Meprin Alpha Mediates CCL2 Activity in Murine Bone Marrow Cells Using a Model of Breast Cancer Chemotherapy.

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Meprins are metalloproteases comprised of hetero or homo-oligomers of alpha and beta subunits. These proteases degrade extracellular matrix proteins and have been linked to cancer cell metastasis and leukocyte transmigration. Meprins are also known to cleave cytokines like interleukin-1 and cytokine receptors like the epidermal growth factor receptor to modify their activity in a post-translational manner. Thus the expression of metalloproteases in a tissue can have a profound impact on cytokine activity in tissue microenvironments. In breast cancer, a common occurrence is cancer cell homing to bone marrow. Once in the bone marrow, the cancer cells can elude the apoptotic effects induced by chemotherapy. One potentially important cytokine is the chemokine CCL2, since breast carcinoma patients with elevated CCL2 levels have a poor prognosis. Herein, data is presented supporting the role of meprin alpha in the inactivation of chemokines by N-terminal truncation, including CCL2 (monocyte chemoattractant protein-1), CCL5 (RANTES), CCL3 (macrophage inflammatory proteins-1 alpha) and CCL4 (macrophage inflammatory proteins-1 beta). Data also indicated that while the abundance of MCP-1 transcripts increases after induction of bone marrow apoptosis, the abundance of meprin alpha transcripts decreased below detection. These data support a model where apoptosis via chemotherapeutic agents can increase CCL2 activity in bone marrow due to a decline in meprin alpha thereby supporting cancer cell growth in bone marrow.