Summary

Adipocyte tissue functions mainly as a long term fat storage. However, it is also an important endocrine organ. An imbalance to its normal function induces obesity and associated diseases. atRA, the biologically active form of vitamin A, is an important ligand for RAR nuclear receptor, and supplementary vitamin A has protective effects in many disorders. Other than playing important roles in vision, reproduction, cell proliferation and differentiation, embryogenesis, immune response and growth, this thesis provides the evidence for a nongenomic signaling pathway of atRA and demonstrates how atRA triggers the MEK1 nuclear accumulation by site specific retinoylation of CRM1. This is followed by nuclear MEK1 sequestration of PPARγ away from its target genes and thus inhibiting adipogenesis. Additionally, the nuclear sequestration of MEK1 temporally prevents phosphorylation of cytoplasmic ERK which may be affecting activation of adipocyte differentiation. This result provides a unique insight into atRA-stimulated nongenomic signaling pathway that modulates specific posttranslational modifications and molecular interaction of proteins, which contributes to the slow and continuous nuclear accumulation of important regulatory molecules MEK1 which promote sequestration of nuclear PPARγ phosphorylation and inhibits cytoplasmic ERK1 activation and thus inhibits adipocyte differentiation at early stage.

The phytotherapeutic protein stem bromelain (SBM) is used as an anti-obesity medicine, but its mechanism of action has been elusive. We showed that SBM irreversibly inhibits 3T3L1 adipocyte differentiation by reducing adipogenic gene expression and induces apoptosis and lipolysis in mature adipocytes. At a molecular level, SBM suppressed adipogenesis by downregulating CEBPa and PPARγ independent of CEBPβ gene expression. Moreover, mRNA levels of PPARγ target genes ap2, FAS, LPL, CD36, and ACC were also downregulated by SBM. Additionally, SBM reduced adiponectin expression and secretion. SBM's ability to repress PPARγ expression seems to stem from its ability to inhibit Akt and augment the TNFα pathway. The Akt–TSC2–mTORC1 pathway has recently been described for PPARγ expression in adipocytes. In our experiments, TNFα upregulation compromised cell viability of mature adipocytes (via apoptosis) and induced lipolysis. Lipolytic response was evident by downregulation of anti-lipolytic genes perilipin, phosphodiestersae-3B (PDE3B), and GTP binding

protein ($G_i\alpha_i$), as well as sustained expression of hormone sensitive lipase (HSL). These data indicate that SBM, together with atRA, may be a potent modulator of obesity by repressing the PPARγ-regulated adipogenesis pathway at all stages and by augmenting TNFα-induced lipolysis and apoptosis in mature adipocytes.