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Review

# Tissue invasion and metastasis: Molecular, biological and clinical perspectives

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ABSTRACT

Cancer is a key health issue across the world, causing substantial patient morbidity and mortality. Patient prognosis is tightly linked with metastatic dissemination of the disease to distant sites, with metastatic diseases accounting for a vast percentage of cancer patient mortality. While advances in this area have been made, the process of cancer metastasis and the factors governing cancer spread and establishment at secondary locations is still poorly understood. The current article summarizes recent progress in this area of research, both in the understanding of the underlying biological processes and in the therapeutic strategies for the management of metastasis. This review lists the disruption of E-cadherin and tight junctions, key signaling pathways, including urokinase type plasminogen activator (uPA), phosphatidylinositol 3-kinase/v-akt murine thymoma viral oncogene (PI3K/AKT), focal adhesion kinase (FAK), β-catenin/zinc finger E-box binding homeobox 1 (ZEB-1) and transforming growth factor beta (TGF-β), together with inactivation of activator protein-1 (AP-1) and suppression of matrix metalloproteinase-9 (MMP-9) activity as key targets and the use of phytochemicals, or natural products, such as those from *Agaricus blazei*, *Albatrellus confluens*, *Cordyceps militaris*, *Ganoderma lucidum*, *Poria cocos* and *Silybum marianum*, together

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with diet derived fatty acids gamma linolenic acid (GLA) and eicosapentanoic acid (EPA) and inhibitory compounds as useful approaches to target tissue invasion and metastasis as well as other hallmark areas of cancer. Together, these strategies could represent new, inexpensive, low toxicity strategies to aid in the management of cancer metastasis as well as having holistic effects against other cancer hallmarks.


## 1. Introduction

The chain of events leading to the malignant transformation of cells, whether through genetic or epigenetic alterations, is complex. Malignant cells possess key hallmarks, namely, uncontrolled growth potentials and the ability to invade surrounding tissues and metastasize [1]. Cancer cells likely possess these innate abilities to some extent, though the degree and timing of invasion and metastasis may vary due to the genetic and epigenetic heterogeneity within the tumor and further signals from extrinsic factors, such as those within that particular microenvironment [2].

Despite substantial effort dedicated to the early detection and prevention of cancer, most patients are likely to have micro- (not visible using conventional methods) or macro- metastases by the time they come to medical attention [3,4]. Cancer patients, both early and late stage, dependent on life span, are likely to develop metastasis. This metastatic spread of the primary tumor accounts for over 90% of patient mortality associated with solid cancers [1,4,5]. Despite this, research into the field of metastasis, in comparison to other key events such as proliferation, *etc.*, is lagging. This is partly due to the complexity of the metastatic process but also due to a lack of sufficient funding and efforts into this area of research. However, significant progress in this vital area of cancer research has been witnessed over the past decade, though much remains to be elucidated before we fully understand this pernicious condition and a number of significant gaps remain to be filled before we can truly understand this complex process.

Diagnosis and treatment of metastatic disease are vital areas in the constant battle many patients face against cancer, yet effective treatments are limited and substantial morbidity and mortality are still associated with metastatic disease [5,6]. This, together with the complexities surrounding the metastatic process (summarized in Fig. 1) and the complex nature and heterogeneity of metastatic tumors, fully supports and justifies further research dedicated to the discovery of a less toxic means to treat this condition. This is the major mission of getting to know cancer (GTKC). This review aims to discuss key knowledge gaps, explore potential targets in tackling metastasis and also potential methods, including phytochemicals, small molecule inhibitors and natural compounds in devising new strategies for treating metastasis.

## 2. Cellular properties and metastasis

### 2.1. Cell–cell adhesion

In cancers derived from the epithelium, inter-cellular structures and cell–cell adhesion are key factors in maintaining a coherent primary tumor mass [7,8]. Abnormalities in these structures, through mutation or dysregulation, can lead to the dissociation of the primary tumor and an enhanced potential for dissemination and metastatic spread of cancer cells to secondary locations [7–9]. Key structures involved in maintaining this adhesiveness between cells include adherens junctions (including desmosomes), tight junctions (TJ) and gap junctions. While gap junctions confer a weak adhesion structure and TJs, a modest one, the adherens junctions provide the most powerful source of adhesion in epithelial cells. Perhaps one of the strongest and most studied regulators of adhesion is E-cadherin (cadherin-1 or CDH1), a member of the cadherin family of proteins. E-cadherin, together with associated catenins, plays a key role in maintaining cell–cell adhesion and is also involved in the regulation of the cell cycle regulators $p27^{kip1}$ and $p57^{kip2}$, which are involved in cell–cell contact inhibition in normal epithelium, but which are lost or disturbed in cancer cells, mainly due to the loss of E-cadherin in cancer cells [8,10,11]. Hence, reduced cell–cell adhesion not only enhances the potential for metastatic dissemination of cancer cells but also, through loss of contact inhibition, promotes uncontrolled cell growth [7]. E-cadherin has also been established as a key mediator of the epithelial – mesenchymal transition (EMT) process (discussed in Section 2.4). Thus, enhanced expression of key cadherin molecules could offer potential as a strategy to control metastatic dissemination, though realizing this potential has proved difficult; thus far there have been few reports identifying viable treatment options in this regard. However, there are a number of noteworthy options, namely the polyunsaturated fatty acids gamma linolenic acid (GLA) and dihomo-γ-linolenic acid (DGLA), both obtainable through the diet. These have been reported to be key regulators of E-cadherin and desmosomal cadherins in cancer cells and have also been reported to have beneficial effects for patients with several cancer types including pancreatic cancer and breast cancer [12–15]. The desirable effects of these essential fatty acids (EFAs) were blocked by non-EFA, as long chained oleic derivatives on human cell lines [16].

#### 2.1.1. Claudins in cancer

The TJ complex is the apical most junctional complex in most types of epithelial and endothelial cells. TJs are the gasket-like seals that encircle each columnar epithelial cell around its apical pole. They serve two roles: (1) they help to maintain cell polarity by physically separating the apical and the basolateral membrane domains and (2) they prevent free interchange of substances by diffusion along the paracellular pathway between the luminal and antiluminal tissue fluid compartments. TJs and their permeability are important in the formation of the blood brain barrier, blood retinal barrier and blood testis barrier. The TJ proteins can be sub-divided into the integral membrane proteins such as occludin, tricellulin, marvelD3, junctional adhesion molecules (JAMs) and the claudin family (currently 27 members [17]) and the cytoplasmic proteins. The cytoplasmic adaptor proteins are the zonula occludens or ZO proteins, and are designated ZO-1, -2, and -3. These proteins link the membrane proteins to the actin cytoskeleton. Traditionally, research efforts focused on barrier and fence functions, however, there is a new movement in the field, which is to understand how TJ proteins participate in cell proliferation, transformation, and metastasis suppression. Recent studies have demonstrated the role of TJs during epithelial tissue remodeling, wound repair, inflammation, and transformation into tumors. Epithelial multilayering was associated with increased TJ permeability [18], activation of protein kinase C (PKC)-α [19] and phosphorylation of TJ proteins [20].

Studies focusing on the molecular architecture of the TJ have now confirmed that the claudin family of proteins is the integral component of the TJ. Loss of cell–cell adhesion is central to the cellular transformation and acquisition of metastatic potential, however, the role the claudin family of proteins may play in a series of pathophysiological events, including human carcinoma development, is only now beginning to be understood. Several