(2006), provides fertile ground for new hypotheses about how organelles are formed and function. Future work that unravels the biological roles of reticulons and DP1/Yop1p promises to yield more fascinating insights.

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Inflammation and Sex Steroid Receptors: A Motif for Change

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Homeostasis in reproductive tissues requires integration of hormonal and inflammatory signals. In this issue of *Cell*, Zhu et al. (2006) discover that proinflammatory signals switch repressed steroid hormone receptors into transcriptional activators by targeting TAB2, an adaptor protein that tethers corepressors. These findings have implications for the treatment of endocrine-resistant cancers.

Inflammation plays a crucial role in the protective response against infections as well as in tissue remodeling in many physiological processes, such as reproduction. The precise control of inflammation is essential for the prevention of chronic inflammatory disorders as well as for inhibiting the exacerbation or progression of diseases such as atherosclerosis and cancer. Natural and synthetic steroids can target distinct steps in the inflammatory process, and considerable progress has been made in elucidating the molecular mechanisms involved. Conversely, relatively little is known about the impact of inflammatory molecules on steroid hormone action. In this issue of *Cell*, Zhu et al. (2006) report that the proinflammatory cytokine interleukin-1β (IL-1β) reverses the inhibitory effects of sex hormone receptor antagonists. This surprising finding may have profound implications for the treatment of certain hormone-dependent cancers. In fact, their observations may be of broader physiological significance as the authors also show that IL-1β reverses the inhibitory effects of natural steroids, more specifically 17-β-estradiol (E_2), in MCF7 breast cancer cells.

The sex steroids (estrogens, androgens, and progestins) are not only indispensable for reproduction but also control many diverse physiological functions in other tissues. They are also implicated in the initiation and progression of many benign and malignant disease processes, perhaps most prominently in breast and prostate cancer. Their action is mediated by specific receptors that are members of the nuclear receptor family of ligand-dependent transcription factors. Consequently selective antagonists for the estrogen receptor and the androgen receptor are widely used for the prevention and treatment of breast and prostate cancers, respectively. Activation or repression of gene transcription by nuclear receptors is dependent on the recruitment of coactivators or corepressors that form scaffolds for the assembly of chromatin remodeling enzyme complexes. The ability of steroid hormones to control the transcription of distinct gene networks in target cells seems to reflect, in part, the recruitment of different chromatin remodeling complexes. The generation of diverse physiological responses, however, requires further

regulation of steroid receptors through crosscoupling with distinct signaling pathways that vary according to the cell type and microenvironment. Deciphering the interactions between these pathways is essential for understanding the cellular responses controlled by steroid hormones in physiological and pathological processes.

Previous observations by Rosenfeld and coworkers have demonstrated that IL-1β causes nuclear export of a specific N-CoR corepressor complex (Baek et al., 2002). A number of laboratories have established that this corepressor is recruited to sex steroid receptors in the presence of synthetic antagonists to prevent transcription from target genes (Jackson et al., 1997; Smith et al., 1997). Zhu et al. (2006) have now discovered that IL-1β is capable of switching these antagonists into agonists and thereby activating, rather than repressing, target gene transcription. A series of experiments led the authors to focus on the function of a nucleocytoplasmic shuttling adaptor protein called TAB2 (Takaesu et al., 2000). They demonstrate that TAB2 binds to an L/HX$_7$LL motif in the N-terminal domain of sex steroid receptors. This domain is absent in other nuclear receptors. In response to IL-1β signals, MEKK1 (MAPK kinase kinase 1), an essential upstream signaling component of the mitogen-activated protein kinase (MAPK) cascade, is recruited to the N-CoR corepressor complex by coactivators, such as Tip60, to phosphorylate TAB2. Once phosphorylated by MEKK1, TAB2 dissociates from the sex steroid hormone receptors and tethers N-CoR away from receptor bound target genes, leading to nuclear export of the N-CoR corepressor complex, as previously reported (Baek et al., 2002). As a consequence, bicalutamide, an anti-androgen, no longer blocks the transcriptional activity of the androgen receptor but, surprisingly, stimulates it, presumably as a consequence of coactivator recruitment (see Figure 1). The ability of IL-1β to convert antagonists into agonists was also found for tamoxifen, an estrogen receptor antagonist, and mifepristone (RU486), a progesterone receptor antagonist.

Breast and prostate tumors are commonly infiltrated by macrophages. High levels of colony-stimulating factor 1 (CSF-1), a cytokine involved in recruiting and activating macrophages, is associated with poor prognosis and resistance to endocrine therapy (McDermott et al., 2002). The authors not only present an attractive paradigm to explain these clinicopathological observations, they also demonstrate that the ability of IL-1β to switch antagonists to agonists can be blocked by disrupting the interaction between TAB2 and the L/HX$_7$LL motif of sex hormone receptors. This approach could potentially be exploited for the prevention or treatment of endocrine-resistant cancers. However, multiple mechanisms are thought to contribute to the acquisition of hormone resistance in cancer, including increased circulating sex hormone levels, hormone hypersensitivity, increased growth factor signaling, downregulation of corepressors, upregulation of coactivators, and suppression or loss of nuclear receptor expression. On the other hand, it is intriguing to note that ERβ, the only sex hormone receptor that seems to lack a conserved L/HX$_7$LL motif, may not have a major role in the development of tamoxifen resistance (Chen et al., 2005). Although tamoxifen is an effective ERα antagonist in breast cancer cells, it can exert agonistic activity in cells of the uterus, thereby increasing the risk of endometrial cancer. It will therefore be interesting to determine if these opposing effects of tamoxifen in vivo can be linked to tissue-specific differences in the number and activation status of local macrophages.

The observation that the sex hormone receptors are inextricably linked to inflammatory mediators through an evolutionarily conserved N-terminal L/HX7LL motif may be of particular relevance to reproduction. Local inflammation in response to tissue accumulation of macrophages and other immune cells precedes every major reproductive event in the ovaries and uterus, from ovulation to implantation and menstruation (Jabbour et al., 2005; Wu et al., 2004). Macrophages are important in these events because

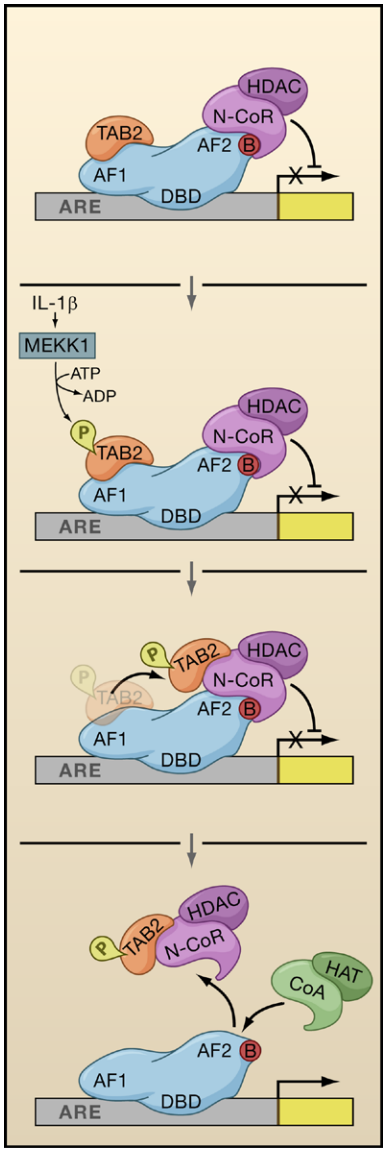

Figure 1. IL-1β Signaling Reverses Transcriptional Repression by Steroid Receptor Antagonists

The androgen receptor (blue) contains an N-terminal activation function 1 (AF-1) domain, a C-terminal activation function 2 (AF-2) domain, and a DNA binding domain (DBD), which binds to the androgen-responsive element (ARE) of target genes. Upon binding of the specific androgen antagonist, bicalutamide (B), AR associates with a nuclear receptor corepressor (N-CoR), which recruits histone deacetylases (HDACs) that repress gene transcription. The proinflammatory cytokine IL-1β activates MEKK1 resulting in phosphorylation of TAB2. Upon phosphorylation, TAB2 changes its conformation, increases its affinity for N-CoR, and relocates to the cytoplasm thereby tethering N-CoR away from AR, culminating in derepression of target gene expression. The subsequent recruitment of coactivators (CoAs) together with histone acetyltransferases (HATs) to AR results in target gene activation.

of their ability to execute diverse functional activities including phagocytosis, matrix degradation and tissue remodeling, and production of growth factors, cytokines, and chemokines. However, the observations of Zhu et al. (2006) suggest that these infiltrating cells may also provide the cellular signals for local expression of genes otherwise repressed by sex hormone receptors. Using breast cancer cells, the authors demonstrate that IL-1β reverses E_2-mediated repression of a limited number of genes, some with relevance to reproduction, by interfering with the N-CoR/TAB2/ERα complex. Functional "switching" of cellular responses to natural hormones by inflammatory cytokines is an attractive model with direct relevance to various reproductive events. For instance, uterine quiescence during pregnancy is dependent upon progesterone-mediated repression of genes that encode proteins associated with muscle contraction. However, transition to muscle contractions during labor does not require a fall in circulating progesterone levels but is invariably preceded by an influx of immune cells into the myometrium and cervix and local expression of inflammatory cytokines (Mendelson and Condon, 2005). Preterm labor is now widely considered to be an inflammatory disease that accounts for the majority of neonatal deaths. Hence, by lifting the veil covering a hitherto unrecognized molecular mechanism, Zhu et al. (2006) have set new challenges. None of these challenges is more important than translating this new molecular information into more effective therapies for hormone-dependent cancers and common reproductive disorders.

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MEDEA Takes Control of Its Own Imprinting

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Genomic imprinting is an essential epigenetic process that controls the size of seeds in flowering plants. In *Arabidopsis*, DEMETER activates the maternal copy of the imprinted *MEDEA* Polycomb gene. In this issue of *Cell*, Gehring et al. (2006) demonstrate that this activation involves DNA demethylation of *MEDEA* by DEMETER. Remarkably, they also find that silencing of the paternal *MEDEA* allele is independent of DNA methylation and is controlled by maternal expression of MEDEA itself.

In flowering plants and placental mammals, some autosomal genes are expressed only from their maternally or paternally inherited copy. These unusual genes are called imprinted genes and play important roles in growth and development (Constância et al., 2004; Autran et al., 2005). In plants, imprinted-gene expression seems to be confined to the endosperm, which originates from fertilization of the central cell—a diploid germ cell—in the female gametophyte. Fertilization of the adjacent haploid cell by a second sperm gives rise to the embryo proper. Thus, two fertilization events generate a seed with a triploid endosperm and a diploid embryo (see