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# Gene Section
## Review

# LPAR2 (lysophosphatidic acid receptor 2)

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## Identity

**Other names:** EDG-4, EDG4, LPA-2, LPA2

**HGNC (Hugo):** LPAR2

**Location:** 19p13.11

**Note**
Found on human chromosome 19p12 (GeneBank Accession number AC002306) and mouse chromosome 8 (Contos and Chun, 2000).

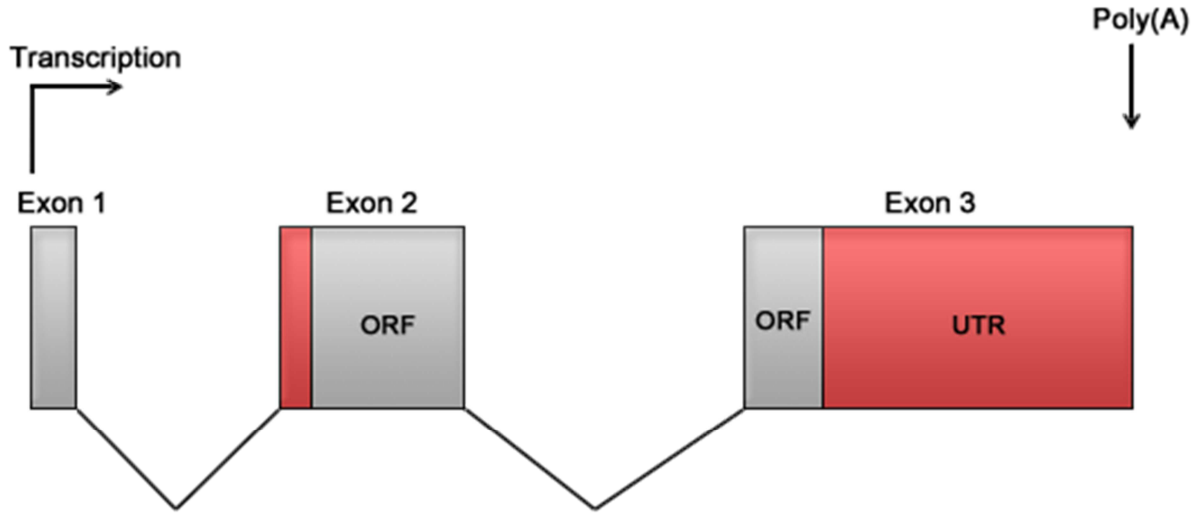
## DNA/RNA

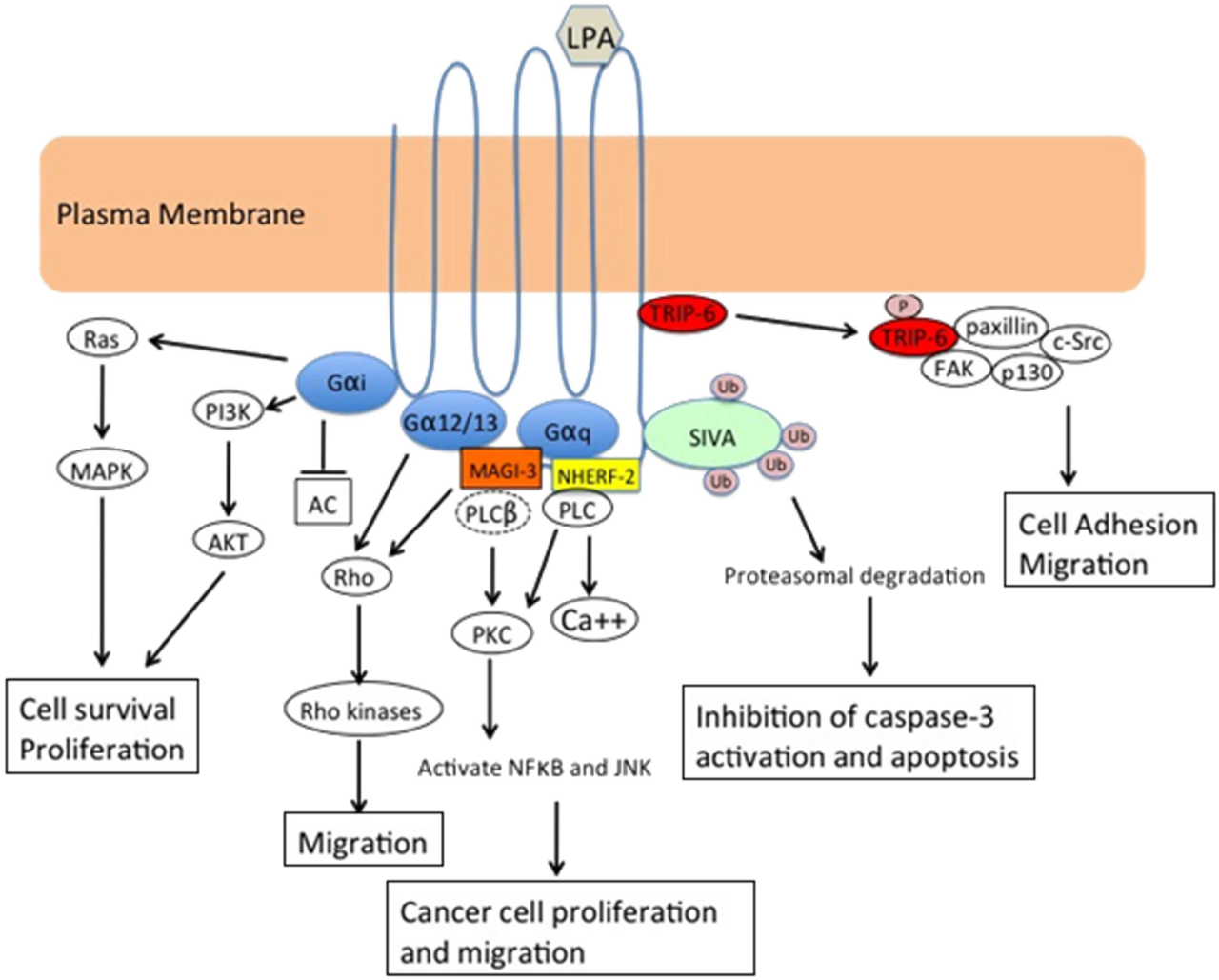
### *Description*

Both human and mouse LPA2 genes are present as a single copy and are divided among three exons with start and stop sites in the second and third exons, respectively (Contos and Chun, 2000). Introns are located upstream of the start codon and separate the coding region from the transmembrane domain VI.
As seen by Northern blot analysis, there are two transcripts sizes for both human and mouse LPA2. In human, the transcript sizes are ~1.8kb and ~10kb and in mouse the transcript sizes are ~3kb and ~7kb (An et al., 1998).

## Protein

**Note**
Human LPA2 encodes a protein with a predicted 351 amino acid residues and molecular weight of 39.1 kDa. There is 90.8% sequence homology between mouse and human LPA2 amino acid sequences and 60% amino acid similarity with LPA1. Mouse LPA2 encodes a protein with a predicted 348 amino acids and molecular weight of 38.9 kDa.






LPA2 is a G protein-coupled receptor (GPCR) that spans the plasma membrane seven times, hence having three extracellular and three intracellular loops. The C-terminus of LPA contains a di-leucine motif and several putative palmitoylated cysteine residues that associate with LIM-domain containing TRIP6 (Thyroid Hormone Receptor-Interacting Protein 6) and Siva-1 protein. LPA-dependent recruitment of TRIP6 to the plasma membrane promotes its phosphorylation and targeting to focal adhesions, and leads to cell adhesion and migration. SIVA-1 gets ubiquitinated in an LPA-dependent manner, leading to its degradation and subsequent decrease in its pro-apoptotic abilities. The last four amino acids at the C-terminus (DSTL) contain a PDZ-binding motif and interact with NHERF2 and MAGI-3. NHERF2 clusters LPA2 and PLC-β, which then signals downstream IP3-dependent Ca++ mobilization and DAG-dependent PKC activation. MAGI-3 has been shown to interact with LPA2 and regulate the activation of Erk and RhoA, leading to cell migration. MAGI-3 has also been shown to reciprocally regulate PLC-β and inhibit NHERF2-promoted tumor cell migration and invasion (Lee et al., 2011). LPA2 also couples to Gαi, Gα12/13, and Gαq, activating downstream signaling pathways that lead to cell survival, proliferation, and motility.

## Description

LPA2 is a G-protein coupled receptor (GPCR) that belongs to the endothelial differentiation gene (Edg) family of receptors. It was first identified in 1998 following a search in the GenBank for homologs to human EDG2 (LPA1) (An et al., 1998; Contos and Chun, 1998).

## Expression

LPA2 has a more restricted expression pattern than that of LPA1. More information is currently available for LPA2 mRNA expression than protein expression, and there is a current need for well-validated LPA2-specific antibodies.

Human: LPA2 mRNA is expressed in a variety of tissues including human testis, leukocytes, prostate, spleen, thymus, pancreas, and bone marrow (An et al., 1998; Fang et al., 2002). The expression of LPA2 has also been noted in freshly isolated human blood CD4+ T cells, B cells, and Jurkat T cells (Zheng et al., 2000; Goetzl et al., 2000; Rubenfeld et al., 2006) as well as monocyte-derived dendritic cells (Chen et al., 2006; Oz-Arslan et al., 2006). Interestingly, Zheng et al. reported that LPA2 expression decreases in PMA-activated CD4+ T cells, while others reported increased expression of LPA2 after T cell activation, hence future studies are needed to dissect the expression of LPA2 during the activation of T cells (Zheng et al., 2000; Rubenfeld et al., 2006). LPA2 is also expressed on the apical surface of intestinal epithelial cells (Li et al., 2005) and in the airway epithelia cells of human lung tissue (Barekzi et al., 2006). In addition, LPA2 is

expressed in epithelial cell lines: A549 and BEAS-2B (Barekzi et al., 2006). Interestingly, IL-13 and IFN-gamma reduced LPA2 mRNA levels in the A549 cell line (Barekzi et al., 2006).

In addition to its normal expression, LPA is also commonly increased in a number of human malignancies. LPA2 is aberrantly expressed in various cancer cells including ovarian cancer cell lines (Fang et al., 2000; Fang et al., 2002; Goetzl et al., 1999), the cervical cancer cell lines CaSki, HeLa, and SiHa (Chen et al., 2011), colorectal cancer (Shida et al., 2004), thyroid cancer (Schulte et al., 2001) and invasive ductal carcinoma breast cancer (Kitayama et al., 2004; Chen et al., 2007). It has been noted that LPA2 overexpression is more commonly seen in postmenopausal breast cancer patients than in premenopausal patients (Kitayama et al., 2004). It is also expressed in nasal polyp tissue from subjects with chronic hyperplastic eosinophilic sinusitis (CHES) (Barekzi et al., 2006).

In mice, LPA2 mRNA is expressed in kidney, uterus, and testis at relatively high levels, and moderately expressed in the lung. Lower levels of LPA2 are also seen in spleen, thymus, stomach, brain, and heart.

## Localisation

LPA2 is a GPCR that spans the plasma membrane seven times and contains three extracellular loops and three intracellular loops. LPA2 is unique from the other LPA receptors as it contains two distinct protein-protein interaction domains in the carboxyl-terminal tail (aa 296-351). In the proximal region, LPA2 contains a di-leucine motif and several putative palmitoylated cysteine residues. This region is responsible for associating with zinc-finger proteins, including TRIP6 (Xu et al., 2004) and the proapoptotic Siva-1 protein (Lin et al., 2007). In the distal region, there are several serine and threonine residues that can be phosphorylated by G protein-coupled receptor kinases (GRKs) and may be involved in β-arrestin binding and receptor internalization. The last four amino acids of this region (DSTL) contains a class I PDZ-binding motif and mediates interactions with a number of proteins such as Na+/H+ exchanger regulatory factor 2 (NHERF2) (Oh et al., 2004; Yun et al., 2005), PDZ-RhoGEF and LARG (Yamada et al., 2005), and MAGI-3 (Zhang et al., 2007).

## Function

LPA2 is a GPCR that couples with and activates three heterotrimeric G proteins: Gi, Gq, G12/13. These G proteins transmit signals through downstream signaling molecules that include phosphatidylinositol 3-kinase, phospholipase C, Ras, Rac, and Rho. Activation of LPA2 therefore induces a range of cellular responses including cell survival and differentiation, cell migration, and roles in cancer metastasis.

For example, LPA2 signaling is associated with cell survival and proliferation in ovarian cancer cells (Goetzl et al., 1999) and rescues intestinal epithelial cells-6 (IEC-6) from apoptosis through inhibition of caspase-3 activation (Deng et al., 2002). Likewise, LPA2 targets the pro-apoptotic Siva-1 protein for LPA-dependent ubiquitination and degradation, thereby down regulating the pro-apoptotic activity of Siva-1 during the DNA damage response (Lin et al., 2007).

LPA2 is also involved in promoting cell motility. Jurkat cells that express LPA2 were reported to have enhanced trans-Matrigel migration (Zheng et al., 2001). It has also been shown that LPA binding to LPA2 leads to the recruitment of TRIP6, a focal adhesion molecule, to the C terminus of LPA2 at the plasma membrane. This promotes its targeting to focal adhesions and co-localization with actin, thereby regulating LPA-induced cell migration (Xu et al., 2004; Lai et al., 2005). The PTPL1 phosphatase dephosphorylates TRIP6 and attenuates LPA-induced cell migration, thus acting as a negative regulator of cell motility (Lai et al., 2007). LPA2 has also been identified to be involved in regulating smooth muscle cell migration in the context of vascular injury (Panchatcharam et al., 2008).

Recently, two groups have implicated LPA2 signaling in TGF-β activation in mouse models of lung fibrosis and ischemia-reperfusion injury. These studies have shown that LPA2 signaling through Gαq in human epithelial cells and proximal tubule cells activates RhoA and Rho kinase, leading to the activation of αvβ6 integrin. This in turn, leads to the binding of latent TGF-β to αvβ6, and subsequent activation of TGF-β (Xu et al., 2009; Geng et al., 2012).

LPA2 signaling has emerged as a potential factor in many cancer pathways. There is high expression of LPA2 in human thyroid cancer (Schulte et al., 2001), colorectal cancer (Shida et al., 2004), as well as in human invasive breast ductal carcinoma (Kitayama et al., 2004). LPA2 is involved in tumor growth and tumor angiogenesis of in vivo cervical cancer cells (Chen et al., 2011; Yu et al., 2008). LPA2 mediates mitogenic signals and cytokine production in human colonic epithelial cells (Yun et al., 2005). In pancreatic cancer cells, signaling through LPA2 leads to the inhibition of EGF-induced migration and invasion (Komachi et al., 2009).

It also mediates chemotaxis in a Rho-dependent manner in breast carcinoma cells (Chen et al., 2007). In ovarian cancer cells, LPA2 signaling through Gαi/src leads to transactivation of EGFR and COX-2 expression, and increased ovarian cancer motility and aggressiveness (Jeong et al., 2008). A role for LPA2 and endometrial cancer invasion and MMP7 activation has also been shown (Mayer Hope et al., 2009).

It has been reported that homozygous knock-out $lpa2^{-/-}$ mice display no obvious phenotypic abnormalities and are born at expected frequencies (Contos et al., 2002). Zhao et al. reported that heterozygous $lpa2^{+/-}$ mice are partially protected from lung inflammation following Schistosoma egg allergen (SEA) challenge (Zhao et al., 2009). However, Emo et al. revealed that allergic lung

inflammation is significantly greater in lpa2$^{-/-}$ mice, suggesting that LPA2 plays a role in suppressing dendritic cell activation and allergic immune responses (Emo et al., 2012).

### Homology

LPA2 has ~60% homology to LPA1.

## Mutations

**Note**

The first human LPA2 cDNA clone was derived from an ovarian tumor library, however it differed from reported human LPA2 sequences (An et al., 1998). The protein product from the ovarian tumor lacks the last four amino acids (DSTL) and is 31 amino acid residues longer at the C-terminus relative to the predicted protein product. The extra amino acids are the result of a guanine nucleotide deletion in the fourth to last codon (Contos and Chun, 2000). Additionally, in two human colon cancer cell lines, DLD1 and SW48, LPA2 and LPA4 were found to contain five mutations of G/C to A/T transitions (Tsujino et al., 2010). These mutated LPA2 receptors may alter LPA2 signaling through its respective G proteins and downstream pathways, and play a role in cancer progression.

## Implicated in

### Ovarian cancer

**Note**

LPA is present at high levels in the ascites fluid of ovarian cancer patients (Mills et al., 1990; Xu et al., 1995), and LPA2 is aberrantly expressed in ovarian cancer cells, compared to normal ovarian epithelial cells (Fang et al., 2000; Fang et al., 2002). LPA2 is expressed at high levels on OV202 primary culture ovarian cancer cells, as well as in several established ovarian cancer cells lines, and is involved in promoting cancer cell proliferation (Goetzl et al., 1999). LPA can promote angiogenesis by increasing VEGF protein levels in SKOV-3, CAOV-3, and OVCAR-3 cells, which are LPA2-expressing ovarian cancer cell lines (Hu et al., 2001). Additionally, LPA2 signaling through Gαi/src leads to transactivation of EGFR and COX-2 expression, and increased ovarian cancer motility and aggressiveness (Jeong et al., 2008). Furthermore, LPA stimulates expression of IL-8 and IL-6 in ovarian cancer cell lines (Schwartz et al., 2001) and ovarian cancer patients have elevated IL-8 and IL-6 cytokine levels in serum and ascitic fluid (Ivarsson et al., 2000; Penson et al., 2000). Fang et al. demonstrated that the IL-8 gene promoter contains a fragment 133-bp upstream of the transcription initiation site that has binding sites for NF-KB/RELA and AP-1 and is responsible for responses to LPA (Fang et al., 2004). Using a lentivirus to over-express LPA2, it was also shown that LPA2 elicited the most optimal responses to LPA, compared to other LPA receptors, and that LPA2 is able to couple LPA to IL-8 and IL-6 expression in ovarian cancer cells (Fang et al., 2004).

Using an siRNA approach to knock-down LPA2 in SKOV-3 ovarian cancer cells, Wang et al. showed that the levels of LPA-induced urokinase plasminogen activator (uPA), which is a serine protease inversely correlated with prognosis in ovarian cancer, is greatly decreased. LPA2-siRNA treated cells were also less invasive and less migratory in vitro (Wang et al., 2008).

### Cervical cancer

**Note**

Three cancer cell lines (CaSki, HeLa, and SiHa) express LPA2 mRNA, however it appears that LPA2 in these cells does not play a significant role in cancer cell proliferation in vitro (Chen et al., 2012). On the other hand, cervical cancer tumor growth and angiogenesis in vivo is dependent on LPA2 and LPA3. It was found that LPA induced IL-8 production in these cell lines, and when LPA2/3 is blocked, IL-8 expression was attenuated. Using in vitro angiogenesis assays, it was shown that the LPA-induced IL-8 expression in the cervical cancer cell lines led to increased angiogenesis, in an LPA2/3 dependent manner (Chen et al., 2012).

### Colorectal cancer

**Note**

LPA2 is highly expressed at the mRNA and protein levels in human colorectal cancers (Shida et al., 2004). In CACO-2 colon cancer cells, LPA2 interacts with Na+/H+ exchanger regulatory factor 2 (NHERF2) and mediates downstream signaling such as the activation of Akt, Erk1, Erk2, and IL-8 (Yun et al., 2005). MAGI-3 has also been shown to reciprocally regulate PLC-β and inhibit NHERF2-promoted tumor cell migration and invasion (Lee et al., 2011). The importance of LPA2 in contributing to colon cancer progression was elucidated using LPA2 knock-out (LPA2$^{-/-}$) mice. These studies revealed that colon cancer was markedly diminished in LPA2$^{-/-}$ mice, with less epithelial cells proliferation, decreased MCP-1 and MIF levels, and decreased inflammatory macrophage infiltrates (Lin et al., 2009).

### Thyroid cancer

**Note**

LPA2 mRNA expression is increased in both human papillary and follicular differentiated thyroid cancer, compared to normal thyroid or goiters, suggesting its role in thyroid cancer pathogenesis (Schulte et al., 2001).

### Breast cancer

**Note**

In human invasive ductal carcinoma (breast cancer) tissue, LPA2 mRNA and protein expression are enhanced (Kitayama et al., 2004; Li et al., 2009). Interestingly, immunohistochemical analyses revealed that LPA2 is upregulated more frequently in

postmenopausal women than in premenopausal women, suggesting that the over-expression of LPA2 is associated with the progression of breast cancer in postmenopausal women (Kitayama et al., 2004).
The breast cancer cell lines BT-20, MCF-7, MDA-MB-453, and MDA-MB-468 show predominant expression of LPA2 (Chen et al., 2007). When examining the BT-20 cell line closely, it was found that LPA activates RhoA, leading to increased chemotaxis. By knocking down LPA2 with siRNA, it was confirmed that LPA2 mediates the activation of RhoA and enhanced migration, and can act cooperatively with LPA1 (Chen et al., 2007).

### Pancreatic cancer

**Note**
LPA2 inhibits the migration of invasive pancreatic cancer cells, while LPA1 stimulates migration of these cells (Komachi et al., 2009). The inhibitory migration response can be attenuated when LPA2 is knocked down using siRNA, or when LPA2 is agonized using an LPA2-specific agonist, LP-105. By blocking Gα12/13 and deactivating Rho, it has been suggested that LPA-LPA2 inhibits EGF-induced migration through the Gα12/13 and Rho-signaling pathways (Komachi et al., 2009).

### Endometrial cancer

**Note**
HEC1A endometrial cancer cells predominantly express LPA2 and its expression is increased upon LPA stimulation (Mayer Hope et al., 2009). When LPA2 is knocked down using siRNA, HEC1A cell invasion and MMP-7 and MMP-2 secretion and activation is markedly reduced, however the migration capacity of the cells is not significantly changed (Mayer Hope et al., 2009).

### Gastric cancer

**Note**
In the gastric cancer cell lines, MKN28, MKN45, MKN74, and KATO III, LPA2 mRNA is significantly expressed (Shida et al., 2004). In chemotaxis assays, LPA was not able to induce migration of MKN28 or MKN74 cells, however, when hepatocyte growth factor (HGF) was added, LPA induced dose-dependent cell migration. In addition, using immunoprecipitation analysis, it was shown that LPA induced tyrosine phosphorylation of c-Met in these cells, suggesting that LPA and HGF induce a cooperative migratory response caused by the transactivation of c-Met (Shida et al., 2004).
LPA2 is over-expressed in human gastric cancer, and is found more frequently in the intestinal type (67%) than in the diffuse type gastric cancer (32%) (Yamashita et al., 2006). However, LPA2 expression is more correlated with a higher rate of lymphatic invasion, venous invasion, and lymph node metastasis in diffuse-type gastric than in intestinal type gastric cancer (Yamashita et al., 2006).

### Allergic lung inflammation

**Note**
In a murine model of allergic airway inflammation using SEA-sensitization, Zhao et al. show that $Lpa2^{+/-}$ heterozygous mice have reduced airway inflammation and pathogenesis of asthma (Zhao et al., 2009). This suggests that LPA2 may play a critical role in the detrimental effects of the onset of asthma in this model of the disease. However, recently a novel role for LPA2 in suppressing dendritic cell activation and allergic immune responses has been reported (Emo et al., 2012). Emo et al. showed that Lpa2-deficient bone marrow-derived dendritic cells are hyperactive compared to wild-type cells in that they can stimulate greater CD4+ T cell proliferation and induce higher levels of IL-13 secretion from T cells in co-culture.
In a model of allergic airway inflammation, Lpa2-deficient mice succumbed to greater allergic lung inflammation, as seen by higher BAL cell counts, increased eosinophilia, increased airway hyperresponsiveness, and greater serum IgE levels. These data suggest that LPA2 may be acting as an inhibitory receptor to possibly dampen innate immune responses, particularly in this model of allergic airway inflammation.

**Disease**
Asthma.

### Fibrosis

**Note**
TGF-β has known roles in the pathogenesis of lung inflammation and fibrosis. In models of bleomycin-induced lung injury and renal ischemia-reperfusion injury, LPA2 signaling through Gαq activates αvβ6 integrin through a Rho and Rho-kinase dependent mechanism. Activated αvβ6 can bind to latent TGF-β, leading to its activation (Xu et al., 2009; Geng et al., 2012).

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