Literature search

CADH5 (VE-cadherin)

Physiological functions:

- VE-cadherin is specifically expressed in endothelial cells [1].
- CDH5 is a cell membrane glycoprotein found at adherens junctions where it acts as an adhesion receptor between non-proliferative endothelial cells [2].
- VE-cadherin plays a pivotal role in the control of vascular integrity and permeability, and contributes to endothelial cell assembly in tubular structures [3].

CADH5 in cancer:

- VE-cadherin expression was observed at the cell surface of cancer cells that had undergone EMT and had down-regulated E-cadherin [4]. (**VE-cadherin is an EMT marker**)
- VE-cadherin **regulates activity of the high affinity receptors**: the vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β and fibroblast growth factor (FGF) [4].
- Functional analyses revealed that VE-cadherin expression in a mouse mammary carcinoma model could promote tumor cell proliferation and invasion **by stimulating TGF-β signaling** [3]
- Correlation between CADH5 and **tumour aggressiveness**
    - Implicated in aggressive breast cancer [3].
    - VE-cadherin was exclusively expressed by highly aggressive melanoma cells and was undetectable in the poorly aggressive tumor cells. Down-regulation of VE-cadherin expression in the aggressive melanoma cells abrogated their ability to form vasculogenic networks [5]

Possible roles of CADH5 in cancer:

- Tumour angiogenesis
- Regulation of the TGFbeta pathway

Integrin beta 4 (ITGB4)

Physiological functions:

- Integrin α6β4 is an essential component of the hemidesmosome that provides stable adhesion of basal epithelial cells to the underlying basement membrane

ITGB4 in cancer:

- Association of integrin α6β4 with laminin substrates significantly promotes cancer cell **adhesion, migration, invasion, proliferation, and tumorigenesis** through the activation of Rac1, PKC, PI3K, and ERK signaling pathways [6]
- During cancer progression, integrin α6β4 is released form hemidesmosomes and the number of hemidesmosomes is decreased, which facilitates the cancer cell migration and invasion. Serine phosphorylation of integrin β4 cytoplasmic domain by PKC induces **relocation of integrin α6β4 from hemidesmosomes to cell protrusion**s in cancer cells [6].
- A cDNA microarray analysis using clinical samples of pancreatic ductal adenocarcinoma revealed that high levels of integrin β4 expression were significantly **correlated with the hallmarks of EMT** [6].
- Overexpression of integrin β4 promoted **cell motility** of pancreatic ductal adenocarcinoma cell lines [6].

References:

1. Lampugnani, M.G., et al., *A novel endothelial-specific membrane protein is a marker of cell-cell contacts.* J Cell Biol, 1992. **118**(6): p. 1511-22.
2. Giannotta, M., M. Trani, and E. Dejana, *VE-cadherin and endothelial adherens junctions: active guardians of vascular integrity.* Dev Cell, 2013. **26**(5): p. 441-54.
3. Labelle, M., et al., *Vascular endothelial cadherin promotes breast cancer progression via transforming growth factor beta signaling.* Cancer Res, 2008. **68**(5): p. 1388-97.
4. Breier, G., M. Grosser, and M. Rezaei, *Endothelial cadherins in cancer.* Cell Tissue Res, 2014. **355**(3): p. 523-7.
5. Hendrix, M.J., et al., *Expression and functional significance of VE-cadherin in aggressive human melanoma cells: role in vasculogenic mimicry.* Proc Natl Acad Sci U S A, 2001. **98**(14): p. 8018-23.
6. Kariya, Y., Y. Kariya, and J. Gu, *Roles of Integrin alpha6beta4 Glycosylation in Cancer.* Cancers (Basel), 2017. **9**(7).