Unconventional Protein Secretion as a Target for New Drug Development

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Most eukaryotic secretory or membrane proteins reach the plasma membrane through the conventional endoplasmic reticulum (ER)-Golgi pathway. However, evidence suggests that many cytoplasmic, nuclear, and signal-peptide-containing proteins also can reach the cell surface via a Golgi-bypassing route. Unconventional protein secretion (UPS) can be classified into two broad categories: (i) the extracellular secretion of cytosolic proteins that do not bear a signal peptide (i.e. leaderless proteins) and (ii) the cell-surface trafficking of transmembrane proteins via a route that bypasses the Golgi. Understanding the UPS pathways is not only important for elucidating the mechanisms of intracellular trafficking pathways, but also has important ramifications for human health, because many of the proteins that are unconventionally secreted from mammalian cells and microorganisms are associated with human diseases, from common inflammatory diseases to the lethal genetic disease of cystic fibrosis. Therefore, it is timely and appropriate to summarize and analyze the mechanisms of UPS involvement in disease pathogenesis, which may be helpful for the development of new therapeutic approaches. In this review, we discuss the intracellular trafficking pathways of UPS cargos, particularly those related to human diseases. We also outline the disease mechanism and the therapeutic potentials of new strategies for treating UPS-associated diseases.