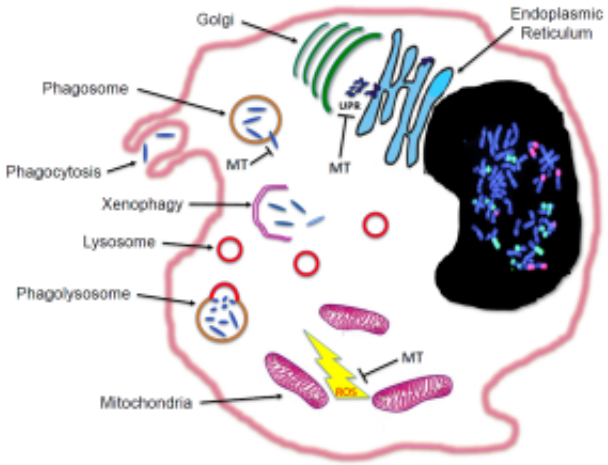
Psychological stress can influence key immune activities and an important protein in the response to infection

The central role played by our immune system is to protect us against infections. In doing so, the immune response creates a localized toxic inflammatory environment that makes it difficult for the infectious agent to survive. In that region, our own cells will also be exposed to these toxic molecules (which include highly reactive molecules such as hydrogen peroxide and hypochlorite, the active ingredient in bleach). These bystander cells in the infected tissue attempt to cope with those toxicants by producing stress response proteins such as metallothionein (MT).



Our previous work has shown that MT can have significant effects on how the immune response proceeds. For example, we have shown that MT released from cells can influence the influx and activation of the immune cells that create this toxic environment, and that a monoclonal antibody we have made to the MT protein can block the progressive and chronic inflammation that can be associated with inflammatory bowel disease. MT is a very interesting and unusual protein. It is quite small as proteins go (only 7kDa), and of the 61 amino acids that make up the primary sequence in a consensus protein, about 33% of them are cysteines. This means that the protein is a powerful anti-oxidant, and enables the protein to serve both as a reservoir of essential metals such as zinc and copper, and as a way to sequester toxic metals such as mercury and cadmium. As a reservoir for Zn and Cu, MT may influence other metalloproteins, such as metalloproteases, which affect cell migration and alter expression of checkpoint regulators of immune activation. Synthesis of MT can be turned on by a broad spectrum of inducers, such as infection, exposure to physical stress or chemical toxic molecules, and by psychological stressors. Our recent report (Emeny *et al.*, Cell Stress Chaperones 2015 Nov) has shown that either abnormally high or abnormally low expression of MT can interfere with the interaction of a psychological stress and infection that ordinarily combine to enhance suppression of host defenses. This suggests that MT is working on multiple cellular processes that regulate immunity. In addition to MT's role as a modifier of chemotaxis, another report (Mondal *et al*., Toxicol Appl Pharmacol. 2015 Sep 21) has indicated that the physical, psychological, and infectious stresses can each lead to endoplasmic

reticulum stress, which suggests that MT may be regulating intracellular organelles that are important in the capture and killing of pathogens. The figure identifies potential sites at which MT can be affecting host defenses: lessening escape of pathogens from the phagosome; promoting xenophagy (the “eating” of “strangers” after re-encapsulation of pathogens that have escaped the phagosome); reducing the release of oxidants from mitochondria (reactive oxygen species, ROS); and lowering the unfolded protein response (UPR) with intracellular aggregation of proteins interfering with cell biology and promoting cell damage. Thus, it appears that MT can influence immunity at multiple levels. These results may indicate new opportunities for therapeutic intervention in infections.

Publication

Metallothionein differentially affects the host response to Listeria infection both with and without an additional stress from cold-restraint.
Emeny RT, Kasten-Jolly J, Mondal T, Lynes MA, Lawrence DA
Cell Stress Chaperones. 2015 Nov