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Review Article

Modulation of the Extracellular Matrix by Trace Elements, Selenium, Zinc and Manganese in Different Pathologies: An Overview

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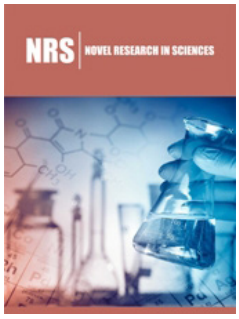

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Trace Elements

An adequate tissue level of Trace Elements (TE) is associated with good human health, and the excess or deficiency of TE has been correlated with the appearance of different diseases, including autoimmune, metabolic, neurodegenerative, muscular, cancer, among others [1-4]. Many TEs are essential for numerous biological, chemical, and molecular processes, regulate cellular homeostasis, cellular and humoral immune responses, and are cofactors for many enzymes and antioxidant molecules [5,6]. Among the TEs, Zinc (Zn), Selenium (Se) and Manganese (Mn) play a fundamental role in both maintenance and immune support due to their antioxidant performance [7]. Zinc, a component of more than 200 enzymes, plays an important role in nucleic acid metabolism, cell replication, tissue repair, and growth through its role in nucleic acid polymerases. These zinc-dependent enzymes include the potentially rate-limiting enzymes involved in DNA synthesis. Zinc also has many recognized and biologically important interactions with hormones and plays a role in the production, storage, and secretion of individual hormones.

Severe, moderate, and marginal zinc deficiencies have been reported [8]. We have previously demonstrated the protective effect of a new combination of three TEs: Se, Zn and Mn (OLs) against high doses of chemotherapy and radiotherapy in healthy tissues due to their antioxidant properties [9-11]. Selenium, via selenoproteins, plays an important role in many of the cellular activities that underlie metastasis, including cell adhesion, Extracellular Matrix (ECM) degradation and migration, invasion into the blood, and extravasation into secondary tissues and angiogenesis [12]. Methylselenol generated from Selenmethionine induces cell proliferation, adhesion, and integrin expression in B16F10 murine melanoma cells, which are metastatic to the lungs of syngeneic C57BL/6J mice [12].

Reduced integrin expression inhibits melanoma adhesion to the ECM by increasing apoptosis, which is closely related to the effects of both Selenmethionine and the enzyme that converts it to methylselenol, methioninase. Another example of an interaction between Se, integrins, ECM, and growth factors is neuropilin-2 (NRP-2), which is a receptor for VEGF and other growth factors that interacts with α5 integrin on endothelial cells to mediate extravasation in murine and zebrafish, xenograft models of clear cell renal cell carcinoma and pancreatic adenocarcinoma [13]. It can be suggested that the integrin switch also evidences a close relationship between Se and ECM, activating or blocking integrin-dependent cell survival signaling pathways, including PI3K/AKT, MEK/ERK, FAK, NFkB and/or ILK. In

addition, integrin-linked kinase is a multifunctional intracellular effector of cell-matrix interactions [13,14]. Integrins are also expressed on mesenchymal stem cells and bind to the ECM through fibronectin [15]. In addition, divalent cations such as Mn are known to strongly influence integrin affinity for ligands and, consequently, cell adhesion to ECM proteins [16], regulating Anoikis, a type of cell death.

Extracellular Matrix

On the other hand, the extracellular matrix is a dynamic network of macromolecules that provides structural and functional support to cells and tissues. The set of genes that code for ECM and ECM-associated proteins is known as Matrisome [17,18]. The ECM plays key regulatory roles, from cell fate to signaling, functions, properties, and morphology in health and disease, primarily through the ECM's matricellular proteins, such as hevin (also known as SPARC- like 1), SC-1, Mast 9, Ecm 1 SMOC 1 and 2, and several of the testicanes [19] and enzymes, such as matrix metalloproteinases and specific glycosidases, including heparanase and hyaluronidases. The ECM comprises a well-organized network with significant functions of its constituents, such as collagens, elastin, laminins and tenascins, proteoglycans and glycosaminoglycans, hyaluronan, cell receptors such as CD44 and integrins, responsible for cell fate [20]. Many of these mechanisms, such as cell proliferation and survival, migration, differentiation, autophagy, angiogenesis, regulation of immunity, are regulated by the ECM and in turn are shared by many pathologies, eg. cancer, autoimmune, cardiovascular, muscular diseases, etc. It should be noted that the ECM matricellular proteins lack direct primary structural functions in the ECM [21]. The ECM known as the pericellular matrix is a tightly organized network that is in contact with cells by creating cross-links through integrins, Discoidin Domain Receptors (DDRs), and PGs such as syndecans [22], which regulate, for example, Anoikis. Taking into account all these observations, it can be suggested that the proliferative arrest of disseminated tumor cells is attributable, in part, to syndecan-mediated binding of ECM proteins [22].

ECM, OLs, Sclerosis and Colorectal Cancer

Systemic sclerosis is an autoimmune disease that presents a progressive accumulation of ECM components, affecting the skin, gastrointestinal tract, lung, heart and kidney. Our laboratory demonstrated that in a Bleomycin-Induced Scleroderma (BLM) mouse model, treatment with a combination of OLs significantly reduced BLM-induced scleroderma through ECM modulation of antioxidant and immune pathways [23]. Colorectal Cancer (CRC) is one of the most common malignancies of the digestive tract in the world. CRC is the 3rd most common cancer in men and the 2nd most common cancer in women. There were more than 1.9 million new cases of colorectal cancer in 2020 [24]. ECM and CRC are closely related as Secreted Acidic Protein Rich in Cysteine (SPARC), also known as osteonectin and BM-40, a multifunctional matricellular, associates with the ECM and is abundantly expressed in the basal lamina [25]. The Dimethylhydrazine (DMH)-induced CRC model is well known and several substances, such as epigallocatechin gallate, a poly hydroxy phenolic compound, metformin and Se, reduce the incidence of CRC in this experimental model [26]. Metformin activates AMPK and induces G1 cell cycle arrest by inhibiting cyclin D1 expression, a pathway involved in ECM regulation [27]. AMPK activation can increase p53 gene expression and play an antitumor role. Low concentration of metformin can induce p53-dependent cellular senescence of liver cancer cells by activating AMPK [28].

Wang Y et al. [26] demonstrated that inhibitory pathways related to CRC have gene regulation, such as: deregulated genes enriched in hsa05210 (CRC), hsa04115 (p53 signaling pathway) and hsa04151 (PI3K-Akt signaling pathway), GO:0043124 (negative regulation p53 I-kappaB kinase/NF-kappaB signaling pathway), GO :0043409 (negative regulation of the mitogen-activated protein kinase cascade) and GO: 2001244 (positive regulation of the intrinsic apoptotic signaling pathway). SPARC, at its central location, participates in these regulations. In our laboratory, CRC in DMH-induced and OLs-treated rats showed a dramatic decrease in the number and type of tumors (unpublished results). SPARC cytosolic, integrins, autophagy, DNA repair, metalloprotease activation, and mast cell type 1 were evaluated. Our results showed that OLs-associated ECM and, regulated by matricellular ECM proteins, control tumorigenesis in DMH-induced CRC in rats. Our results showed that CRC in DMH-induced, and OL-treated mice showed a drastic decrease in the number and type of tumors (unpublished results). Cytosolic SPARC, integrins, autophagy, DNA repair, metalloproteases, and type 1 mast cell activation were evaluated. Our results showed that ECM associated with OLs and regulated by matricellular ECM proteins, control tumorigenesis in CRC induced by DMH in both experimental models. In conclusion, the trace elements Zn, Se and Mn are fully involved in the modulation of the extracellular matrix in different pathologies.

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