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Gene Section
Review

ITGA1 (integrin, alpha 1)

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Abstract

The α1 integrin subunit (SU) belongs to a large family of α and β subunits that are noncovalently linked to constitute αβ transmembrane units. To date, 18 α and 8 β subunits are known to form 24 αβ units (Takada et al., 2007; Barczyk et al., 2010) which are involved in cell-cell and cell-matrix attachment and can drive inside-out and outside-in cell signaling (Shattil et al., 2010). Integrins are known to participate in different cell processes including cell shape, differentiation, migration, survival and proliferation (Giancotti, 1997; Vachon, 2011; Beauséjour et al., 2012). The α1 SU was discovered in 1986 as the Very Late Antigen 1 (VLA1) and is highly expressed in activated lymphocytes in the joints of patients with rheumatoid arthritis (Hemler et al., 1986). In fibroblasts, α1 is known to activate the RAS/ERK proliferative pathway and has a pro-invasive function in certain cancers. In megakaryocyte differentiation α1 is silenced by DNA methylation but not histone modification (Cheli et al., 2007). Different transcription factors involved in cancer progression can bind to the ITGA1 promoter. Integrin α1 transcriptional regulation remains to be further defined.

Identity

Other names: CD49a, VLA1

HGNC (Hugo): ITGA1

Location: 5q11.2

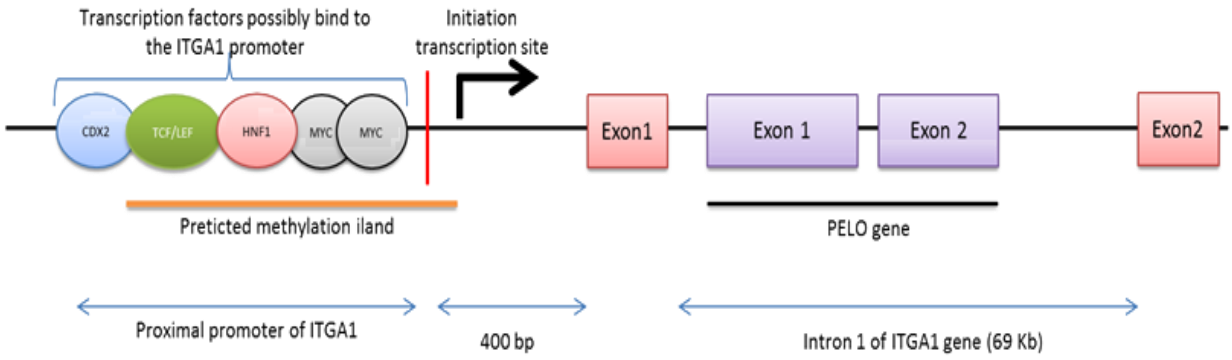

Figure 1. The human ITGA1 gene is located on chromosome 5 at locus q11.2 and contains 29 exons. Only exons 1 and 2 are presented in this diagram. The first intron of ITGA1, which is 69 kb, contains the two exons of the PELO gene. The proximal promoter sequence immediately preceeding the initiation transcription site (red line) includes a CpG island (underlined in orange) and is predicted to be methylated. This region contains possible regulatory elements for different transcription factors known to be involved in various cancers (see text below).

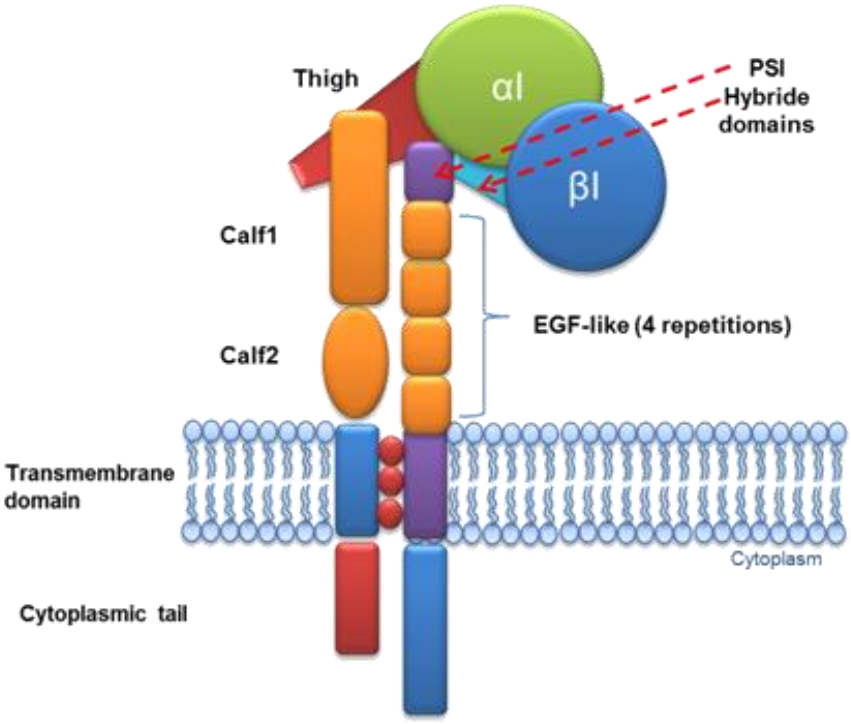

Figure 2. αβ heterodimer domain composition. The two subunits have external domains, a transmembrane domain and a small cytoplasmic tail. α1 is the largest a subunit, but has the smallest cytoplasmic tail. It contains the I (inserted) domain implicated in collagen binding. α1 has no disulfide junctions (no cleavage under reduced conditions) and forms a heterodimer only with the β1 subunit. When inactive the integrin heterodimer is under a bent conformation. Once activated it becomes open and elongated which enhances ligand binding affinity (Arnaout et al., 2005; Shattil et al., 2010).

DNA/RNA

Description

The ITGA1 gene is 165354 bp in length and contains 29 exons that encode a protein of 1179 aa.

Transcription

Transcriptional regulation of the α1 integrin SU: transcriptional regulation of ITGA1 was first described in smooth muscle cells of the chicken in the proximal promoter of ITGA1 containing the CArG box for the serum response factor (SRF) (Obata et al., 1997). Cheli et al. also reported that ITGA1 expression is predominantly regulated by DNA methylation and not histone modification in human HEK293 cells (Cheli et al., 2007). The proximal promoter region of the ITGA1 gene contains CpG islands which are selectively and fully methylated during differentiation of mononuclear cells into the megakaryocyte lineage. This mechanism could be responsible for the silencing of ITGA1 expression in differentiated intestinal cells. Our in silico analysis of the proximal promoter of ITGA1 revealed the presence of a number of response elements for nuclear factors known to be implicated in cancer progression such as TCF/LEF and c-Myc (unpublished data). Further studies are needed to determine a functional relationship between these factors and ITGA1 expression.

Protein

Note

Protein access number: P56199. NCBI reference sequence: NP_852478.1.

Expression

Expression and localisation: the α1 integrin SU (figure 2) is highly expressed in various areas of the stroma. As reported previously, α1 is present in fibroblasts, endothelial cells and smooth muscle cells (Gardner, 2014). In the gut, α1 is expressed in myofibroblast cells surrounding the crypts of the colon and small intestinal mucosa (Boudjadi et al., 2013). α1 is present in epithelial cells of the endometrium, kidney and intestine. In the latter, α1 is present only in proliferating crypt cells while its exclusive partner β1 is constitutively expressed in all intestinal cells (Beaulieu, 1992; Boudjadi et al., 2013). In these cells, α1 is observed in the basolateral portion of the cytoplasmic membrane (figure 3).

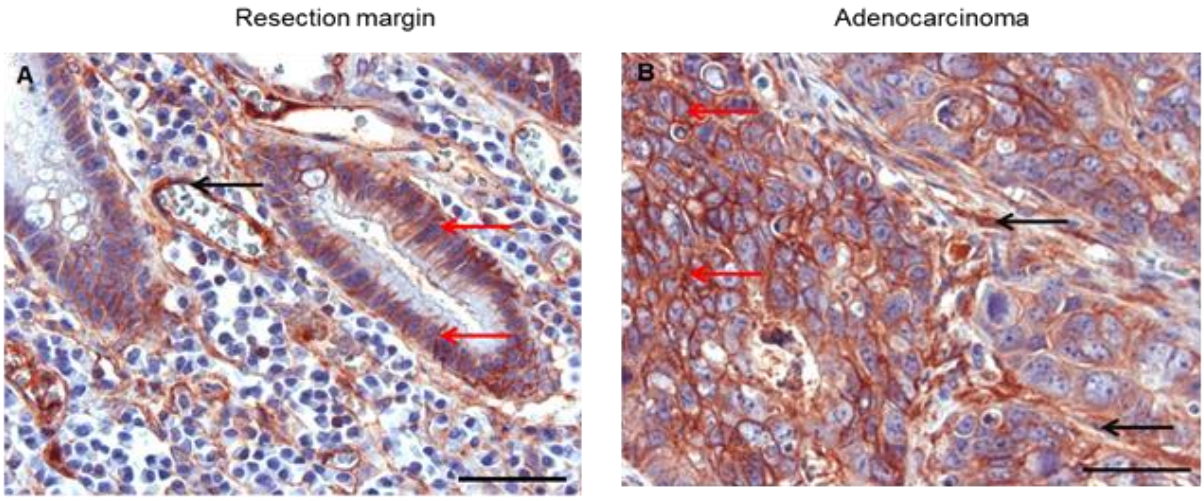

Figure 3. Immunohistochemical images showing examples of α1 integrin subunit expression in the gut. (A) Resection margin and (B) corresponding matched colorectal adenocarcinoma specimens. α1 is predominantly expressed in the proliferative cells of the crypt (A; red arrows) at the basolateral domain of normal epithelial cells, and also in the endothelial cells (A; black arrow). In adenocarcinomas, α1 is highly expressed in tumour epithelial cells (B; red arrows) and reactive stromal cells (B; black arrows). Scale bars = 50 µm.

Function

α1β1 is the main cell receptor for collagen IV and with a lower affinity for collagen I, whereas α2β1 has a higher affinity for collagen I (Barczyk et al., 2010). α1β1 recognizes the GEFOGER sequence within the tertiary structure of collagen IV.

It is important for cell anchorage to the extracellular matrix and is implicated in focal adhesions and cell migration.

The presence of α1β1 in proliferating cells is supported by the reported role for α1, via caveolin-1 and Shc, in the downstream activation of the Ras/MEK/ERK proliferative pathway (Giancotti, 2000).

In endothelial cells, using a selective mutagenesis approach, specific amino acids in the α1 cytoplasmic tail are shown to drive various functions and pathways. While Lys^{1147} is important only for tubulogenesis, Pro^{1142} and Leu^{1145} are required for ERK activation and cell proliferation. Lys^{1146} is involved in cell adhesion, migration (activation of p38 MAPK) and tubulogenesis (activation of p38 MAPK and PI3K). Interestingly, substitution of the Lys^{1151} positively charged amino acid at the COOH-terminus of the α1 tail results in a complete loss of the above functions. This positively charged amino acid could be required for α1 orientation relative to the β1 tail, compromising binding to signal molecules (Abair et al., 2008).

Mutations

Note

No mutation known for human ITGA1 gene.

Implicated in

Lung cancer

Note

In mouse models, the α1β1 integrin mediates cell invasion through the regulation of stromelysin-1 expression (Lochter et al., 1999) and, together with the Kras oncogenic factor, potentiates tumour growth and cell motility (Macias-Perez et al., 2008).

Colorectal cancer

Note

Integrin α1β1 is up-regulated in 65% of colon adenocarcinomas compared to matched margins. Expression is found to be higher in epithelial cells and the surrounding reactive cells (Boudjadi et al., 2013).

Also, α1β1 is present in the early stages of colorectal cancer which could constitute a useful early diagnostic marker.

Hepatocellular carcinoma

Note

In a fibrotic microenvironment similar to that of hepatocellular carcinoma, α1β1 has been reported to be able to enhance cell invasion through the fibrotic matrix (Yang et al., 2003).

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