PROTEOLYSIS

1) protein maturation + targeting → selective + limited

a) removal of signal peptide ("presequence") from pre-proteins

b) transformation of pro-proteins (zymogens) into active proteins

pre-pro-insulin → pre-insulin → insulin

pro-chymotrypsin = trypsinogen → trypsin

POMC → peptides

etc.

2) protein degradation into

cytosol

EUCARYOTES: DUAL SYSTEM

a) amino acids → in lysozomes

b) short peptides → in proteasomes = dependent on ATP

(~ 9 aa)

Function:

a) to eliminate abnormal proteins

b) to eliminate superfluous proteins + regulatory proteins (inhibitors) – to permit the regulation of cellular metabolism

Cells continuously synthesize proteins from and degrade them to their component aa's = CONSTANT TURNOVER OF CELLULAR PROTEINS

Proteins have a very different half-life:

enzymes that occupy important metabolic control points ← a few minutes: ornithine decarboxylase ~ 11 min

RNA polymerase I ~ 78 min

enzymes that have nearly constant catalytic activities under all physiological conditions ← weeks or more: LDH ~ 130 h

cytochrome c ~ 150 h

LYSOSOMES

organelles 0.1 – 0.8 µm
form by budding from the Golgi app.
multiply by fission
bounded by a single membrane
→ usually membranous bags containing a large (~50) variety of hydrolytic enzymes acting at acidic pH (pH optimum ~ 5):

nucleases
proteases — CATHEPSINES & CASPASES
lipases
phosphatases
glycosidases
phospholipases
sulphatases

↓
protection of cell content (pH ~ 7,4) against accidental release of lysosomal enzymes (lysosomal leakage).

FUNCTION :

1) to digest materials introduced by endocytosis
2) to recycle intracell. constituents by fusion with membrane enclosed bits of cytoplasm known as autophagic vacuoles and subsequently breaking down their content

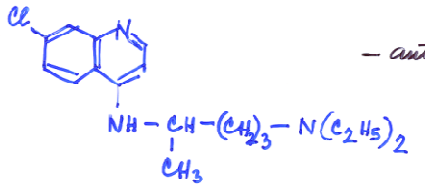
DIGESTION
is mostly nonselective = in well nourished cells
but becomes selective = activated by a prolonged fast :
to prevent depletion of essential enzymes & regulat. pr.
and to preferentially degrade proteins containing the pentapeptide Lys-Phe-Glu-Arg-Gln (KFERQ) or a closely related sequences.

KFERQ proteins are selectively lost in fasting animals from tissues that atrophy in response to fasting (liver, kidney) but not from tissues that do not do so (brain, testes). KFERQ proteins are specifically recognized and delivered to lysosomes by a 73 kD recognition protein (Hsp 70 family member)

INCREASED LYSOSOMAL ACTIVITY

- in Diabetes mellitus – degradation of proteins
- disuse, denervation of muscles, traumatic injury – muscle wastage
- regression of uterus after childbirth – organ reduction from 2kg → 50g in 9 days
- rheumatoid arthritis – extracell. release of lysosomal enzymes, break down of surrounding tissues
- porphyrias – accumulation of porphyrins / or their precursors (PBG) in the skin (a hereditary disease) → photodynamic effect: ↑ photosensitivity → ROS → break down of lysosomal membranes → skin ulcers + scars

LYSOSOMAL INHIBITORS

chloroquine  – antimalarial drug

a weak base, penetrates the lysosomal membrane in a neutral form, ↑ intralysosomal pH → inhibition of the lysosomal f.

in Plasmodium falciparum – chloroquine (quinine) blocks the crystallization of toxic heme into nontoxic β-hematin brown granules