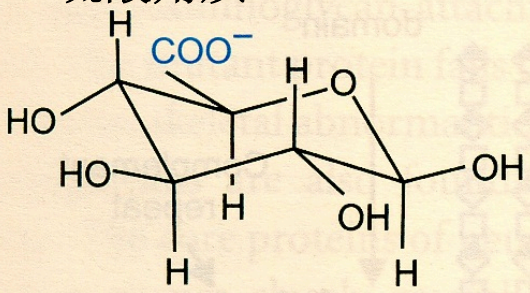
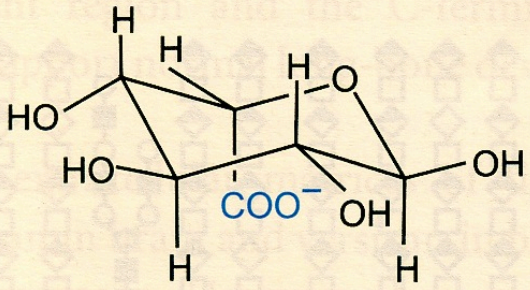
2.5 Proteoglycans(蛋白聚糖) are heavily O-glycosylated proteins that give strength to the extracellular matrix

- Proteoglycans bind water, but they provide structure rather than lubrication
- O-linked glycans of a mucin is small
- Glycans attached to proteoglycans are very large, containing as many as 100 residues
- Linear chains consisting of alternating amino sugars and hexopyranosides
- Names of glycosaminoglycans (GAG) reflect the tissue originally isolated

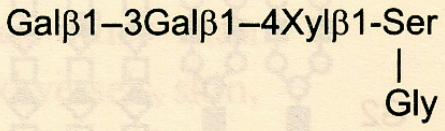
Glycosaminoglycan	A unit	B unit	Protein core	Linkage	Tissues
Hyaluronic acid 透明质酸	GlcA	GlcNAc	No	None	Connective tissues, skin, cartilage, synovial fluid
Chondroitin sulphate 硫酸软骨素	GlcA	GalNAc	Yes	*O*-Xylose	Cartilage, cornea, bone, skin, arteries
Dermatan sulphate 硫酸皮肤素	GlcA/IdoA	GalNAc	Yes	*O*-Xylose	Skin, blood vessels, heart valves
Heparan sulphate 硫酸乙酰肝素	GlcA/IdoA	GlcNAc	Yes	*O*-Xylose	Lung, arteries, cell surfaces
Keratan sulphate 硫酸角质	Gal	GlcNAc	Yes	*N*-GlcNAc	Cartilage, cornea



D-Glucuronic acid (GlcA)



L-Iduronic acid (IdoA)

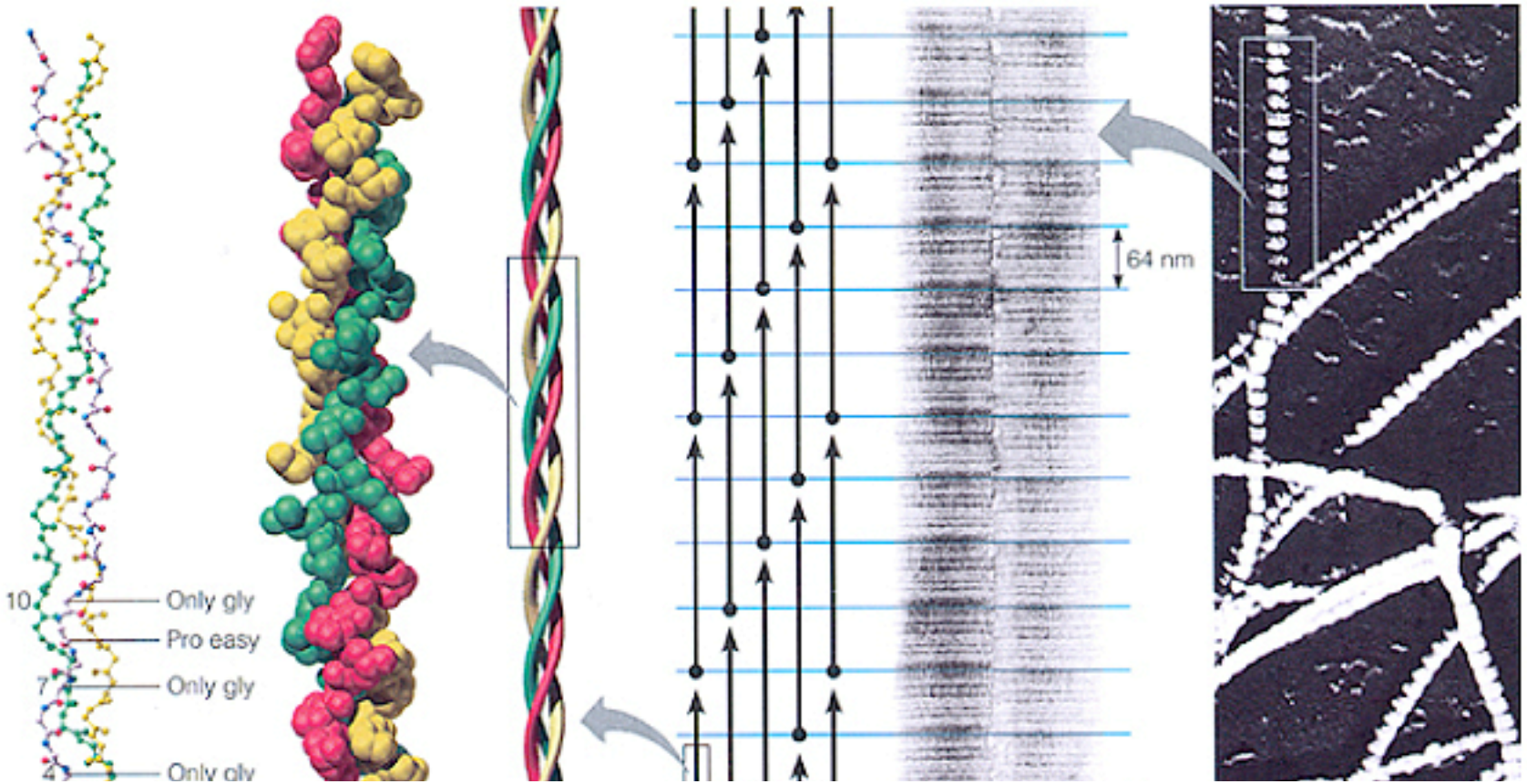


O-Xylose linkage region

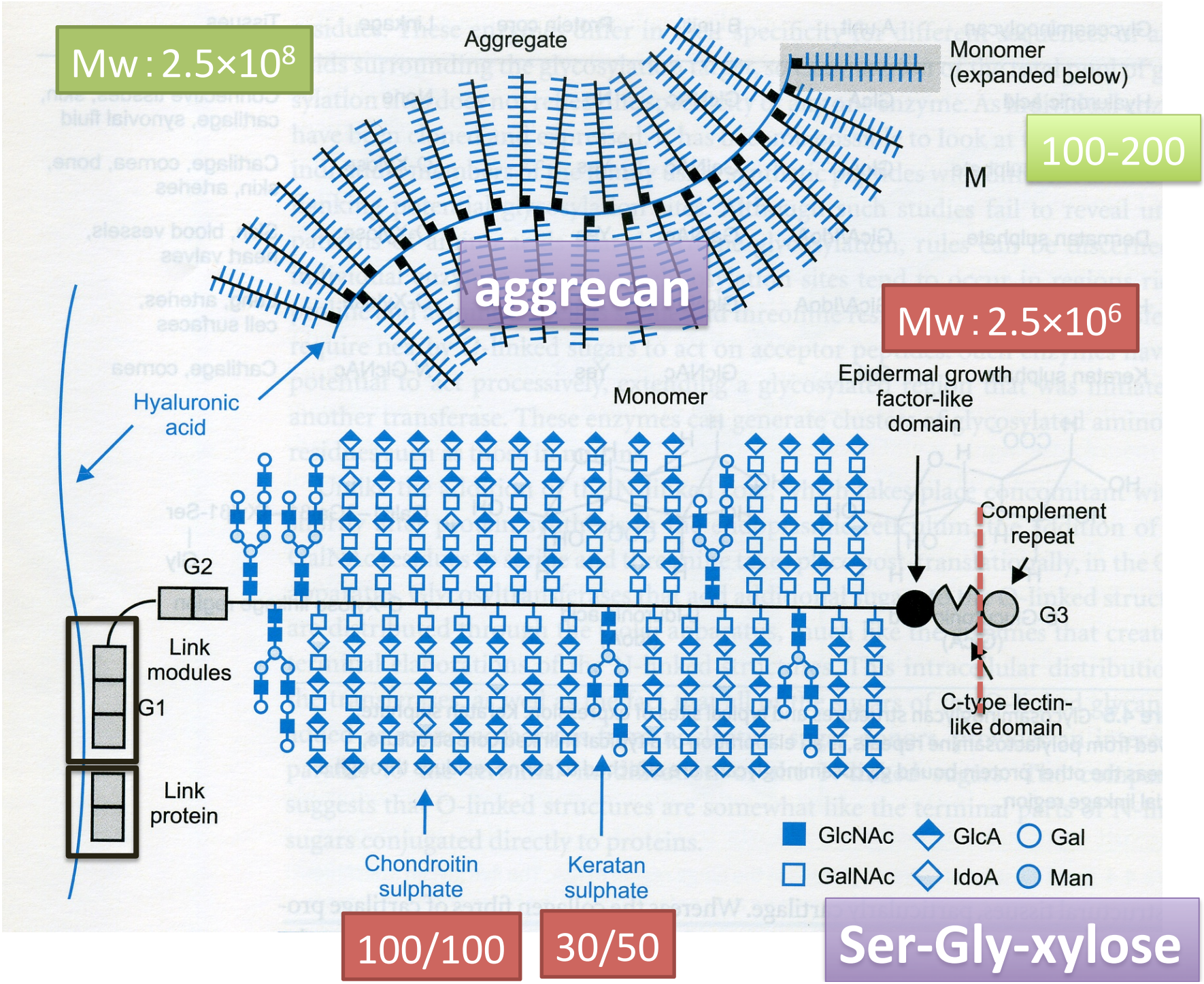
Hyalin (透明素) membrane, cartilage (软骨), and skin

- Two major classes: those found in extracellular matrix and those located in plasma membranes
- Those found in structure tissues are best understood: e.g. cartilage (软骨)
- The collagen (胶原蛋白) fibres of cartilage provide stiffness (resistance to bending) and strength (resistance to pulling)
- Proteoglycans provide resilience(弹性), resistant to compression (压缩) under pressure
- This function depends on a high degree of supramolecular organization

Collagen

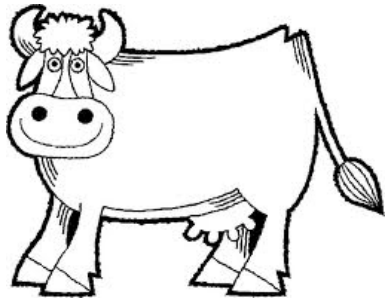


chempolymerproject.wikispaces.com


Mw : 2.5×10^8
Aggregate
Monomer
(expanded below)
100-200
M
aggrecan
Mw : 2.5×10^6
Hyaluronic
acid
Monomer
Epidermal growth
factor-like
domain
Complement
repeat
G2
G3
Link
modules
G1
Link
protein
C-type lectin-
like domain
Chondroitin
sulphate
Keratan
sulphate
GlcNAc
GlcA
Gal
GalNAc
IdoA
Man
100/100
30/50
Ser-Gly-xylose

- Providing resilience in cartilage is a consequence of their highly hydrated state
- Water binding is mediated by the sugars and large amount of sulphate residues
- Resulting large volume occupied by an aggregate
- It can only be reduced under pressure, by releasing water
- Aggregates are molecular shock absorbers or very stiff sponges
- Releasing water slowly under pressure and taking it back up when pressure is released

Cartilage in various joints (关节) and in vertebral discs (椎盘) effectively cushions (缓冲) the jolts (震动)



GAG-attachment regions become longer

Segments of the aggrecan gene encoding this portion are expanded

- In fowls (鸡)
- Naturally occurring nanomelia (短肢畸形) mutation (突变) results in a truncated aggrecan core protein lacking much of the GAG and C-terminal G3 globular domain
- The mutant protein fails to support normal long-bone development, resulting in drastic skeletal (骨骼) abnormalities (异常)

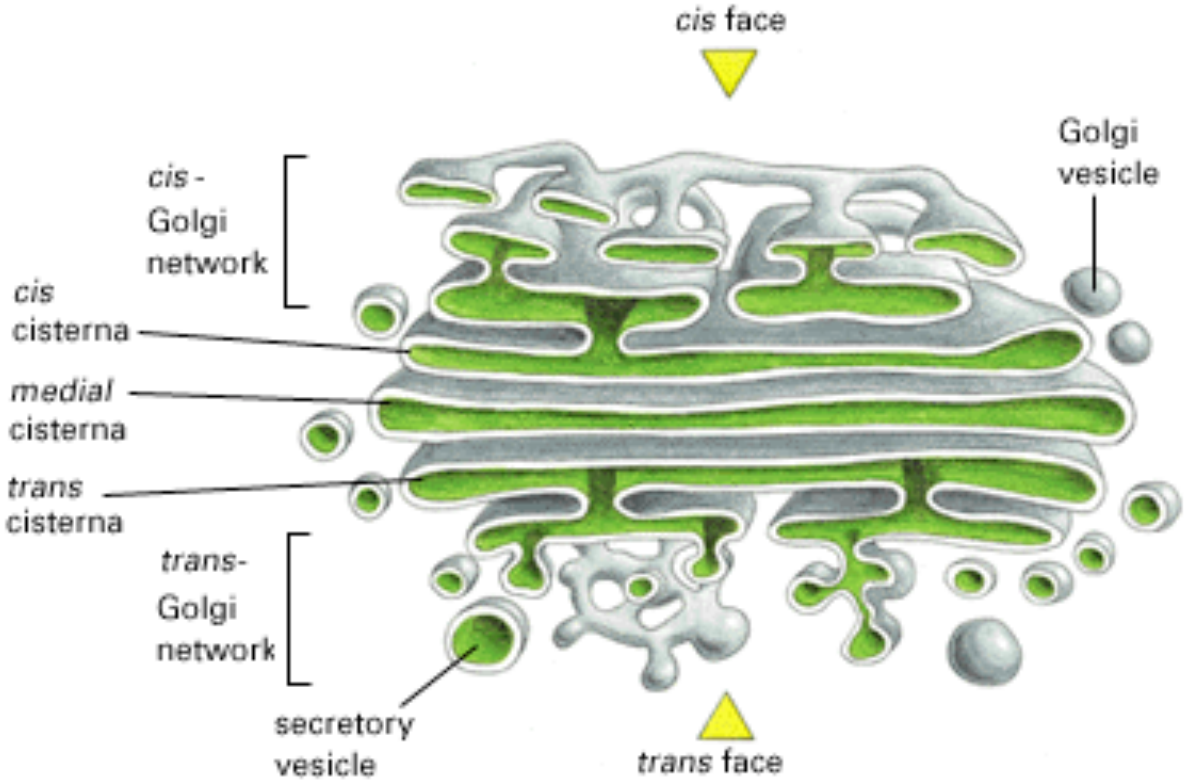
- Proteoglycans found in extracellular matrices of tissue other than cartilage
- Core proteins of neurocan in brain and versican in blood vessels, skin, and other tissues closely resemble aggrecan
- Different GAG can be conjugated
- E.g. Perlican, a complex modular protein consisting of multiple copies of at least six different types of globular domain and bearing just a few GAG chains
- No details of selections of GAG providing physical and organizational properties that suit the requirement of individual tissues

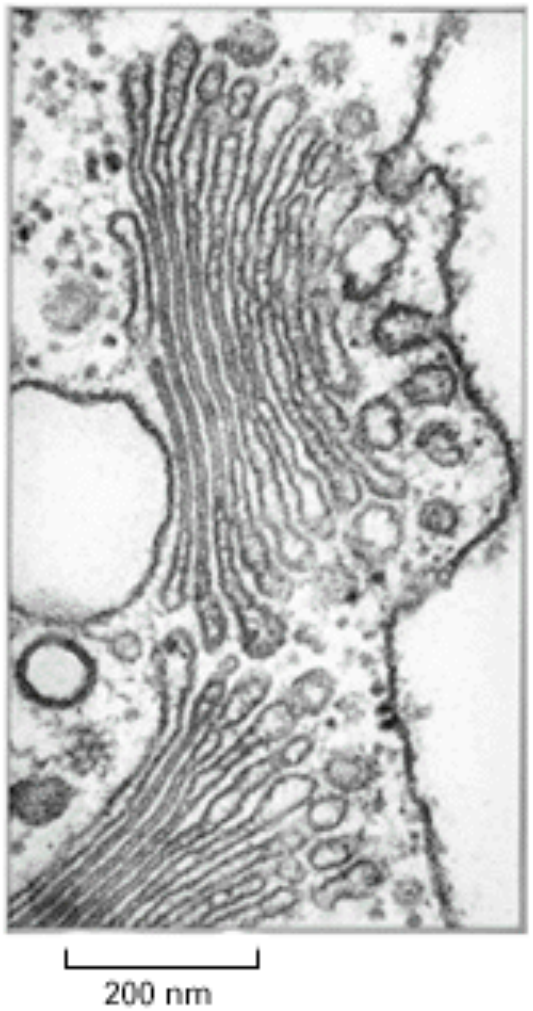
2.6 Biosynthesis of proteoglycans requires several modifying enzymes in addition to glycosyltransferases

- Target sequences for GAG attachment: serine-glycine
- Not all of them are derivatized in this way
- Additional signals in protein structure defines attachment sites
- Addition of chains in clusters results from processive activity of the core xylosyltransferase
- Adjacent Ser-Gly are targets for the enzyme after glycosylation of an initial sequence
- A cluster of negative charges directs the enzyme

- Assembled by successive one-step additions of monosaccharides
- After assembly of the common trisaccharide core, the attachment of different GAG to different proteoglycan core partly reflects different patterns of transferase expression in different tissues
- Synthetic results indicate pattern of flanking AAs influence the type of chain to be synthesized

- Elongation of GAG involves sequential addition of alternating sugar and sugar acid
- Heparan: coupled Glucuronic acid and GlcNAc-Transferases
- Not clear what determines the ultimate size of the GAG chains
- Unlike polylactosamine chains, no competing capping rxn
- **Overall residence time in the appropriate compartments of the Golgi apparatus (高尔基体) or the physical dimensions of the cisternae may limit the size of the chains**



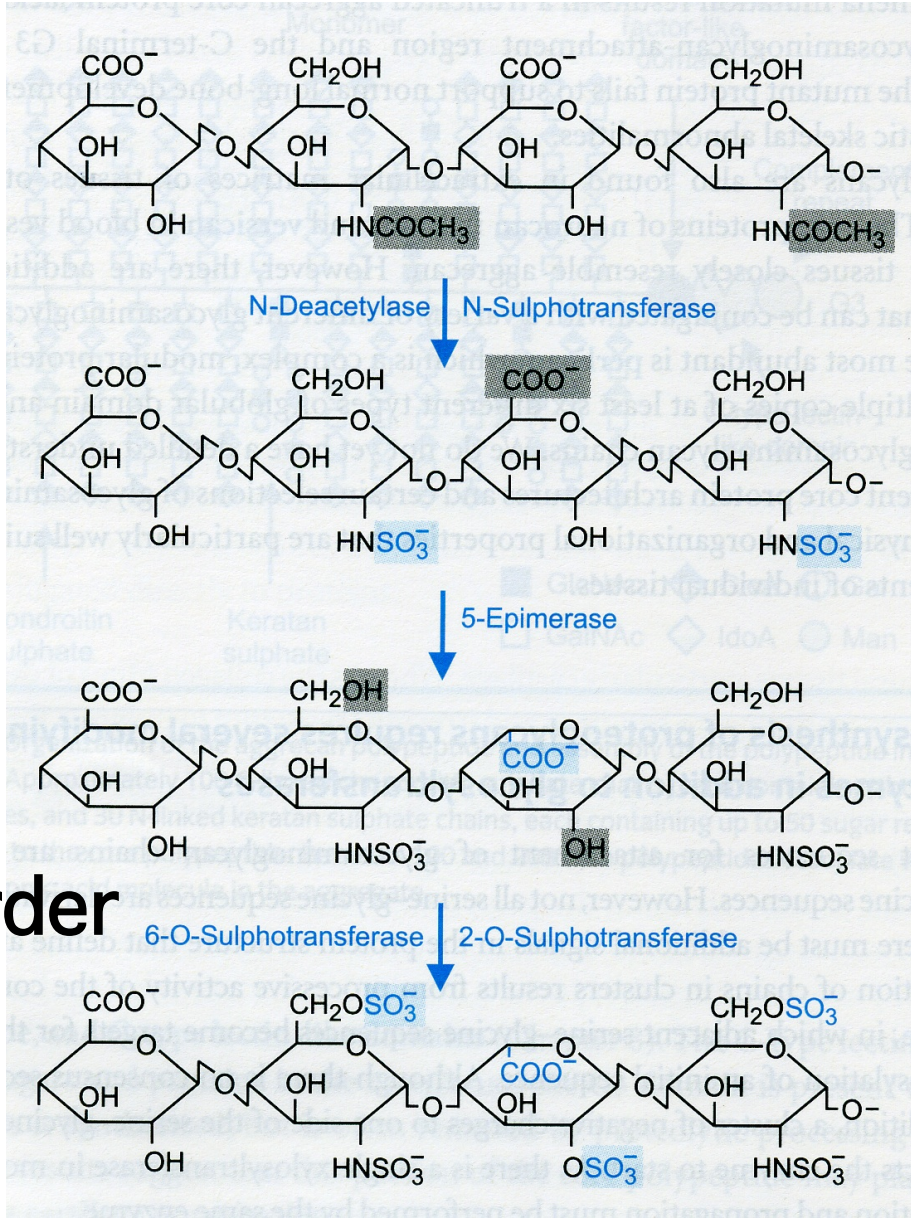


http://219.221.200.61/ywwy/zbsw%28E%29/edetail7.htm

Final structures are the result of a further series of modifications to the initially synthesized GAG

Establish sequences involved in growth factor (生长因子) and fibronectin (纤维连接蛋白) binding

Untemplated
Separately
Obligatory (强制的) order



2.7 unusual types of O-linked glycosylation are found on some proteins

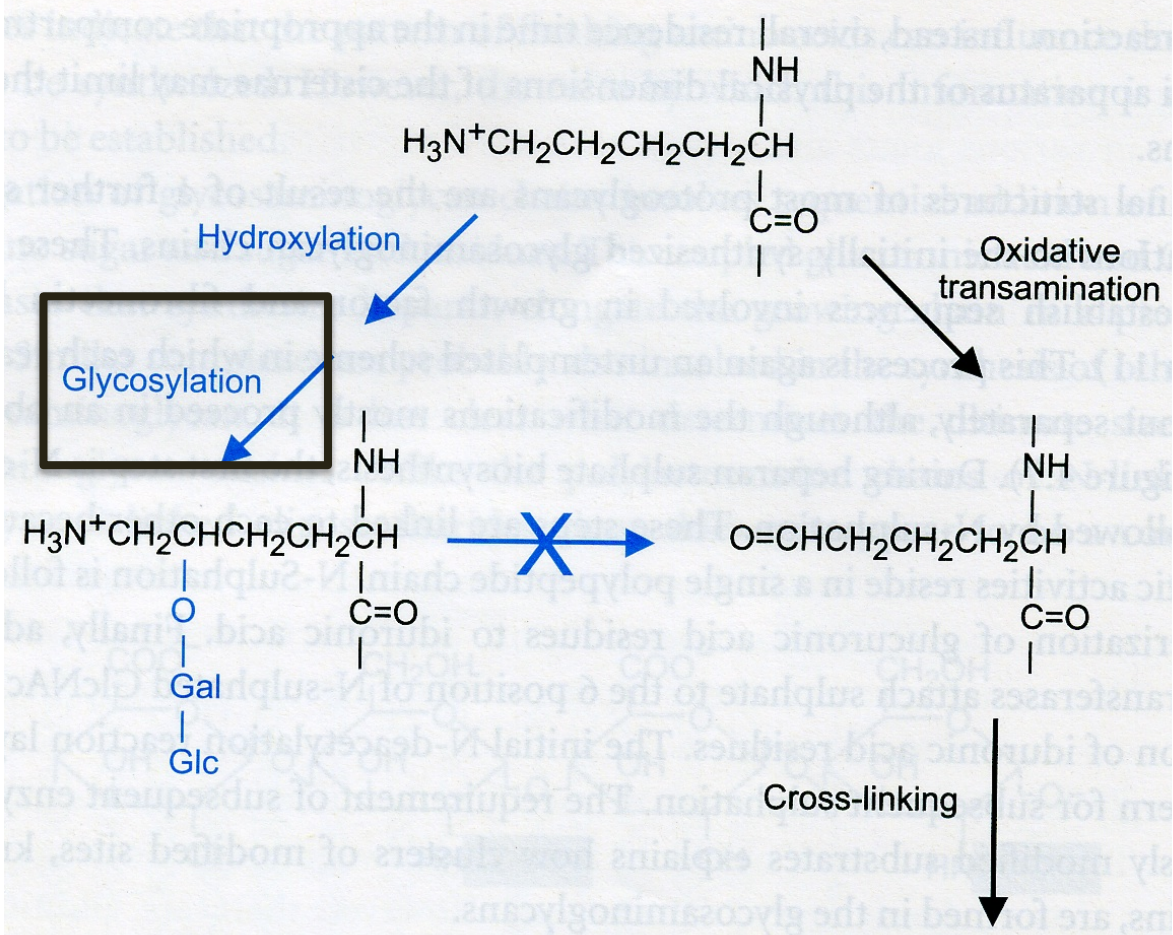
- Much of variety in O-linked glycosylation comes from different terminal elaborations attached to the core structures
- Other linkages:
- Fucose and mannose linked to Ser or Thr in cell-surface and secreted proteins
- Sugars attached to the OH of tyrosine
- Glc-tyrosine linkage found in the core region of glycogen, as the anchor for growth of the branched glycogen

Ubiquitous O-glycosylation: found in collagens and proteins with collagen-like triple-helical domains

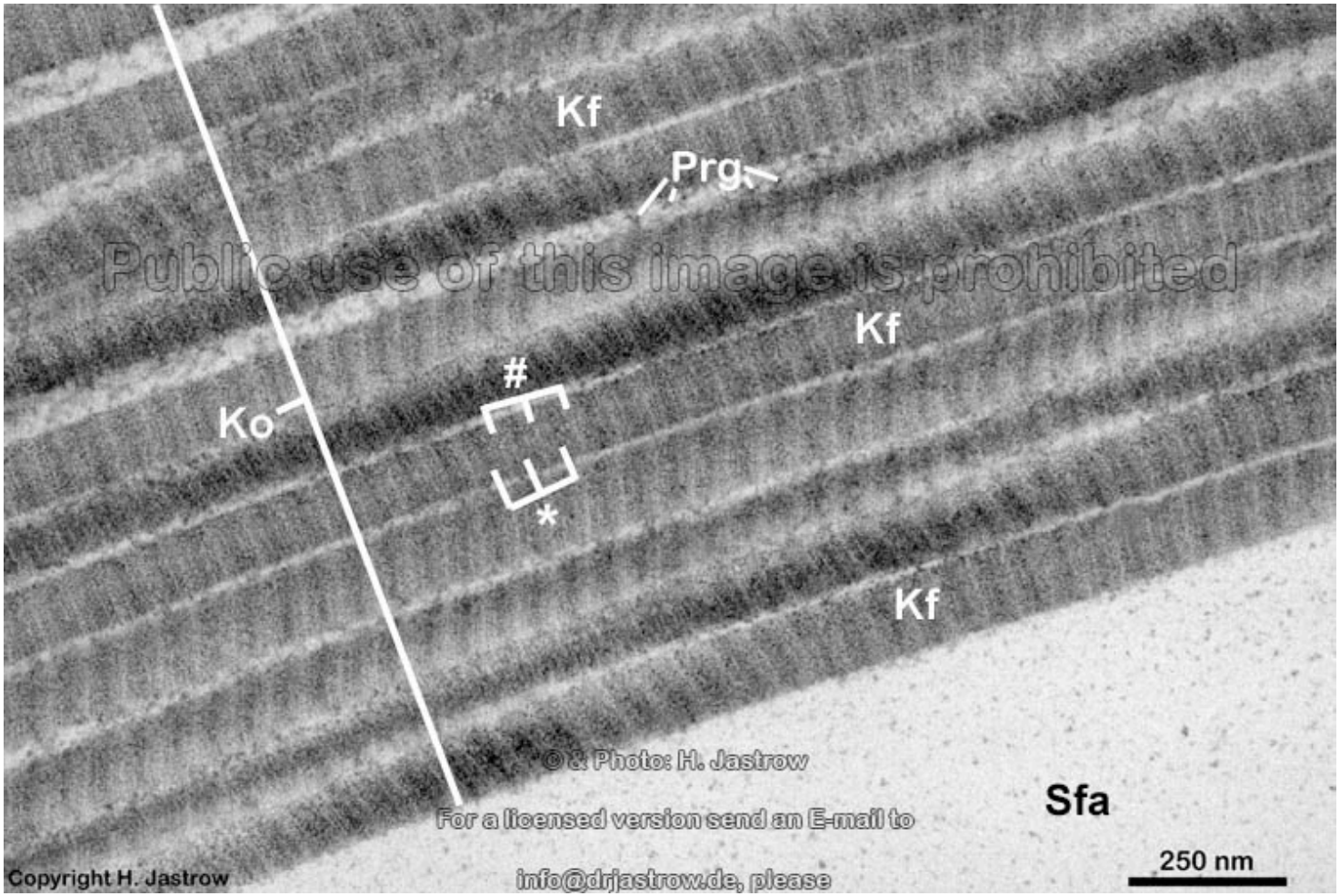
Lysine found at Yaa of Gly-Xaa-Yaa triplets are modified by lysyl hydroxylase, generating 4-hydroxylysine

No effect on triple helix

But affect cross-linking of fibres formed by bundling of triple-helical domains



Highly ordered supramolecular structure

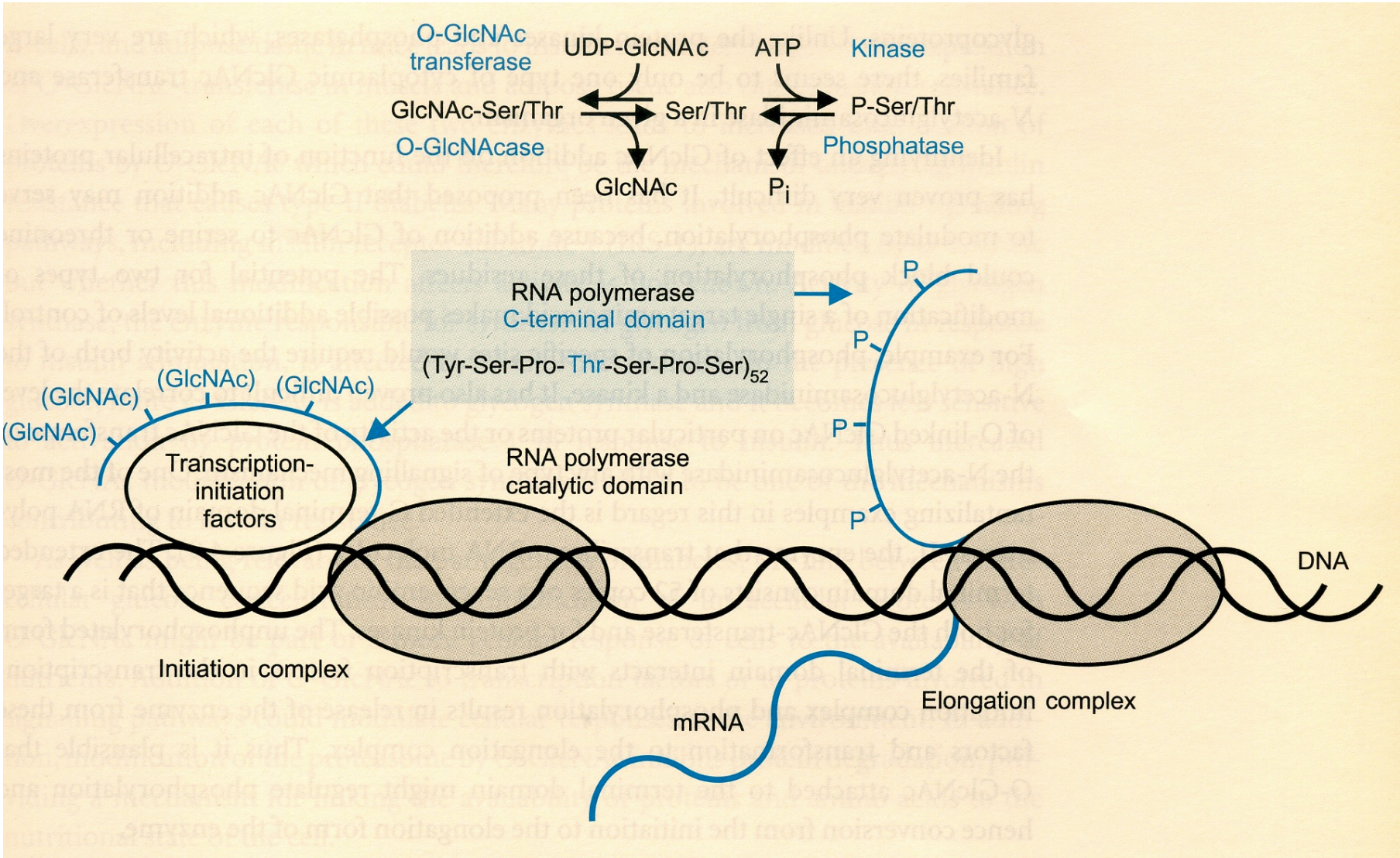


http://www.uni-mainz.de/FB/Medizin/Anatomie/workshop/EM/eigeneEM/BG/HomoBG7okbE.html

2.8 Cytoplasmic and nuclear proteins can be modified by addition of O-linked N-acetylglucosamine

- Although most glycosylation of proteins occurs in extracytoplasmic compartments
- O-GlcNAc is quite common in the cytoplasm (细胞质)and nucleus (细胞核)
- A soluble GlcNAc-transferase catalyses attachment of GlcNAc in β1 linkage to Ser and Thr
- Almost unique among glycosylations: reversible
- A soluble N-acetylglucosaminidase removes the GlcNAc, which can then be replaced by the transferase

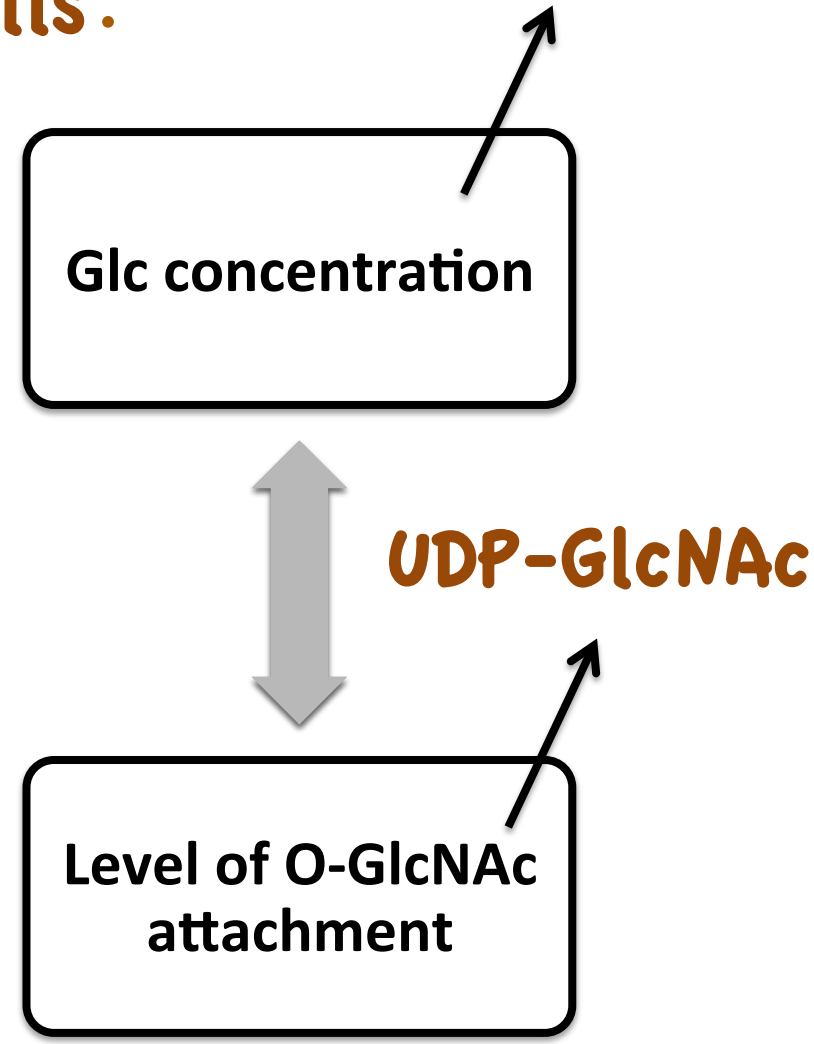
The extent of GlcNAc modification of any particular ser/thr reflects a dynamic balance between the actions of the transferase and glycosidase.



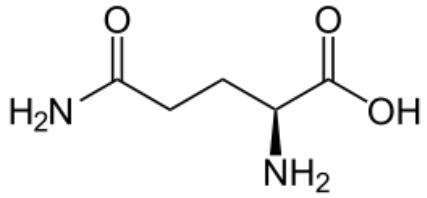
- Long list of proteins as targets for O-GlcNAc
- Some associate with the nucleus and nuclear pore complex, including many transcription factors (转录因子)
- Now they encompass every category of proteins, exposed to cytoplasm, of the cytoskeleton and plasma membrane and soluble proteins
- O-GlcNAc has been identified in all eukaryotic cells (真核细胞), including single-celled organisms, e.g. yeast

2.9 O-linked N-acetylglucosamine is part of a metabolic sensor system that is affected in diabetes

In some cells:



Hexosamine biosynthetic pathway



Glucose → Fructose-6-phosphate

谷氨酸(Glutamine)
Amido transfer and
Isomerization

Overexpression of this amido transferase

glutamine:fructose-6-phosphate amidotransferase

Glucoamine-6-phosphate → UDP-GlcNAc

Insulin resistance

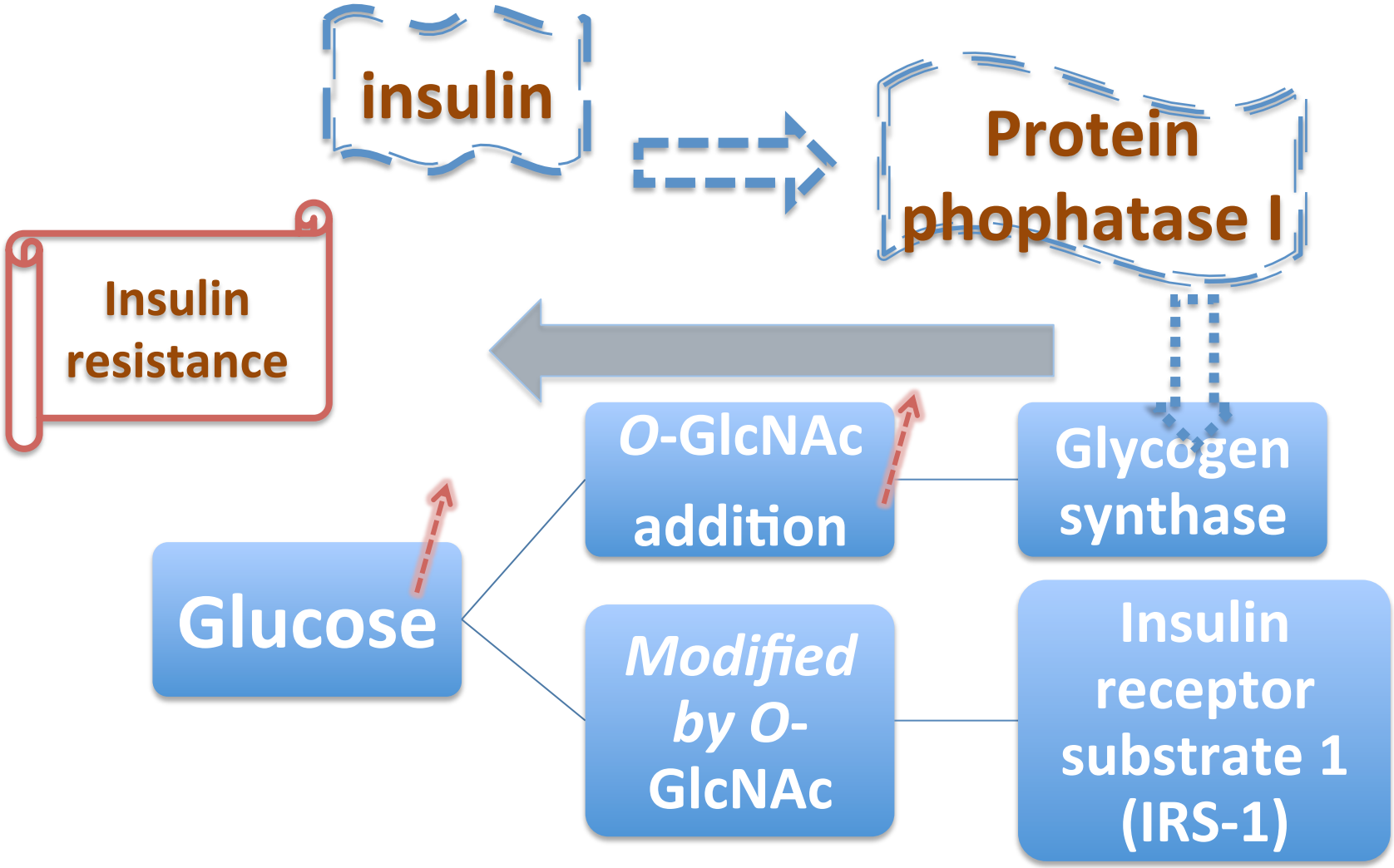
Concentration sensitive

Over expression

Type II diabetes

O-GlcNAc transferase activity activity

- Increased glucose flux in insulin-sensitive tissues
- Linking to the development of insulin resistance that causes type 2 diabetes
- Evidence:
- Overexpression of amidotransferase in skeletal muscle, pancreatic β-cells, and adipose tissue
- Overexpression of O-GlcNAc transferase in muscle and adipose tissue also causes insulin resistance
- Leads to increased modification of resistance that causes type II diabetes



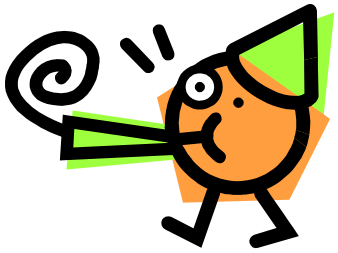
Glycogen Synthase: Responsible for Synthesis of Glycogen From Glc in Response to Insulin Stimulation

- Glucose concentration----modification of intracellular protein with O-GlcNAc
- Part of general response of cells to the availability of nutrients
- Addition of O-GlcNAc to transcription factors or to proteins involved in signalling pathways could modulate cellular responses to the environment
- Modification of the proteasome inhibits protein degradation
- Providing a mechanism for linking the availability of proteins and AAs to the nutritional state of the cell

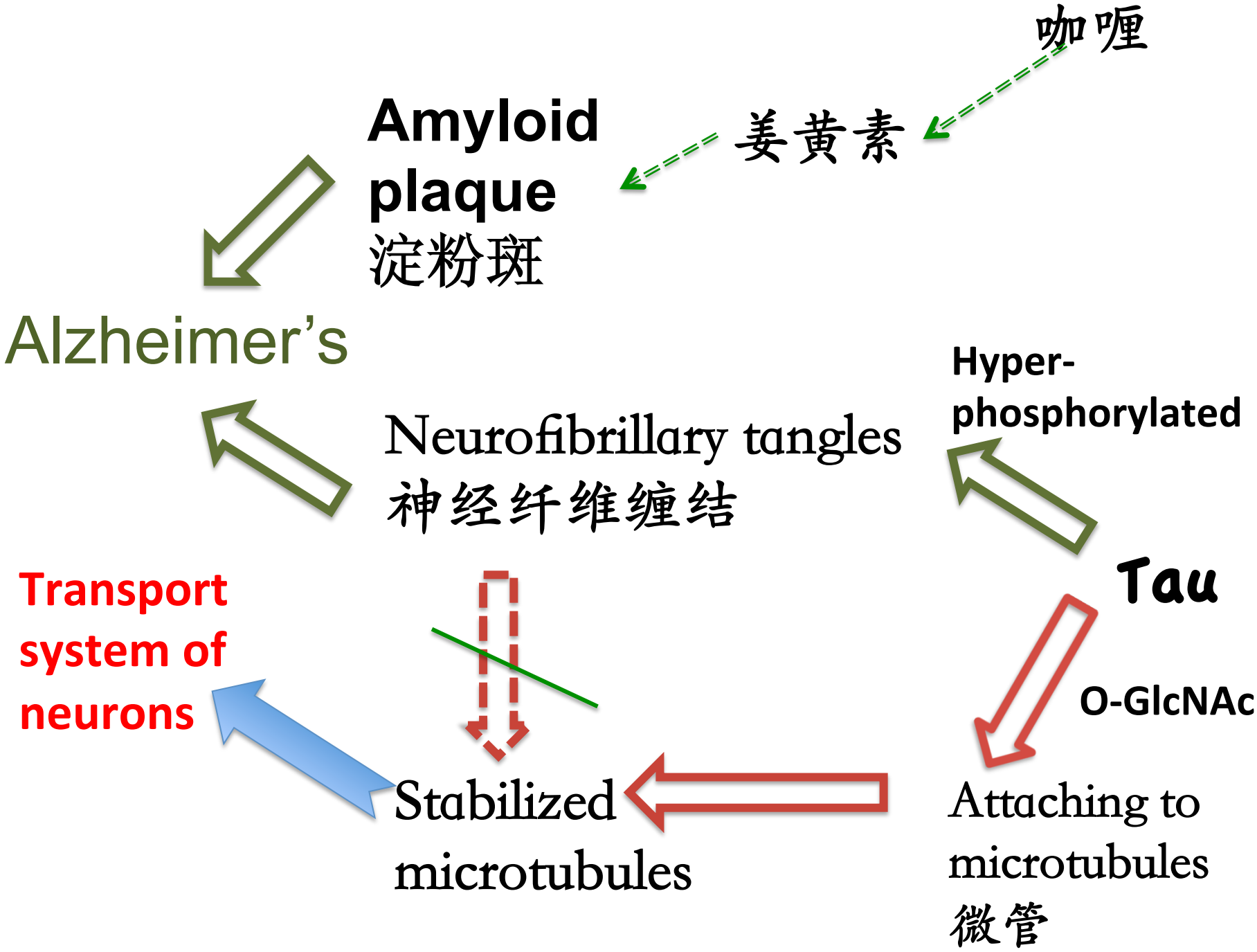
- Cells lacking GlcNAc-transferase for making O-GlcNAc are not viable
- This modification plays an essential part in cell physiology
- Galactosyltransferase introduced into cells causes modification of the O-GlcNAc with a galactose and prevents its release by N-acetylglucosminidase
- These cells die within one cell cycle, confirming one essential role of G-GlcNAc
- **A vital and unique role in the control of cellular processes**

Changes in O-linked N-acetylglucosamine are linked to Alzheimer's disease (老年痴呆症)

Glycobiology of disease



- Many brain proteins are modified by O-linked GlcNAc and involved in the pathology of neurodegenerative diseases such as Alzheimer's disease
- Microtubule-associated protein tau contains O-linked GlcNAc
- Six isoforms of tau in human brain, all involved in stabilizing microtubules that assemble from tubulin monomers
- Aggregated tau is the main component of filaments that accumulate in degenerating neurons
- In Alzheimer's disease and neurodegenerative desease


咖喱
姜黄素
Amyloid plaque
淀粉斑
Alzheimer's
Hyper-phosphorylated
Neurofibrillary tangles
神经纤维缠结
Tau
Transport system of neurons
O-GlcNAc
Stabilized microtubules
Attaching to microtubules
微管