Sulforaphane beats steroid resistance in COPD

Chronic obstructive pulmonary disease (COPD) is caused primarily by cigarette smoking, which leads to persistent inflammation in the airways and subsequent destruction of the lung tissue. Given the central role of inflammation, it is surprising that individuals with COPD derive little benefit from treatment with corticosteroids, which are potent antiinflammatory drugs. This is largely because the activity of histone deacetylase 2 (HDAC2), which is critical for the antiinflammatory effects of corticosteroids, is markedly reduced in individuals with COPD. In this issue (4289–4302), Malhotra, Thimmulappa, and colleagues report both the mechanism behind the decreased HDAC2 activity in individuals with COPD and a potential therapeutic to target it. In brief, they found that *S*-nitrosylation of HDAC2 was increased in peripheral lung tissues and alveolar macrophages from patients with COPD and that this reduced HDAC2 activity and promoted corticosteroid insensitivity. Treatment with sulforaphane — a small-molecule activator of the transcription factor nuclear factor erythroid 2–related factor 2 (NRF2) that is obtained from cruciferous vegetables such as broccoli — led to HDAC2 denitrosylation and restoration of HDAC2 activity and corticosteroid sensitivity. Malhotra, Thimmulappa, and colleagues therefore suggest that sulforaphane could be used to augment the antiinflammatory effects of corticosteroids in individuals with COPD.

Faciogenital dysplasia: pathway to disease

Faciogenital dysplasia (FGDY; also known as Aarskog syndrome) is an X-linked syndrome characterized predominantly by multiple skeletal defects. It is caused by mutations in the FYVE, RhoGEF, and PH domain–containing 1 (*FGD1*) gene, but how these mutations adversely affect skeletal development has remained an unanswered question. Work by Zou, Greenblatt, and colleagues has now uncovered a potential answer to this question and identified a candidate therapeutic approach (4383–4392). Initial analysis determined that FGD1 activates a signaling pathway in osteoblasts that involves the MAP3K mixed-lineage kinase 3 (MLK3). Further analysis revealed that MLK3 regulates the activity of p38 MAPK and ERK, which in turn phosphorylate and activate Runx2, the master regulator of osteoblast differentiation. The relevance of this signaling pathway to disease was highlighted by several observations, among them that FGDY-associated mutant forms of FGD1 were unable to activate MLK3 and that mice lacking MLK3 and mice expressing a mutant MLK3 resistant to activation by FGD1 exhibited multiple skeletal defects that resembled those seen in individuals with FGDY. Zou, Greenblatt, and colleagues therefore suggest that modulating the MAPK signaling pathway they uncovered may benefit individuals with FGDY.

B cells bad for lymphoma therapy

There are many types of non-Hodgkin lymphomas (NHLs); together, they account for approximately 4% of all cancer diagnoses. The majority of NHLs arise from B cells and express the B cell marker CD20. Treatment therefore often includes the chimeric CD20 mAb rituximab. Although effective in many patients, for a substantial number, it does not result in a durable response. Horikawa, Minard-Colin, and colleagues set out to investigate whether this is because treatment with CD20 mAbs fails to deplete all endogenous nonmalignant B cells in some patients, in particular those cells in the tissues (4268–4280). In a mouse model of NHL, the authors found that if endogenous tissue B cells were not eliminated by treatment with a CD20 mAb, the antilymphoma efficacy of treatment with CD20 mAbs was substantially reduced. Further analysis identified a rare population of IL-10–producing regulatory B cells (B10 cells) as the inhibitors of lymphoma clearance in these mice. Importantly, coadministration of a TLR3 agonist abrogated the inhibitory effects of endogenous B10 cells during CD20 mAb treatment. Horikawa, Minard-Colin, and colleagues therefore suggest that either eliminating B10 cells or coadministrating TLR3 agonists could provide a way to improve the efficacy of CD20 mAb therapies in individuals with NHL.

SIRT(ain) benefit of reducing calories

Insulin resistance, particularly in skeletal muscle, is a major risk factor for the development of type 2 diabetes. Reducing caloric intake by 10%–40% below ad libitum enhances the sensitivity of skeletal muscle to insulin. Defining the molecular signals within skeletal muscle linking caloric restriction (CR) to improved insulin action could provide new targets for therapeutics to reduce insulin resistance and its associated health risks. In this issue (4281–4288), Schenk and colleagues report that the mouse ortholog of *Sir2*, sirtuin 1 (Sirt1), has an integral role within skeletal muscle in linking CR to improved insulin action. Upon upregulation in mouse skeletal muscle by CR, Sirt1 was found to deacetylate and reduce the transcriptional activity of STAT3, resulting in decreased expression of the p55α/p50α regulatory subunits of PI3K. This promoted more efficient PI3K signaling during insulin stimulation and thereby enhanced the sensitivity of mouse skeletal muscle to insulin. Thus, these data identify a molecular mechanism by which Sirt1 can translate decreases in nutrient intake into enhanced skeletal muscle insulin sensitivity.