

# The Participation of Cell Adhesion Molecules in Cancer Progression: A Recent Review

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## Abstract

Cell Adhesion Molecules (CAMs) are proteins found on the surface of the cell and are responsible for binding to components of the extra cellular matrix or to receptors on other cells. CAMs are highly essential for cell proliferation, and differentiation, as well as migration. There are four important families of CAMs, namely Integrins, Cadherins, Selectins and the Immunoglobulin Super family (IgSF). Integrins are involved in the metastasis of cancer cells and angiogenesis. Selectins are vital to inflammation and the progression of cancer. Cadherins play a prominent role in tumor growth. Members of the IgSF are involved in the inflammation process. CAMs play critical roles in the progression of cancer. Novel approaches can be developed using a combination of cytotoxic and Heparin-based drugs to treat malignant tumors.

**Keywords:** Cell Adhesion Molecules, Integrins, Selectins, Cadherins, Immunoglobulin Superfamily, Metastasis

## 1. Introduction

Cell adhesion molecules (CAMs) are proteins found on the cell surface which are responsible for binding to components of the extra cellular matrix or to receptors on other cells. These proteins are highly essential for cell proliferation, migration and differentiation. There are four important CAM families, namely Integrins, Cadherins, Selectins and the Immunoglobulin Superfamily (IgSF). Defects in CAM structure disrupt cell-cell and cell-matrix interactions, thus affecting the cell's advancement through normal check points, facilitating metastasis and tumor formation (Johnson, 1999). Metastasis is the transformation of a normal cell to cancerous cells, and can be caused by "genotypic stress, tissue hypoxia, nutrient depletion and loss of adhesion" (Gupta & Massagué, 2006).

### 1.1 E-Cadherins may induce in Tumor Growth and Metastasis

Cadherins are Ca<sup>++</sup> dependent adhesion molecules (Lodish, et al., 2003). They are major cell-cell adhesion molecules in tumors as well as in normal tissues. A sudden change of Cadherin function may cause temporal or permanent disaggregation of tumor cells and thus promote the invasion and metastasis of such cells. In particular, E-Cadherin has been identified as a tumor suppressor gene which when mutated may also relay tumor- and metastasis-inducing signals to the cells (Christofori & Semb, 1999). Because E-Cadherin promotes adhesion and development of normal epithelial architecture and phenotype, its down-regulation in cancer cells is linked to an increase in motility, invasiveness, and overall metastasis. E-Cadherin also interacts with epidermal growth factor (EGF) receptor to suppress receptor tyrosine kinase signaling, which regulates cell proliferation (Andrews, Kim, & Hens, 2012).

### 1.2 Selectin are involved in Inflammation and Progression of Cancer

Selectins are vascular CAMs which act as adhesives in interactions between platelets, endothelium and leucocytes during blood circulation (Cotran & Kumar, 1994). There are three subsets of Selectins namely P-Selectin, L-Selectin, and E-Selectin (Ulbrich, Eriksson, & Lindbom, 2003). P-Selectin the largest molecule and is stored in  $\alpha$ -granules, the storage granules of platelets and in Weibel-Palade bodies of endothelial cells. It is translocated to the cell surface of activated endothelial cells and platelets (Borsig, Wong, Hynes, Vark, & Vark, 2002). E-Selectin requires de novo transcription and is not expressed under baseline conditions but is rapidly induced by inflammatory cytokines. P-Selectins and E-Selectins support 'rolling' at lower velocities (Ley, Laudanna, Cybulsky, & Nourshargh, 2007). Metastasis is initiated when malignant cells enter the blood stream by penetrating the tissue surrounding the primary tumor. The rapid expression of P-Selectin on cell surfaces of endothelial cells and platelets upon activation makes P-Selectin a likely candidate involved in the metastatic process and its deficiency attenuates tumor growth and metastasis (Borsig, Wong, Hynes, Vark, & Vark, 2002) (Zhang, et al., 2002). Tumor cells can invade distant sites by taking over Selectin-dependent 'rolling' and cell tethering interactions by recognition of carbohydrate ligands (Barthel, Gavino, Descheny, & Dimitroff, 2007) (Hill, 2012) thus showing 'leukocyte mimicry' (Witz, 2006).

### 1.3 Integrins play an active role in Metastasis and Angiogenesis

Integrins are membrane proteins with functions in cell signaling and cell-matrix adhesion (Lodish, et al., 2003). They are heterodimeric, made of various types of  $\alpha$ -chains and  $\beta$ -chains. At least 24 types of Integrins have been identified in vertebrates (Lodish, et al., 2003). Integrins have been shown to participate in tumor metastasis (Desgrosellier & Cheresh, 2010) (Bendas & Borsig, 2012). The expression of  $\alpha v \beta 3$ ,  $\alpha v \beta 5$ ,  $\alpha 5 \beta 1$  and  $\alpha 5 \beta 6$  on tumor cells has been correlated with metastasis in skin, breast, lung, prostate, and pancreatic cancer (Desgrosellier & Cheresh, 2010). Integrins are possibly involved in angiogenesis, tumor cell seeding and establishment of tumor cells in the site of metastasis. For example, for a tumor which spreads through the hematogenous route, a tumor cell from the primary tumor interacts with Integrin  $\alpha IIb \beta 3$  found on platelets (Bendas & Borsig, 2012). The ability of Integrins to form interactions with a diverse range of extracellular matrix components like fibronectin, osteonectin and vitronectin determine the site to where the tumor can spread. (Bendas & Borsig, 2012). Blood vessels supplying the tumor cells are often found to express  $\alpha v \beta 3$  and  $\alpha v \beta 5$ , a feature not seen in other vessels (Brooks, Clark, & Cheresh, 1994).

### 1.4 Immunoglobulin Super family members help cancer cells invade new sites

The Immunoglobulin Super family comprises intra-cellular adhesion molecules (ICAM), vascular cell adhesion molecules (V-CAM), neural cell adhesion molecules (N-CAM) and platelet endothelial cell adhesion molecules (PE-CAM) (Simmons, 1999). We know that IgSF members particularly play a vital role in inflammation and immune-based reactions which involve extravasations of leukocytes. Tumor cells may be able to take over this mechanism and invade new sites by displaying 'leukocyte mimicry' (Witz, 2006). Several tumors express ICAM1 in various cancers and carcinomas which correlate with the pattern of spread and potential for metastasis (Johnson, 1999).

## 2. Discussion

A growing body of evidence suggests that certain Integrins, (together with Selectins) mediate the spread of tumors. It has been shown that Selectins play a role in inflammation and the progression of cancer (Ley, 2003). While IgSF members are not directly involved in cancer progression, their role in inflammation and the mechanism of extravasations of leukocytes can be exploited by the tumor cells to invade new sites. Tumor suppressor E-Cadherin may actively induce tumor growth if mutated (Christofori & Semb, 1999). It is clear that Cell Adhesion Molecules are pivotal in the formation of tumors, metastasis, invasion and angiogenesis. Targeting specific CAMs is a possible avenue of therapy which could slow down, or even stop metastasis and invasion. For example, Bendas & Borsig (2012) discuss a number of clinical studies which point to the role of Heparin in inhibiting Integrins and affecting key steps in the "metastatic cascade". In addition they also target Selectins, which could help attenuate metastasis (Bendas & Borsig, 2012).

## 3. Conclusion

Cell-adhesion molecules play pivotal roles throughout the various stages of cancer. There are many cytotoxic drugs which target the cancer cells themselves. However, more therapies could be developed to target cell-adhesion molecules and slow down the metastatic spread. For example, Heparin has been shown to affect important steps in the metastasis cascade (Bendas & Borsig, 2012). A novel chemotherapy approach can be formulated using a combination of cytotoxic and Heparin based drugs to treat malignant tumors and thus improve the prognosis for many cancer patients.

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