Tetrathiomolybdate

National Cancer Institute

Source

National Cancer Institute. Tetrathiomolybdate. NCI Thesaurus. Code C160684.

An orally bioavailable metal copper (Cu) chelator, with potential antiangiogenic, anti-metastatic and antitumor activities. Upon oral administration, tetrathiomolybdate (TM) targets and binds to copper and food protein in the gastrointestinal (GI) tract, thereby forming stable complexes and preventing copper uptake and reabsorption. Additionally, absorbed free TM targets and binds to copper and serum albumin in the bloodstream. This depletes systemic copper reserves and deprives the tumor microenvironment (TME) from copper. Chelation of copper by TM downregulates the expression of angiogenic factors of which copper is a cofactor, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), and prevents the production of nuclear factor-kappa B (NF-kB). Copper deprivation also inhibits the activity and levels of copper-dependent angiogenic enzymes, such as vascular endothelial growth factor receptor (VEGFR). This modulates the activity of VEGFR-positive endothelial progenitor cells (EPCs) that are necessary for metastasis. EPC deficiency results in the inhibition of angiogenesis and prevents metastasis. TM also inhibits the activities of other copper-containing metalloenzymes, including superoxide dismutase 1 (SOD1) in endothelial cells, cytochrome C oxidase, vascular adhesion protein-1 (VAP-1), antioxidant 1 copper chaperone (ATOX-1) and matrix metalloproteinase 9 (MMP-9). Inhibition of these enzymes interferes with the activation of several signal transduction pathways required for cellular proliferation and angiogenesis. TM also inhibits the activity and levels of lysyl oxidase-like 2 (LOXL2; lysyl oxidase homolog 2), a copper dependent amine oxidase that is critical for modeling the pre-metastatic niche and promotes metastasis, tumor cell migration and invasiveness. In addition, copper depletion also attenuates the activation of host cells within the tumor microenvironment including cancer-associated fibroblasts (CAFs), modulates tumor associated macrophages (TAMs) and promotes cytotoxic T-lymphocyte (CTL)-mediated anti-tumor immune responses.