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ALCAM:

Basis Sequence: Mouse

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Protein Function

ALCAM functions as a cell–cell adhesion molecule and engages in homotypic (ALCAM–ALCAM) and heterotypic (ALCAM–CD6) interactions between adjacent cells. These interactions are mediated through its most amino-terminal V domain (D1). In ALCAM-ALCAM interactions this seems to be a D1–D1 interaction (Tanaka *et al*. 1991; van Kempen *et al*. 2001), while in ALCAM–CD6 interactions the ALCAM D1 domain binds to the membrane-proximal scavenger receptor cysteine rich (SRCR) domain of CD6 (Bowen *et al*. 1996). ALCAM is also capable of oligomerizing through lateral interactions between adjacent ALCAM molecules in the same cell. These interactions occur through the D3–D5 domains proximal to the membrane (van Kempen *et al*. 2001). ALCAM expression is most apparent at areas of cell–cell contact, where it may interact with other cell–cell adhesion molecules. In fact, upon reconstitution of the α-catenin/E-cadherin complex by α-N-catenin transfection, ALCAM relocalizes to the cell membrane and co-localizes with E-cadherin at the cell membrane in prostate cancer cells. In addition, these cells reverted to an epithelial-like morphology (Tomita *et al*. 2000) further defining a functional role for ALCAM in cell–cell adhesion. The amino-terminal V-type Ig domain is required for cell–cell adhesive interactions and is, in fact, expressed as an isolated, alternatively spliced isoform (Ikeda and Quertermous 2004).

While the participation of ALCAM in several biological processes has been verified, the exact molecular mechanism remains unclear. The highly conserved nature of the short cytoplasmic domain suggests that ALCAM functions, in part, by conveying extracellular signals to the cytoplasm. Although named primarily for its role in leukocytes, ALCAM exhibits broad expression including neuronal tissues, epithelial cells, and hematopoietic progenitor cells. In spite of the participation of ALCAM in many biological processes, ALCAM knockout mice are viable, fertile and have no outward visible defects. A full analysis of the literature requires consideration of all its alternate names, including CD166, MEMD, SC-1, BEN, GRASP, DM-GRASP, HCA, and SB-10.

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ALCAM in hematopoietic cells

ALCAM received this name when it was identified in activated leukocytes as the only known ligand for CD6 (Bowen *et al*. 1995), and the ALCAM–CD6 interaction is required for optimal activation of T-cells (Gimferrer *et al*. 2004; Hassan *et al*. 2006; Singer *et al*. 1996; Zimmerman *et al*. 2006). Moreover, ALCAM plays a critical role in mediating the transmigration of T-cells and monocytes across the blood–brain barrier (Cayrol *et al*. 2008; Lee and Imhof 2008). Through its heterotypic interaction with CD6, ALCAM seems to be important for formation of the immunological synapse at the T-cell:antigen-presenting cell (APC) interface during antigen presentation (Castro *et al*. 2007). In fact, optimal T-cell activation requires CD6–ALCAM engagement (Hassan *et al*. 2004; Hassan *et al*. 2006). Moreover, unlike other adhesion molecules in the immunological synapse, ALCAM is required for the whole process of T-cell activation (Zimmerman *et al*. 2006).

ALCAM in development

ALCAM is expressed in human blastocysts, but not in embryos at the 8-cell or morula stages. ALCAM expression reappears in most developing tissues (Diekmann and Stuermer 2009; Fraboulet *et al*. 2000; Hirata *et al*. 2006; Pourquié *et al*. 1992). Nevertheless, the adhesive role of ALCAM is apparent in development, where the loss of ALCAM function results in loss of cell adhesion and cardiac morphogenesis in the *Xenopus* model system (Gessert *et al*. 2008). ALCAM functions in hematopoietic and endothelial development and is highly associated with hematopoiesis and vasculogenesis (Ohneda *et al*. 2001). Neuronal outgrowth studies in chick and zebra fish further define ALCAM as a guidance protein for cellular migration and neuronal outgrowth during development (Diekmann and Stuermer 2009; Heffron and Golden 2000; Ott *et al*. 2001).

ALCAM in multipotent and stem cells

Although ALCAM was initially used to delineate hematopoietic stem cells (Ohneda *et al*. 2001), the molecule has been used broadly as a surface marker (under the name CD166) in a panel of markers (including CD44, CD90, CD105, CD73, CD29 and CD133) to define multipotent cells from a variety of tissues, including umbilical cord blood (Prat-Vidal *et al*. 2007), bone marrow (Liu *et al*. 2008), testes (Gonzalez *et al*. 2009), fetal lung (Hua *et al*. 2009), intervertebral disc (Risbud *et al*. 2007), and dental pulp (Karaöz *et al*. 2010). More recently, the expression of CD166 as a marker of cancer stem cells has become of significant interest (Dalerba *et al*. 2007; Horst *et al*. 2009; Stuelten *et al*. 2010). While ALCAM is clearly a defining feature of stem cells, it is unclear if there is a functional contribution to the multipotent capacity of these cells.

ALCAM in the neural network

The abundance of ALCAM in neuronal tissue is reflected in its sequential discovery in neurons and related tissues from various species as DM-GRASP (Burns *et al*. 1991), SC-1 (Tanaka *et al*. 1991), neurolin (Paschke *et al*. 1992), and BEN (Corbel *et al*. 1992). ALCAM controls the extension of axons (Avci *et al*. 2004; DeBernardo and Chang 1995; Ott *et al*. 2001; Pollerberg and Mack 1994) and is involved in axonal guidance and mapping (Buhusi *et al*. 2009; Ott *et al*. 1998). While ALCAM knockout mice are outwardly normal in

appearance, they do have physiological deficiencies, including a delay in maturation of neuromuscular junctions and defects in axon fasciculation (Buhusi *et al*. 2009; Weiner *et al*. 2004). ALCAM-blocking antibodies induce aberrant branching in zebra fish motor axons during development (Ott *et al*. 2001). During *in vitro* experiments axon outgrowth can be guided by ALCAM-coated surfaces, thereby providing conclusive evidence of ALCAM as a migration-guiding factor (Avci *et al*. 2004; DeBernardo and Chang 1995).

ALCAM in cancer

Cancer-associated ALCAM was first identified as MEMD in melanoma cell lines (Degen *et al*. 1998). ALCAM has subsequently been found to be expressed in almost all cancers, although it is distinctly absent in myeloma. Although the pathological function of ALCAM is not fully understood, *in vivo* mouse studies demonstrate its participation in cancer progression (Choi *et al*. 2000; Lunter *et al*. 2005; van Kempen *et al*. 2004). Truncation of ALCAM can be achieved by ADAM17 and may facilitate migration (Rosso *et al*. 2007). Indeed the upregulation of truncated ALCAM that lacks the D1 domain (ΔN-ALCAM) promotes metastasis, while the ectopic expression of soluble amino-terminal D1 (V) domain inhibits metastasis (Lunter *et al*. 2005; van Kilsdonk *et al*. 2008). The distinct upregulation of ALCAM in some cancers but downregulation in others has created a paradox in terms of its contribution to cancer progression (Ofori-Acquah and King 2008). Histological analysis has emphasized that the cytoplasmic localization of ALCAM correlates more strongly with cancer progression than the overall expression level (Kahlert *et al*. 2009; Sawhney *et al*. 2009; Mezzanzanica *et al*. 2008; Burkhardt *et al*. 2006). Although somewhat contradictory, recent research using blocking antibodies confirms that the presence of ALCAM can contribute to the metastatic process (Wiiger *et al*. 2010; Kahlert *et al*. 2009), while expression analysis illustrates that the absence of ALCAM can convey resistance to treatment (Ihnen *et al*. 2010). It is likely that the role of ALCAM in cancer depends on the tissue from which the tumor developed.

ALCAM expression has been used increasingly as a biomarker of cancer progression in prostate cancer (Kristiansen *et al*. 2005), colorectal cancer (Weichert *et al*. 2004), breast cancer (Davies and Jiang 2010; Davies *et al*. 2008; Ihnen *et al*. 2010), oral cancers (Sawhney *et al*. 2009; van den Brand *et al*. 2010), pancreatic cancer (Kahlert *et al*. 2009), neuroblastoma (Corrias *et al*. 2010), ovarian cancer (Mezzanzanica *et al*. 2008), and melanoma (van Kempen *et al*. 2000). Serum levels of ALCAM are also explored as a diagnostic tool for cancer (Hong *et al*. 2010; Kulasingam *et al*. 2009; Vaisocherová *et al*. 2009).

ALCAM in the bone marrow

ALCAM was defined initially as a hematopoietic cell antigen present in bone marrow (Bruder *et al*. 1997; Uchida *et al*. 1997). Indeed, ALCAM is a surface marker of the earliest hematopoietic precursor populations, the mesenchymal stem cells, and stromal cell populations present in the bone (Bruder *et al*. 1998; Cortés *et al*. 1999; Nakamura *et al*. 2010). Along with CD90 and CD105, ALCAM defines a multipotent progenitor cell population capable of chondrogenic, osteogenic and adipogenic differentiation (Choi *et al*. 2008; Delorme and Charbord 2007; Stewart *et al*. 2003). Early observations by Bruder *et al*.

indicated a functional role for ALCAM in the bone marrow. They determined that anti-ALCAM fragment, antigen binding (Fab) fragments promote osteogenic differentiation (Bruder *et al*. 1998). Indeed ALCAM delineates subpopulations of the endosteal niche, where its expression defines populations of mature osteoblasts and mesenchymal stem cells (Arai *et al*. 2002; Chitteti *et al*. 2010; Nakamura *et al*. 2010). In particular, Chitteti *et al*. defined mature osteoblasts specifically as $CD45^{-}CD31^{-}Ter119^{-}Sca1^{-}ALCAM^{+}$ (Chitteti *et al*. 2010).

Regulation of Activity

Since cell–cell adhesion is the primary activity of ALCAM, this can be regulated by its availability and ability to bind to proximal partners. ALCAM is dysregulated in a number of cancers, including, but not limited to, melanoma, colorectal, breast and prostate. Immunohistochemical analysis showed that ALCAM was overexpressed in low-grade carcinoma. However, in some high grade carcinomas ALCAM was either localized to the cytoplasm or lost altogether (Burkhardt *et al*. 2006; Kristiansen *et al*. 2003; Mezzanzanica *et al*. 2008; Zheng *et al*. 2004). Although there is differential ALCAM expression in cancer, the mechanism by which it is regulated is unknown.

At the subcellular level, cytoskeleton disruption via chemical treatment in erythroleukemic K562 cells with cytochalasin D promotes lateral movement of ALCAM and promotes ALCAM-mediated adhesion regulated through cytoskeleton-dependent clustering (Nelissen *et al*. 2000), suggesting ALCAM clustering is necessary to form stable cell adhesion complexes (van Kempen *et al*. 2001; van Kilsdonk *et al*. 2008).

ALCAM can be shed from the cell surface. Currently ADAM17, a member of the disintegrin and metalloproteinase family, is the only known protease able to cleave ALCAM (Bech-Serra *et al*. 2006). Cleavage of ALCAM is thought to occur at the membrane proximal region, generating a soluble ALCAM component containing the five extracellular domains and a truncated membrane-bound ALCAM containing the transmembrane and cytoplasmic domains. Lastly, the expression of the soluble D1 domain (sALCAM, the most amino-terminal V domain) (Ikeda and Quertermous 2004) could potentially disrupt the interaction between full-length membrane-anchored ALCAM molecules (van Kilsdonk *et al*. 2008).

Interactions with Ligands and Other Proteins

In addition to the well established homophilic interactions, ALCAM was identified as the only known ligand for CD6, a member of the SRCR protein superfamily (Bowen *et al*. 1995; van Kempen *et al*. 2001). In contrast with the relatively weak and transient homophilic ALCAM–ALCAM interactions, ALCAM–CD6 interactions are robust and persistent (Hassan *et al*. 2004; Te Riet *et al*. 2007). These interactions are thought to be important for T-cell proliferation and maturation (Zimmerman *et al*. 2006). In both instances it is the amino-terminal V domain that is engaged in the protein–protein interactions. For neuronal guidance, ALCAM has been suggested to interact with L1CAM (L1-cellular adhesion molecule, also known by the chick homolog NgCAM). This interaction seems to target

retinal axons during development (Avci *et al*. 2004; Buhusi *et al*. 2009; DeBernardo and Chang 1996).

ALCAM co-localizes with E-cadherin through an α-catenin-dependent process, although no direct interaction has been confirmed (Tomita *et al*. 2000). ALCAM also requires active protein kinase C α (PKC-α) for ALCAM-mediated cell adhesion. However, no physical association between these proteins has been confirmed (Zimmerman *et al*. 2004). Association with the actin cytoskeleton is confirmed and regulates ALCAM clustering. The interactions that connect ALCAM to the cytoskeleton are unknown (Nelissen *et al*. 2000; Te Riet *et al*. 2007), although preliminary findings from Sawhney *et al*. (2009) suggest the scaffolding proteins 14-3-3ζ and 14-3-3σ may be involved.

The cytoplasmic tail has only been documented to interact with ubiquitin. Ubiquitination seems to control ALCAM endocytosis and thereby affect its role in axon navigation (Thelen *et al*. 2008).

ALCAM was also shown to interact with EGFR (Wu *et al*. 2006); however, this observation was made in an epidermoid carcinoma cell line (A431) and has not been confirmed elsewhere.

Recently, ALCAM was shown to specifically bind galectin-8 sequestered in the extracellular matrix (Cárdenas Delgado *et al*. 2010). This interaction influenced endothelial cell migration and tubule morphogenesis. Anti-ALCAM antibody studies suggest that this interaction involves the same domain that is required for homotypic ALCAM–ALCAM, as well as CD6, binding.

Regulation of Concentration

ALCAM concentrations in the cell can be regulated by expression, endocytosis, and shedding from the cell surface. No defined studies have been found that define ALCAM expression and the regulation of its promoter. ALCAM endocytosis seems to be regulated by ubiquitination (Thelen *et al*. 2008). Shedding of the molecule is possible through ADAM17 (Rosso *et al*. 2007).

Subcellular Localization

On the cell surface in the blood–brain barrier endothelium, ALCAM is concentrated in cholesterol-enriched microdomains, or lipid rafts (Cayrol *et al*. 2008). In highly specialized lung microvascular endothelial cells, ALCAM is localized to the adherence junctions, and participates in a complex containing vascular endothelial (VE) cadherin and neural (N) cadherin (Ofori-Acquah and King 2008). ALCAM is continuously recycled through endocytic pathways and is readily detectable in early endosomes. On the cell surface, ALCAM co-localizes with clathrin, but not caveolin-1 (Piazza *et al*. 2005). In several neoplasia, ALCAM overexpression is associated with diffuse cytoplasmic staining (Burkhardt *et al*. 2006; Sawhney *et al*. 2009; Weichert *et al*. 2004).

Major Sites of Expression

ALCAM is expressed in most epithelial cells, hematopoietic cell populations (particularly activated T-cells), the central nervous system, endothelial cells, and most stem cell populations.

Phenotypes

ALCAM knockout mice have been generated. These mice exhibit no defects in fertility, nor any outward physiological defects, and have normal organ development and a normal lifespan (Weiner *et al*. 2004). However, upon detailed analysis, an axon fasciculation defect and a neuromuscular synapse defect have been identified (Buhusi *et al*. 2009). It seems that ALCAM is required for targeting retinal axons to their termination zones in two brain targets: the superior colliculus and the lateral geniculate nucleus (Buhusi *et al*. 2009).

Splice Variants

Currently, soluble ALCAM (sALCAM, the most amino-terminal V domain) is the only known isoform (Ikeda and Quertermous 2004).

Antibodies

The ALCAM antibodies AZN-L50 (Nelissen *et al*. 2000) and A8 (Buckley *et al*. 2005) were reported.

The anti-ALCAM antibody HPA010926 was also characterized by the Human Protein Atlas project and is available through Sigma (US) or Atlas Antibodies (Europe).

Other defined antibodies that are commercially available with their application are listed below:

R&D Systems anti-ALCAM (Clone 105902)

Mouse Monoclonal Biotin-Conjugated, Human

Western blot, Flow Cytometry

LifeSpan Biosciences anti-CD166 (3A6)

Mouse Monoclonal

LifeSpan Biosciences anti-CD166 (7H119)

Mouse Monoclonal (Biotin), Human

Immunohistochemistry (IHC)

Santa Cruz Biotechnology, anti-ALCAM (3H1929)

Mouse Monoclonal, Human

Flow Cytometry

Santa Cruz Biotechnology anti-ALCAM (6A66)

Mouse Monoclonal, Human/rat

Immunoprecipitation (IP), Immunocytochemistry

Millipore, anti-CD166 (Clone 3A6)

Mouse Monoclonal, Human

IP, IHC, Flow Cytometry, Enzyme-linked immunosorbent assay

Vector Lab. Cat. No. VP-C375

Mouse Monoclonal (clone MOG/07)

Western blot, IHC

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