25]
		PaCa	- chemotherapeutic resistance to 5FU and gemcitabine [26-28] - EMT; activation of local invasion but suppression of distal metastatic dissemination [5, 29-32] - Hypomethylation/increased expression of MET and ITGA2 genes associated with poor patient survival [33]
		PrCa	- marker of PrCa SCs [34-38] - tropism for bone invasion and metastasis; upregulation corresponds with LN metastases [39-41]
		T-cell ALL	- doxorubicin chemotherapeutic resistance [42, 43] - apoptotic resistance via death-receptor pathways [44, 45]
	α3β1	MM	- low expression in benign lesions; exhibits progressive upregulation correlating with dermal invasiveness and potentially metastatic sites [1]

α4β1	MM	- expression low to absent in early disease, emergent and upregulated during disease progression in patient Bx [1, 25, 46, 47]
α5β1	MM	- induction and/or upregulation of expression associated with progression in patient Bx [1]
	OvCa	- expression significantly correlates with higher clinical stage [48]
α6β1	BrCa	- correlates with decreased OS; of potential prognostic value [49] - expression elevated in BrCa cells compared to benign mammary cells and confers radiation resistance via a ITGA6/PI3K-Akt/MEK-ERK signalling axis [50] - ITGA6 is a HIF-dependent target gene; high ITGA6 expression promotes invasion and tumour-initiating features in murine models of MBC [51]
	MM	- expression significantly higher in benign compared to metastatic lesions [25]
	PrCa	- expression maintained or overexpressed in grade I and II tumours; correlates with LN metastases [41]
α7	ESCC	- ITGA7 expression clinically associated with poor differentiation, LN metastases and worse prognosis; ITGA7 expression confers stemness and is a putative SC marker in ESCC [52]
	glioblastoma	- ITGA7 overexpression negatively correlates with patient survival in low- and high-grade glioma; functional abrogation of ITGA7 impairs laminin-induced signalling and delays tumour engraftment, reduces tumour size and invasiveness [53]
	HCC	- truncating mutations leading to downregulation of functional ITGA7 and risk of recurrence are clinically reported [54]
	PrCa	- ITGA7 expression is downregulated by truncating mutations and is associated with increased disease recurrence [54] - mechanistic dissection of ITGA7 tumour suppressor functions in PrCa reported ITGA7 interacts with and potentiates serine protease activity critical for apoptosis to promote cell death [55]
α8	mHCC	- ITGA8 expression upregulated at all disease stages in liver tumours arising in the PDGFC-transgenic mouse model [56]
α9β1	BrCa	- tumour α9β1 expression is significantly associated with reduced OS and reduced DMFS in a BrCa cohort (n=141); reported as a novel marker of basal-like BrCa subtype; expression confers a more aggressive BrCa cell phenotype in vitro [57] - CpG methylation leading to epigenetic silencing of ITGA9 is reported in a small BrCa cohort (n=38) [58]
	PrCa	- implicated in PrCa bone metastases by preferentially binding Tn-C expressed in bone endosteum[59]
	SCLC	- high tumoural α9β1 expression is predictive of poor survival [60]
α10	BrCa	- based on bioinformatic mining of publically available datasets, ITGA10 expression is

		LC	downregulated in BrCa, NSCLC and MM [61]
		MM	
		MFS	- ITGA10 expression in high-grade MFS was significantly associated with disease-specific death and distant metastases attributed to an α10-dependent TRIO/RICTOR oncogenic signalling axis [62]
	α11	NSCLC	- ITGA11 overexpression is a tumour biomarker gene in NSCLC [63] - expression of ITGA11 potentiates tumourigenicity of NSCLC cells in vitro [64]
β3	β3	MM	- exclusive expression in vertical growth phase and metastatic disease [25, 46] - expression upregulated during disease progression, correlating with decreased OS and lung and LN metastasis [1, 3]
	αvβ3	BrCa	- variable expression at primary sites but highly abundant expression in bone-metastases [9, 65]
		GaCa	- endothelial cell expression correlates with survival [66, 67]
		glioma	- expression prevalent in astrocytes and endothelial cells, correlating with high grade [66, 68, 69]
		MM	- gain of αvβ3 (with accompanying loss of αvβ5) occurs during tumour progression [70]
		PaCa	- expression in primary tumour correlates with LN metastases but not tumour size nor grade [71]
		PrCa	- activated αvβ3 significantly upregulated in bone metastases [72]
		SCC	- correlates with significant reduction in post-radiotherapy PFS and CSS [73]
β4	(α6)β4	BrCa	- no demonstrable prognostic value in early stage disease but ITGB4 expression upregulated in high grade BrCa suggesting a role in tumour progression [74]
		MM	- downregulation putatively associated with disease progression [1]
		PrCa	- ITGB4 and cognate ligand laminin-5 are expressed in normal and PIN tissue but expression is absent in malignant tissue [75, 76]
β5	αvβ5	BrCa	- significantly reduced in primary BrCa cells compared to benign breast tissue [77]
		GaCa	- high expression in stromal and endothelial cells; prognostic in intestinal-type carcinomas
		NSCLC	- high expression in tumour and stromal cells but shows no correlation with survival [66, 78]
		PrCa	- activated αvβ5 significantly upregulated in bone metastases [72]
β6	αvβ6	BCC	- high expression associated with infiltrative subtype [66, 79]
		BrCa	- overexpression is protumorigenic; therapeutic functional blockade with antibody 264RAD potentiates trastuzumab efficacy in HER-2-driven BrCa [80]

			- expression in myoepithelial cells predictive of invasive progression and disease recurrence in DCIS [81]
		CRC	- high expression observed at invasive tumour front; correlates with decreased survival [82, 83]
		CxCa	- expression low in normal cervical tissue but upregulated in CIN; high expression associated with decreased OS and DFS in CxCa [84]
		EndoCa	- frequently overexpressed but shows no correlation with LN metastasis [85]
		GaCa	- potential utility as a prognostic marker in early stage disease [86]
		HCC	- expression differentiates cholangiocarcinoma from HCC [87]
		LC	- high expression in NSCLC correlating with reduced survival; frequently expressed in brain metastases[88, 89]
		OSCC	- expression imparts a pro-invasive and more aggressive phenotype and is requisite for OSCC MMP-9-mediated invasion [90-93]
		OvCa	- expression shows correlation with disease grade [94]
		PaCa	- frequently overexpressed [66, 95]
		PrCa	- expression absent or weak [96]
		SCC	- loss of αvβ5 and gain of αvβ6 confers a survival advantage by promoting Akt-dependent survival signals to circumvent anoikis [97]
β8	ανβ8	BrCa LC MM RCC	- expression significantly increased in brain metastases compared with primary tumour sites [98]
		HCC	- overexpression associated with gefitinib resistance; ITGB8 silencing reverses gefitinib resistance in the HepG2/G HCC cell line [99]

Abbreviations: ALL – acute lymphoblastic leukaemia; BCC – basal cell carcinoma; BrCa – breast cancer; Bx – biopsies; CIN – cervical intraepithelial neoplasia; CRC – colorectal cancer; CSS – cause-specific survival; CxCa – cervical cancer; DFS – disease-free survival; DMFS – distal metastasis-free survival; EndoCa – endometrial cancer; ER – oestrogen receptor; ESCC – oesophageal squamous cell carcinoma; GaCa – gastric cancer; HCC – hepatocellular carcinoma; mHCC – murine model of HCC; HIF – hypoxia-inducible factor; HISC – HPV-induced squamous carcinoma; LC – lung cancer; LN – lymph node; MBC – metastatic BrCa; MFS – myxofibrosarcoma; MM – malignant melanoma; NSCLC – non-small cell lung cancer; OS – overall survival; OSCC – oral squamous cell carcinoma; OvCa – ovarian cancer; PaCa – pancreatic cancer, PDGFC – platelet-derived growth factor-C; PFS – progression-free survival; PrCa – prostate cancer; PIN – prostatic intraepithelial neoplasia; RCC – renal cell carcinoma; RICTOR – rapamycin-insensitive companion of mTOR; SC – stem cell; SCC – squamous cell carcinoma; SCLC – small cell lung cancer; TCGA – The Cancer Genome Atlas; TRIO – tri-Rho guanine nucleotide exchange factor

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