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An interlocked feed-forward loop circuit can explain the phenotypic heterogeneity of fat-cell differentiation.

Adipogenesis, the differentiation process of adipocyte (fat cell) formation from precursor cells contributes to increase of fat tissue in obesity. Population-averaged analysis predicts that during adipogenesis many adipocyte-specific proteins increase monotonically in time. However, previous work has found that some of these proteins, namely the hormone adiponectin, and transcriptional regulators PPAR gamma, and C/EBP alpha, increase and then decrease significantly during differentiation. The observed monotonicity is simply an illusion of population averages. Instead, there is a group of cells with high adiponectin and low lipid droplet level, and another group of cells with high LD, but low adiponectin. It was suggested that these subpopulations correspond to different temporal stages of adipogenesis. Three coupled network motifs found in adipocytes can explain these observations. PPAR gamma and C/EBP alpha trigger an incoherent feedforward loop in adiponectin production, leading to a pulse of adiponectin that disappears after a few days. A coherent feedforward loop in lipid synthesis leads to a delayed production of lipid droplets. Other systems that have an interlocked FFL circuit, also exhibit this pattern of a pulse of 'early' gene expression followed by expression of the 'late' genes.