

HUMAN MACROPHAGES SECRETE A NOVEL HIGH MOLECULAR WEIGHT TUMORICIDAL ACTIVITY DISTINCT FROM BUT SYNERGIZING WITH TUMOR NECROSIS FACTOR ALPHA (TNF- α)

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Human monocyte (MO)-derived macrophages (MAC) can be induced to secrete a tumoricidal activity which is cytolytic for TNF- α insensitive human tumor cell lines. This activity a) is secreted only after combined treatment with interferon-gamma (IFN- γ) and lipopolysaccharides, but is not inducible by either stimulant alone, b) is not secreted by freshly isolated blood MO, c) is tumorspecific and does not significantly affect primary human cells, d) exhibits a molecular mass of about 150 kDa upon gel filtration, and e) is inactivated by heat and trypsin but is insensitive to serine protease inhibitors or neutralizing antibodies to human interleukins 1 and 6 and IFN- α , - β and - γ . An antibody against TNF- α showed some, but only partial inhibition of tumoricidal activity, suggesting TNF- α to have a synergistic effect rather than being a central effector molecule for this activity. This notion was supported by enhancement of low levels of cytolytic activity by addition of rhuTNF- α at concentrations not having any direct cytotoxic effect on the tumor targets used. In conclusion, differentiated human MAC have the capacity to secrete a yet undescribed high molecular weight tumoricidal activity which is different from TNF- α and other known monokines but comprises a novel type of MAC-derived tumoricidal effector molecule(s) of protein nature which, however, may synergize with TNF- α in the selective destruction of tumor cells by MAC. Based on current data, this activity shares several functional and molecular features with a recently described tumoricidal factor of murine MAC termed MTC 170, and may constitute a major common antitumor effector pathway of activated MAC.

J Leukocyte Biol **53**: A582. 1993