The role of the TGF-β superfamily cytokine MIC-1/GDF-15 in anorexia/cachexia of cancer and other diseases

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MIC-1/GDF15 is a TGF-β superfamily cytokine that is overexpressed and secreted by many common cancers. In cancer and other diseases associated with marked increase in its circulating levels, and in experimental animals, it causes anorexia and progressive weight loss leading to cachexia. In experimental animals this can be reproduced by administration of recombinant MIC-1/GDF15 and inhibited by monoclonal antibodies to it.

In mice, MIC-1/GDF15 decreases appetite and consequently food intake, leading to a loss of both fat and lean mass. This change in body weight could not be explained by altered energy expenditure and pair feeding experiments indicated that loss of body weight as well as fat and lean mass, was commensurate with decreased food intake. A body of data now indicates these effects are mediated by direct actions of MIC-1/GDF15 on feeding centres in the brain. A single IP injection of recombinant protein induces rapid activation of neurons in the hypothalamus and brainstem and modifies expression of neuronal peptides important in appetite regulation such as such as NPY and POMC. Further, viral expression of MIC-1/GDF15 in the hypothalamus, or direct injection of tiny amounts of recombinant MIC-1/GDF15 into the brain's lateral ventricle has the same anorexigenic effects as systemically administration of MIC-1/GDF15.

To determine if MIC-1/GDF15 might also participate in physiological regulation of appetite, we have also studied germline MIC-1/GDF15 gene deleted (MIC-$1^{-/-}$) mice. Throughout their first year of life, these mice eat more, weigh more and have greater adiposity than their syngeneic controls, an effect that is more marked in female than male mice. Further, this phenotype can be corrected by infusing MIC-1/GDF15 by osmotic minipump, in amounts sufficient to raise their serum levels into the human normal range.

To further investigate the major sites of action of MIC-1/GDF15 in the brain, we have lesioned brainstem nuclei, which are activated by MIC-1/GDF15. These mice were completely resistant to the anorexigenic actions of MIC-1/GDF15 and as a consequence did not reduce their food intake or loose any body weight. Thus lesioning these brainstem nulclei makes mice resistant to the anorexigenic actions of MIC-1/GDF15.

The available data suggest that overproduction of MIC-1/GDF15 in advanced cancer, and other chronic diseases associated with marked elevation of its serum levels subverts a physiological pathway of energy homeostasis, leading to anorexia and as a consequence, reduction of fat and lean mass which eventually results in cachexia. This suggests that monoclonal antibodies to this cytokine may be an effective therapy for patients with anorexia/cachexia syndromes who have significant elevation in MIC-1/GDF15 serum levels and conversely, recombinant MIC-1/GDF15 might be use to treat patients with severe obesity.