FIGURE 18.1 Inhibition of neutrophil elastase by α_1-antitrypsin and the structural basis of polymerisation. (a) Native α_1-antitrypsin (M) contains three β-sheets and nine α-helixes. After docking (left) the neutrophil elastase (gray) is inactivated by movement from the upper to the lower pole of the protein (right). This is associated with the insertion of the RCL (red) as an extra strand into β-sheet A (green). The enzyme is irreversibly trapped, distorted, and inactivated. (b). The Z mutation of α_1-antitrypsin (Glu342Lys at P_{17}; arrowed) perturbs the structure of β-sheet A (green) and the mobile reactive center loop (red) to form the intermediate M*. The patent β-sheet A can then accept the loop of another molecule (as strand 4) to form a dimer (D) which then extends into polymers (P) [20–22]. It is these polymers that accumulate within hepatocytes to cause liver disease [4]. The position of the lateral hydrophobic pocket that is the target of rational drug design is shown with a blue arrowhead. Note the change in conformation in this region of the molecule as it forms M* and then dimers and polymers.
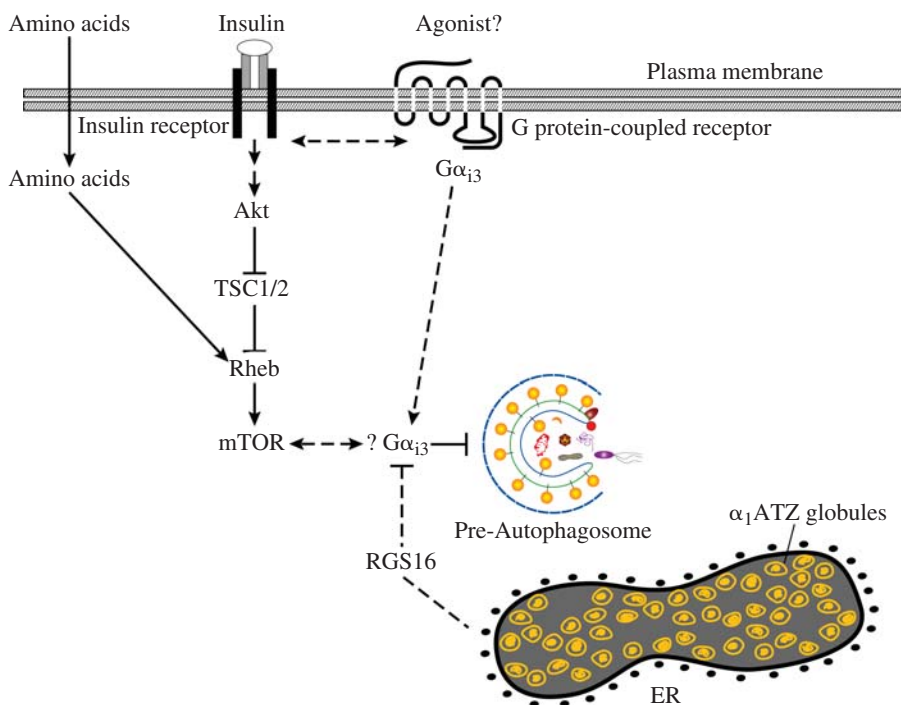
FIGURE 18.2 Theoretical role of RGS16 in activating the hepatic autophagic response in α_1-antitrypsin deficiency. Amino acids and insulin/IGF-1 signaling inhibit autophagy through mTOR. The G protein Gαi3 plays a role in inhibition of autophagy by mTOR. Induction of RGS16 when mutant Z α_1-antitrypsin accumulates in the ER antagonizes Gαi3, thereby de-repressing autophagy. (From D. H., Perlmutter 2007, *Cell Death and Differentiation*, *16*, 39–45.