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Review

# Metals and metastasis: Exploiting the role of metals in cancer metastasis to develop novel anti-metastatic agents

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ABSTRACT

Metastasis is currently the leading cause of cancer related death and is the most feared and difficult to treat outcome for cancer patients. This complex process is regulated by a plethora of signaling pathways and molecules that control cell proliferation, invasion, motility and adhesion. Many of these vital processes that enable metastasis to occur are influenced by metals, which play crucial roles in the function of numerous proteins and enzymes. Importantly, an excess of essential metals such as iron and copper is often associated with carcinogenesis and metastatic disease. As such, metals have emerged as promising and viable therapeutic targets for a new generation of anti-cancer and anti-metastatic agents. Further, the unique properties of metals, including their abilities to redox cycle or to mimic other metals, can also be utilized to more effectively target aggressive and metastatic cancer cells. This review will provide an overview of the role that metals play in the metastatic progression of cancer and the development of novel therapies that either target or utilize metal ions as part of their mechanism of action to inhibit metastasis.



**Contents**



*Abbreviations:* CCBE1, collagen and calcium-binding EGF domains 1; CO, carbon monoxide; CSC, cancer stem cell; CTCs, circulating tumor cells; DpC, di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone; DpT, di-2-pyridylketone thiosemicarbazone; Dp44mT, 2-pyridylketone 4,4-dimethyl-3-thiosemicarbazone; ECM, extracellular matrix; eIF3a, eukaryotic initiation factor 3a; EMT, epithelial to mesenchymal transition; EPC, epithelial progenitor cells; ER, estrogen receptor; FAK, focal adhesion kinase; HIF-1α, hypoxia inducible factor-1α; HO-1, heme-oxygenase-1; JNK, c-Jun *N*-terminal kinase; LOX, lysyl oxidase; LOXL, lysyl oxidase-like; MAPK, mitogen activated protein kinase; MET, mesenchymal to epithelial transition; MMPIs, matrix metalloprotease inhibitors; MPP, matrix metalloproteinase; NDRG1, N-myc downstream-regulated gene 1; NF-κB, nuclear factor κB; PI3K, phosphoinositol 3-kinase; ROS, reactive oxygen species; SMAC, second mitochondria-derived activator of caspases; SOD, superoxide dismutase; SOX9, sex-determining region Y (SRY)-box 9 protein; STAT, signal transducers and activators of transcription; STIM, stromal interaction molecules; Tf, transferrin; TfR1, transferrin receptor 1; TGF-β, transforming growth factor β; TM, tetrathiomolybdate; Triapine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone; ZBP-89, zinc-binding protein-89.

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## 1. Introduction

The human body requires 6 essential metals to ensure optimal health and proper functioning of biological systems. These include iron, zinc, copper, manganese, molybdenum and selenium [1]. While chromium was also considered an essential element for humans, no chromium-containing protein has yet been identified. In fact, while the peptide chromodulin has been suggested to be a chromium-binding candidate, there is evidence that it actually may be an isolation artifact [2]. The essential metals, which are only required in trace amounts, play vital roles in cells, with many being integral for the function of numerous enzymes required for essential biochemical processes [1]. For instance, iron is essential for the function of ribonucleotide reductase, an enzyme required for the rate limiting step of DNA synthesis [3]. Further, zinc is a constituent of over 300 enzymes that play vital roles in gene expression (*e.g.*, zinc-finger transcription factors; [4]). Apart from their role in enzyme function, metals are also required for numerous biological processes such as the transport of oxygen in the blood, which is mediated by hemoglobin, a protein that contains iron [5].

A deficiency of any of these essential metals leads to either functional or structural abnormalities and causes numerous disease states such as anemia resulting from iron deficiency [6], which can be fatal [7]. Conversely, an excess of these metals can also be deleterious and lead to toxicity, inflammation [7] and cancer [8]. As a result, the levels of these essential metals are carefully balanced and a state of homeostasis is maintained within the body [7].

In addition to the essential metals, a number of non-essential metals can also have important implications on human health. In fact, excess environmental exposure to metals such as arsenic, cadmium, lead and nickel has been associated with the development of cancer [8]. Notably, arsenic and cadmium were found to bind to the estrogen receptor (ER) in cancer cells, leading to hormone-independent activation of this receptor and subsequent oncogenic down-stream signaling pathways [9,10]. Further, arsenic, cadmium, lead and nickel were found to increase reactive oxygen species (ROS) leading to oxidative stress [8,11,12], with nickel also inhibiting the DNA repair system, leading to carcinogenesis [13].

Interestingly, many of these non-essential metals can also affect enzyme function. This is particularly evident with the many enzymes that require zinc, which can be substituted by metals such as cadmium, an element that has a very similar atomic structure to zinc [14]. Hence, exposure to high levels of cadmium can have dramatic effects on the thousands of zinc-containing enzymes that regulate critical biological processes, leading to the development of cancer [15]. Many metals have also been found to contribute to the metastatic progression of cancers, having effects on the key biological processes and pathways that control cell motility, invasion and dissemination [16–19].

Consequently, targeting metal ions is an innovative approach for the treatment of aggressive, metastatic cancers. This review will discuss the emerging role of metals specifically in the process of cancer metastasis. Further, the development of compounds that either utilize or target both essential and non-essential metal ions and their applications in the treatment of metastatic cancers will also be examined.

## 2. The beginnings of metastasis

The ability of cancer cells to invade and metastasize to distant sites in the body is the major contributor to the failure of cancer therapies and subsequent patient mortality. In fact, more than 90% of cancer-related deaths are due to metastatic spread [20]. In light of this, understanding the intricate molecular players in the process of metastasis and how these can be targeted therapeutically is vitally important.

Metastasis occurs when cancer cells detach from the primary tumor and spread to other sites in the body to form secondary tumors. This process is characterized by a number of steps, which include: ***(1)*** Cell transformation from an epithelial to a mesenchymal phenotype (*i.e.*, the epithelial to mesenchymal transition; EMT), resulting in reduced adhesion to neighboring cells; ***(2)*** Polarization of cancer cells to facilitate directional movement and migration; ***(3)*** Invasion of cancer cells into surrounding tissues, lymph nodes and blood vessels; ***(4)*** Dissemination *via* the bloodstream to other organs (typically lungs, liver or bone, *etc.*) where the mesenchymal to epithelial transition (MET) facilitates attachment to the endothelium and subsequent invasion; and ***(5)*** Proliferation of the invading cancer cell to form a secondary tumor at the new site [21] (Fig. 1). This dynamic and complex process is driven by a number of signaling pathways that control cell adhesion, motility, invasion and proliferation and will be discussed briefly below.

### 2.1. The epithelial to mesenchymal transition

The EMT is the initial phase of metastasis and is characterized by a morphological change in cancer cells, which undergo a transformation from an epithelial phenotype to a more mesenchymal phenotype that enables efficient cell motility and invasion [21]. A number of signaling cascades can activate this process and these include the transforming growth factor β (TGF-β) and the WNT pathways [22–24]. This phenotypic change leads to dissociation of the adherens and tight junctions on the plasma membrane of tumor cells to enable detachment from neighboring cells [21,25]. The adherens junction is composed of the membrane adhesion protein E-cadherin, which binds E-cadherin from neighboring cells to facilitate cell-cell adhesion [23]. The cytoplasmic domain of E-cadherin interacts with the actin cytoskeleton *via* linker molecules, including α-, β- and γ-catenins [23].

Notably, the extracellular domain of E-cadherin, which is crucial for adhesion, contains several binding sites for calcium ions, which strengthen the extracellular domains and promote trans-junctional interactions [23,26]. A reduction in E-cadherin expression is considered to be a major contributor to the loss of cell adhesion and a significant step towards the development of metastasis [23]. The EMT is further characterized by an up-regulation of molecules such