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In This Issue

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Directed antisense expression moderates feedingand weight gain (See article on pages 1429–1436.) Rats receiving the hormone ghrelin as a direct injection into the hypothalamus respond with vigorous feeding and reduced fat metabolism. Ghrelin stimulates the growth hormone secretogogue receptor (GHS-R) on hypothalamic and pituitary neurons, promoting GH release, and leaving the treated animals in a state of positive energy balance, where they become obese when supplied unlimited food. To test the possibility that hypothalamic ghrelin-responsive neurons mediate the behavioral and metabolic effects of this hormone, Shuto and colleagues generated transgenic rats in which an antisense to the GHS-R mRNA is produced specifically in these cells. The resulting transgenic animals are smaller than controls, even at birth, and females show blunted expression of GH. Surprisingly, although males are apparently normal for GH synthesis and show the normal daily fluctuations in GH release, animals of both sexes are significantly reduced in food intake and body adiposity. This same group has previously shown that a synthetic GHS-R agonist also stimulates food consumption and increases adiposity in wild-type animals, but they find that this drug has no such effects in their transgenic lines. While the relationship between GH production and energy balance remains uncertain, this work clearly supports a role for ghrelin or other GHS-R ligands in the central control of energy balance.Dendritic cell […]

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By John Ashkenas, Science Editor

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Dendritic cell vaccination using a cell-permeant tumor antigen

(See article on pages 1463–1470.)

Dendritic cells (DCs) can process and present tumor cell-specific antigens, activating $CD8^+$ T lymphocytes to destroy tumor cells. Here, Wang and colleagues propose a new route to tumor antigen presentation that they hope will help realize the promise of DC vaccines for treating cancer or blocking metastatic disease. In their method, an appropriate MHC-restricted epitope is generated as a fusion peptide carrying an additional, HIV-derived sequence that allows it to penetrate the DC plasma membrane. Wang et al. have found that such fusion peptides are taken up more readily and presented by DCs more efficiently than occurs following standard DC "pulsing" protocols. Now, they show that this quantitative change in tumor antigen presentation correlates with a qualitative improvement in T cell tumoricidal activity. Working with a peptide that serves as a tumor antigen in both humans and mice, the authors find that transduced DCs activate both $CD4^+$ and $CD8^+$ cells, which act synergistically to suppress tumor growth in mice carrying metastatic melanoma cells. The contribution of $CD4^+$ cells to this process was not anticipated and remains something of a puzzle, since the tumor antigen used is restricted by Class I MHC molecules, which activate $CD8^+$ cells. Nonetheless, control mice receiving the peptide-transduced DCs appear to be completely protected from metastatic disease, while animals lacking either the $CD4^+$ or $CD8^+$ subtype develop a significant number of lung metastases. This procedure seems well suited for DC vaccination in vitro or in vivo, using cell-permeant forms of this or other tumor antigens. Still, concerns about provoking autoimmunity by this means will need to be addressed before it can be considered for use in humans.

NEMO submerged in virus-prone boys

(See article on pages 1501–1509.)

NK cells provide an important line of host defense, acting both with and without help from the clonal immune system to destroy virally infected and malignantly transformed host cells. NK cell biologists distinguish between two modes of cell killing, one dependent on a humoral response to the target cells (antibody dependent cellular cytotoxicity [ADCC]) and the other antibody-independent (NK cell cytotoxicity). To date, they have been unable to tease apart the contributions of these mechanisms to human health, but Orange et al. now report on a mutation of the adaptor protein NEMO that impairs the latter while sparing the former. NEMO is the product of an essential X-linked gene, and it mediates many of the effects of the ubiquitous NFkB pathway. Nevertheless, certain mild mutations in *NEMO* are compatible with development in males. Boys carrying one of these mutations show various developmental and dermatological abnormalities, as well as recurrent bacterial and viral infections, but they can survive well into adolescence. Orange et al. focus here on the unusual properties of the NK cells from three such patients, each of whom carries a distinct *NEMO* missense mutation. NK cells from these boys fail to kill a tumor cell line that is normally targeted by NK cell cytotoxicity, but they are active (even unusually so) in ADCC assays. Orange et al. find that IL-2 supplementation can rescue NK cell cytotoxicity, suggesting a parallel route to cell killing that might be of use in treating these patients or even to enhance NK activity in other settings.