CEACAMs protein and Multiple Myeloma Tumorigenesis

Achinthyaa Kaveri, Grade 12, William Lyon Mackenzie Collegiate Institute, Sun Life Gene Medical Science Institute Cancer Research Program student, Toronto, Ontario, Canada

Abstract:

Multiple myeloma, a cancer of plasma cells, is found in the bone marrow. Plasma cells, a type of white blood cells, make antibodies which are also known as immunoglobulins and they help the body fight infections. Due to the buildup of multiple myeloma cells, other blood cells' development and function are hindered. This may cause anemia and fatigueness, due to the reduction of red blood cells. Myeloma proliferation can also upset the balance of the body's minerals and cause the cells to make substances leading to bone damages; it also presents high calcium levels in the blood. Myeloma cancer cells produce a huge amount of Monoclonal (M) protein (an antibody) whose accumulation can affect the function of kidneys and other organs, leading to complications of multiple myeloma. CEACAMs, particularly CEACAM1 and CEACAM6, have been implicated in immune evasion mechanisms in myeloma cells by inhibiting CD8 T cell reactivation. While CEACAM proteins are involved in the immune microenvironment and play a role in colorectal, lung, and pancreatic cancer, their involvement in multiple myeloma is an area to discover further. Here we review the role of CEACAMs protein in multiple myeloma development.

Key Words: CEACAMs, Multiple Myeloma, Phagocytosis, Immune Microenvironment, Tumorigenesis

Introduction:

Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) belong to a group of mammalian immunoglobulin-related glycoproteins. They are from the CEA protein family which include CEACAMs and pregnancy-specific glycoproteins (PSGs) Paxton et al. 1987; Zhou et al. 2001ref). Belonging to the Ig superfamily proteins. In humans, the CEA family has 35 genes and 21 of those are protein coding. These genes are in contiguous clusters located in chromosome 19 in the 19q13.2 to 19q13.4 in humans (Hammarstrom 1999). The CEACAM family includes 12 human and 5 murine members. These proteins are involved in many biological processes like immune response, blood vessel formation, and cancer.

CEACAMs genes are found in many types of cells: epithelial, endothelial, leukocytes, and dendritic. PSGs however are expressed only in placental trophoblasts (Hammarstrom 1999). CEACAMs are either inserted into cell membranes through a transmembrane domain or linked to the membrane through a semi penetrating glycosylphosphatidylinositol anchorage (Naghibalhossaini et al. 2007) **;** this anchorage has only been detected in primates. The membrane bound CEAMCAMs have a C-terminal domain with cytoplasm that has motifs and signal transduction.(Hammarstrom 1999).

Initially known as a biomarker for colorectal cancer, CEACAMs now are associated with many intracellular signalling processes. CEACAM-1,5,6,19 have been studied for their roles in various cancers with CAR-T targets. CEACAM3 plays an important role in opsonin-independent phagocytosis and bacterial clearance, CEACAM4 is part of the CEACAM protein family, it is a granulocyte orphan receptor, plays a critical role in trigger efficient phagocytosis of attached particles. CEACAM4 also plays a role in the development and onset of cancer. It is found only in myeloid cells, although its exact function remains unclear. CEACAM-16 is linked to autosomal dominant nonsyndromic deafness (ADNSHL). CEACAM family genes can bind to each other.

CEA family members have various physiological and pathological functions(Obrink 1997; Kuespert et al. 2006). CEACAMs play an important role in embryonic development; cell-cell adhesion is important to integrate cells into functional organs(Kuespert et al. 2006). CEACAM group members are also receptors of some bacterial and viral pathogens (Murine hepatitis virus, Haemophilus influenzae, etc) that bind CEACAM proteins through their N-terminals in the IgV-like domain(Bos et al. 1999; Virji et al. 1999, 2000; Villullas et al. 2007). During pregnancy, fetal trophoblasts secrete PSGs that regulate the maternal and fetal interactions (Hau et al. 1985; Ha et al. 2010). Human CEA, also known as CEACAM5, was discovered by Gold and Freedman in the mid of 1965 in the blood of colon cancer patients. Thus, CEACAM5 is an important biomarker in early diagnosis of colon cancer and other cancers(Gaglia et al. 1988; Ballesta et al. 1995). CEACAMs can influence cancer cell survival pathways, such as PI3K/AKT and MAPK, which are crucial in multiple myeloma.

CEACAMs in Multiple Myeloma:

Researchers discover that freshly isolated myeloma cells express CEACAM1 and CEACAM6 on their surface (Mathias Witzens-Harig et al 2008,2013) CEACAM-6 helps stop T-cells from attacking multiple myeloma. Blocking CEACAM 6 molecules on myeloma cells, results in T cell reactivation, and shows the CD8 T cells triggered a strong immune response against myeloma cells in the co culture system. Though when CEACAM1 and CEACAM6 were active, that immune response didn't occur even though memory T cells which were capable of recognizing myeloma antigens were present. The findings suggest that CEACAMs help myeloma cells evade the immune system by playing a role in the suppression of activation of tumor specific CD8 T cells.

CEACAMs 1, 6, and 8 were overexpressed in up to 20% of the patients but not in healthy plasma cell donors. Protein analysis showed that CEACAM 1 and 6 on 25-50% of myeloma cells across 7 patients and on the MM8226 cell line. Blocking CEACAMs on myeloma cells before co-culture with autologous CD8 T cells triggered strong T cell responses in all tested patients (N=6), whereas no response occurred when T cells had the ability to respond to myeloma cells that were unblocked **(**Mathias Witzens-Harig et al 2013).

In some multiple myeloma patients, the tumor marker carcinoembryonic antigen (CEA) is produced. Serum CEA levels are linked to disease activity and IgA levels.

Discussion & Conclusion:

Although CEACAM4's role in cancer biology is underexplored, its involvement in immune processes and potential contributions to tumor progression in multiple myeloma are evident. Targeting CEACAM family members, including CEACAM 4,6 in immunotherapies could enhance the immune system's ability to recognize and attack myeloma cells. Further research is needed to elucidate its functions and therapeutic potentials. CEACAMs play a key role in contributions to tumor progression in multiple myeloma. Exploring CEACAMs functions may offer new insights into therapeutic strategies for treating multiple myeloma and other types of cancer.

References:

1. Mathias Witzens-Harig, Dirk Hose, Michael Hundemer, Simone Jünger, Anthony D. Ho, Jean François Rossi, Kai Neben, Bernard Klein, Hartmut Goldschmidt, Philipp Beckhove, Carcinoembryonic-Antigen-Related Cell Adhesion Molecule (CEACAM) Expression on Multiple Myelomas Inhibits Their Recognition by Autologous Memory CD8 T Cells, Blood, Volume 112, Issue 11, 2008, Page 738, ISSN 0006-4971,

2. Mathias Witzens-Harig, Dirk Hose, Simone Jünger, Christina Pfirschke, Nisit Khandelwal, Ludmila Umansky, Anja Seckinger, Heinke Conrad, Bettina Brackertz, Thierry Rème, Brigitte Gueckel, Tobias Meißner, Michael Hundemer, Anthony D. Ho, Jean-Francois Rossi, Kai Neben, Helga Bernhard, Hartmut Goldschmidt, Bernard Klein, Philipp Beckhove; Tumor cells in multiple myeloma patients inhibit myeloma-reactive T cells through carcinoembryonic
3. Delgado Tasco´n, J., Adrian, J., Kopp, K., Scholz, P., Tschan, M.P., Kuespert, K. and Hauck, C.R. (2015), The granulocyte orphan receptor CEACAM4 is able to trigger phagocytosis of bacteria. Journal of Leukocyte Biology, 97: 521-531
4. Huang, YH., Yoon, C.H., Gandhi, A. *et al.* High-dimensional mapping of human CEACAM1 expression on immune cells and association with melanoma drug resistance. *Commun Med* 4, 128 (2024).
5. Kuespert K, Pils S, Hauck CR. CEACAMs: their role in physiology and pathophysiology. Curr Opin Cell Biol. 2006 Oct;18(5):565-71. doi: 10.1016/j.ceb.2006.08.008. Epub 2006 Aug 17. PMID: 16919437; PMCID: PMC7127089.
6. Villullas S, Hill DJ, Sessions RB, Rea J, Virji M. Mutational analysis of human CEACAM1: the potential of receptor polymorphism in increasing host susceptibility to bacterial infection. Cell Microbiol. 2007 Feb;9(2):329-46. doi: 10.1111/j.1462-5822.2006.00789.x. Epub 2006 Aug 31. PMID: 16953805; PMCID: PMC1859983.
7. Moore T, Dveksler GS. Pregnancy-specific glycoproteins: complex gene families regulating maternal-fetal interactions. Int J Dev Biol. 2014;58(2-4):273-80. doi: 10.1387/ijdb.130329gd. PMID: 25023693.
8. Thomas J, Klebanov A, John S, Miller LS, Vegesna A, Amdur RL, Bhowmick K, Mishra L. CEACAMS 1, 5, and 6 in disease and cancer: interactions with pathogens. Genes Cancer. 2023 Feb 1;14:12-29. doi: 10.18632/genesandcancer.230. PMID: 36741860; PMCID: PMC9891707.
9. antigen-related cell adhesion molecule-6. *Blood* 2013; 121 (22): 4493–4503. doi: https://doi.org/10.1182/blood-2012-05-429415
   Ru-xue Ma, Jian-rui Wei, Yan-wei Hu; Characteristics of Carcinoembryonic Antigen-Related Cell Adhesion Molecules and Their Relationship to Cancer. *Mol Cancer Ther* 1 July 2024; 23 (7): 939–948. https://doi.org/10.1158/1535-7163.MCT-23-0461