Myocardial Hypertrophy

Ralph Knöll
Professor & Chair

Lecture 5

Anatomy

- Four chambers
  (2 atria, 2 ventricles)

  Right side – venous system

  Left side – arterial system

- Valves:
  four different valves

  Tricuspide -, Pulmonal-,

  Mitral-, Aortic valves

- Conduction system
  Sinus node, atrio-ventricular node
  His bundl,

  Purkinje-Fibres

Normal measures

- Weight
  - Men 300 – 350 g
  - Women 250 – 300 g

- Wall thickness
  - right Ventricle 3 – 5 mm
  - left Ventricle 13 – 15 mm

- Ventricle volumes
  - enddiastolic 140 ml per Ventricle
  - stroke volume 70 ml

Cardiomyocytes

- Cell membrane (sarcolemm), T-Tubuli
  - part of conduction system
- Sarcoplasmic Reticulum
  - Calcium Reservoir
- Contractile elements, Cross striation
- Mitochondria
- Nucleus
- Not a syncytium, cardiomyocytes are linked via disci intercalares

Sarcomere

Smallest functional contractile unit

Thick filaments (A-Band – Myosin)

Thin filaments (2-1 und A-Bands – Actin, Tropomyosin, Troponin)

Variable Length of 2.0 – 2.2 µm

More than 2.3 µm: less contractility (Why?)

Calcium influx activates contraction

Calcium efflux (calcium-pump in the SR): relaxation

Sarcomer: smallest functional unit

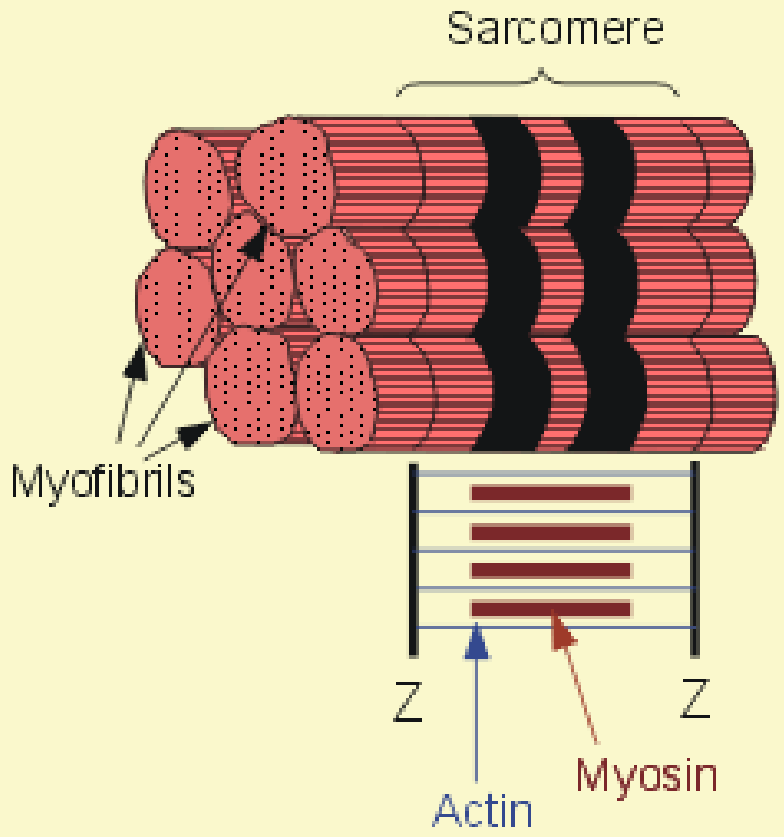
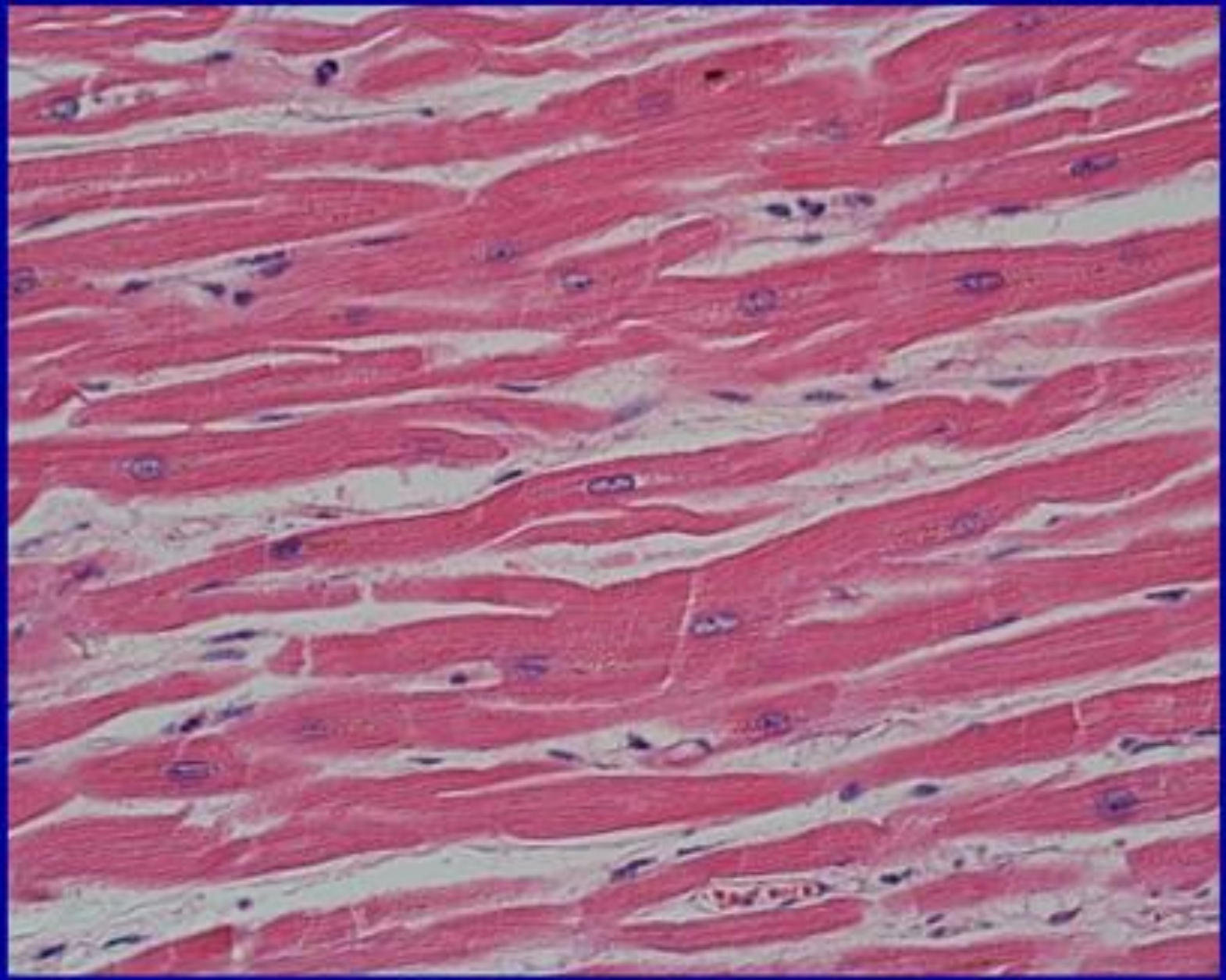


Figure 1. Cardiac myocyte composed of myofibrils, each of which contains myofilaments. The sarcomere lies between two Z-lines.

Kardiomyozyten

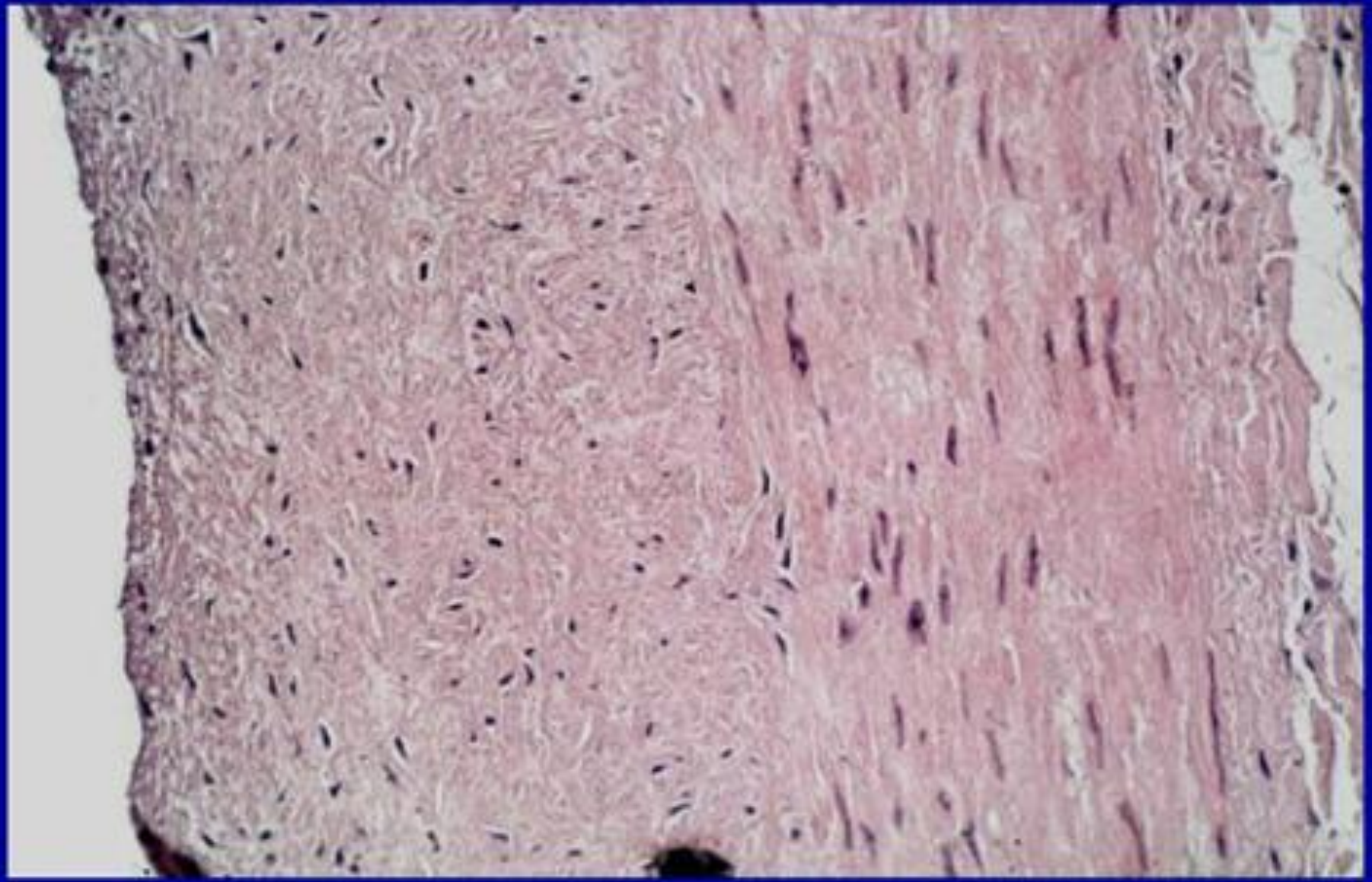


Coronary arteries

- Left coronary artery
- Ramus interventricularis anterior (RIVA, LAD)
  - anterior wall of LV, anterior septum
- Ramus circumflexus (LCX)
  - part of LV
- Right coronary artery (RCX)
  - right ventricle, posterior wall of LV, posterior septum

- Linksversorgungstyp, Rechtsversorgungstyp
- Functionally „End-arteries“
- Subepicardial localization
- Subendocardial myocardium = „difficult to provide with blood supply"

Koronararterie, normal



Hyperplasia

- Definition of Hyperplasia (hy·per·pla·sia):

  (Abnormal) increase in the number of normal cells in normal arrangement in an organ or tissue, which increases its volume

Hypertrophy

Hypertrophy (from Greek ὑπέρ "excess" + τροφή "nourishment") is the increase in the volume of an organ or tissue or due to the enlargement of its component cells.

It should be distinguished from **hyperplasia**, in which the cells remain approximately the same size but increase in number. Although hypertrophy and hyperplasia are two distinct processes, they frequently occur together.

Hypertrophy

- Ventricular hypertrophy is enlargement (hypertrophy) of the muscle tissue that makes up the wall of the heart's pumping chamber (left and / or right ventricles).
- Left ventricular hypertrophy develops in response to some factor, such as high blood pressure (“maladaptive hypertrophy”), or exercise (“adaptive hypertrophy”) that requires the left ventricle to increase pressure / volume work. As the workload increases, the walls of the chamber grow thicker, lose elasticity and eventually may fail to pump with as much force as a normal heart.
- Left ventricular hypertrophy (LVH) is more common in people who have high blood pressure or other heart problems.

Hypertrophy

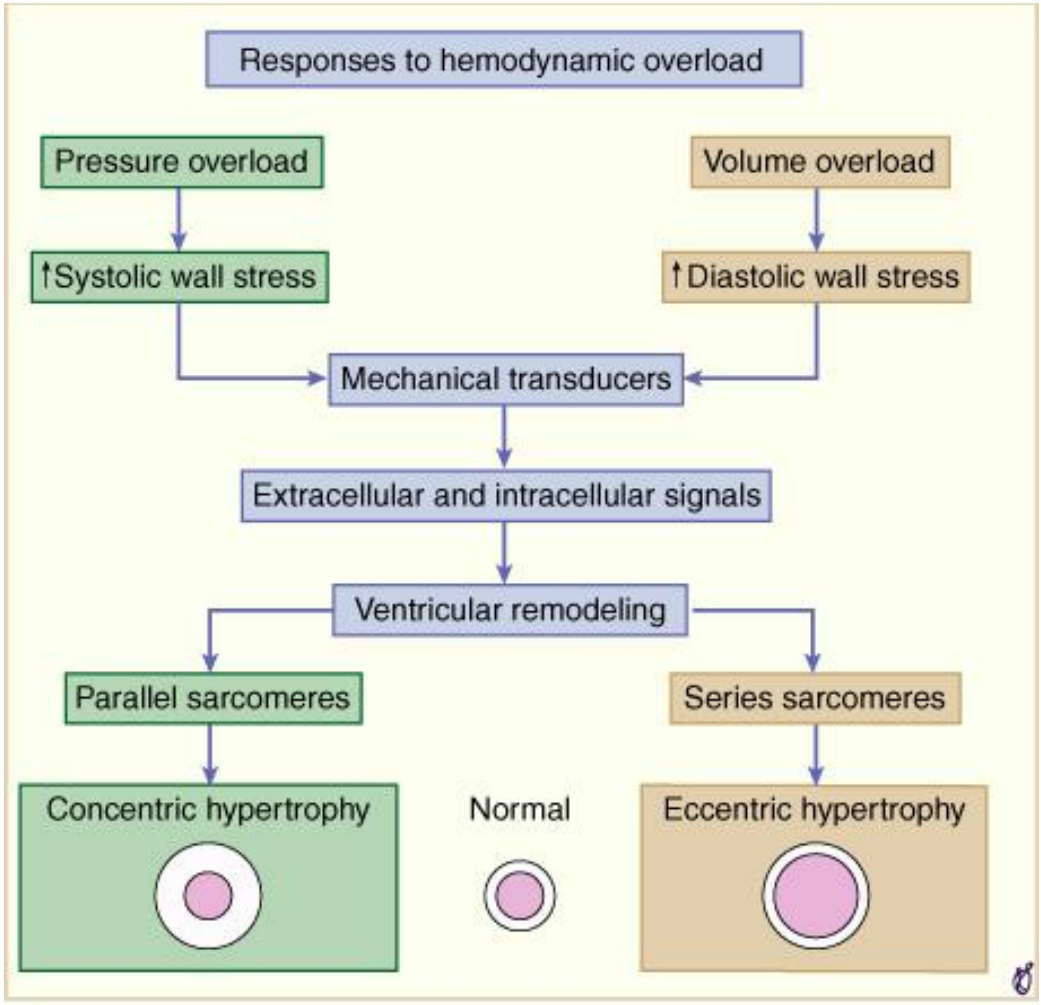
a) Cell biology (increase in cell surface area, proteinsynthesis, proteincontent)

b) Clinical (increased wall thicknesses, heart mass, weight, increased heart weight (HW) per body weight (BW) ratio.

Cardiac Hypertrophy

- Hypertrophy is the net result of a multitude of signals affecting the whole heart. It does not only affect cardiomyocytes, but also endothelial cells, smooth muscle cells as well as any other cell type present in the myocardium.
- Hypertrophy also affects angiogenesis (i.e. a defect in angiogenesis is also associated with maladaptive hypertrophy).

Different types of biomechanical stress may lead to different forms of hypertrophy



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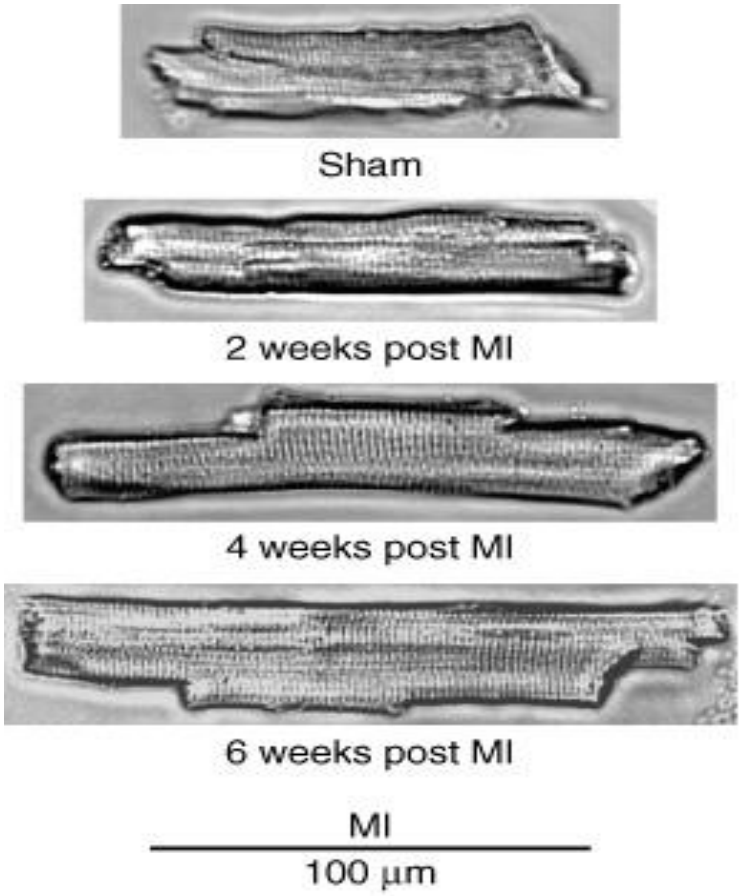
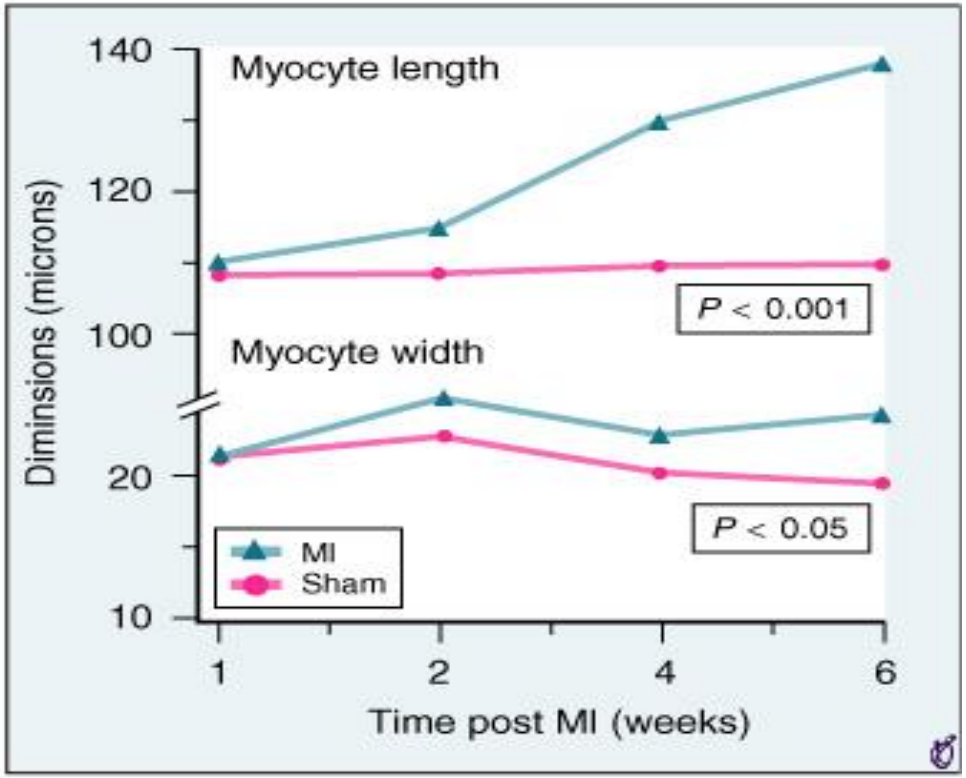
Cardiac overload

- Pressure overload
  - arterial / pulmonal hypertonus
  - valve stenosis
- Volume overload
  - Aortic valve -, Mitral valve – failure
- Loss of myocardial tissue
  - Myocardial infarction, myocarditis, cardiomyopathy

Hypertrophy follwoing myocardial infarction





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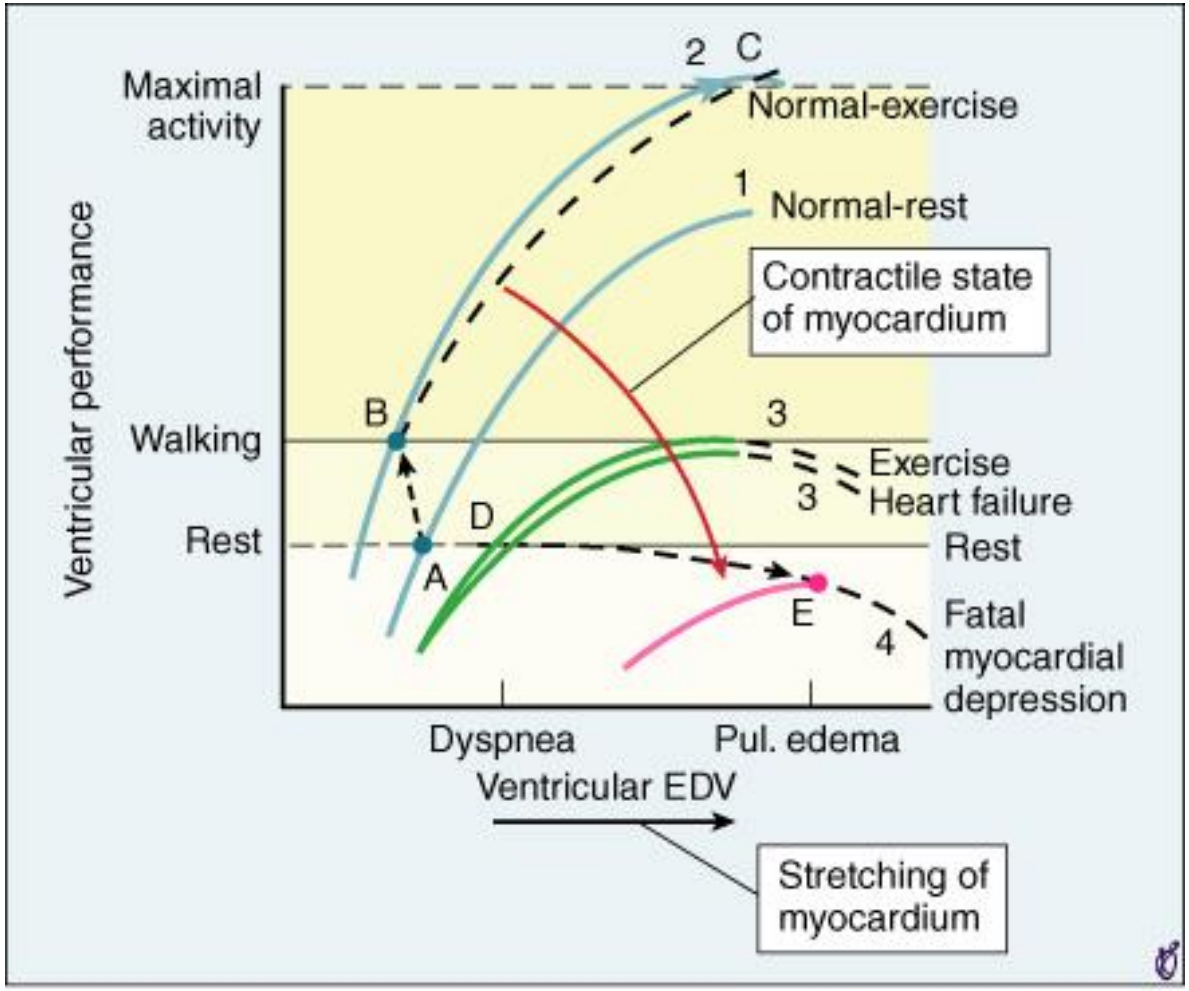
Myocardial Function – the more you stretch the less function



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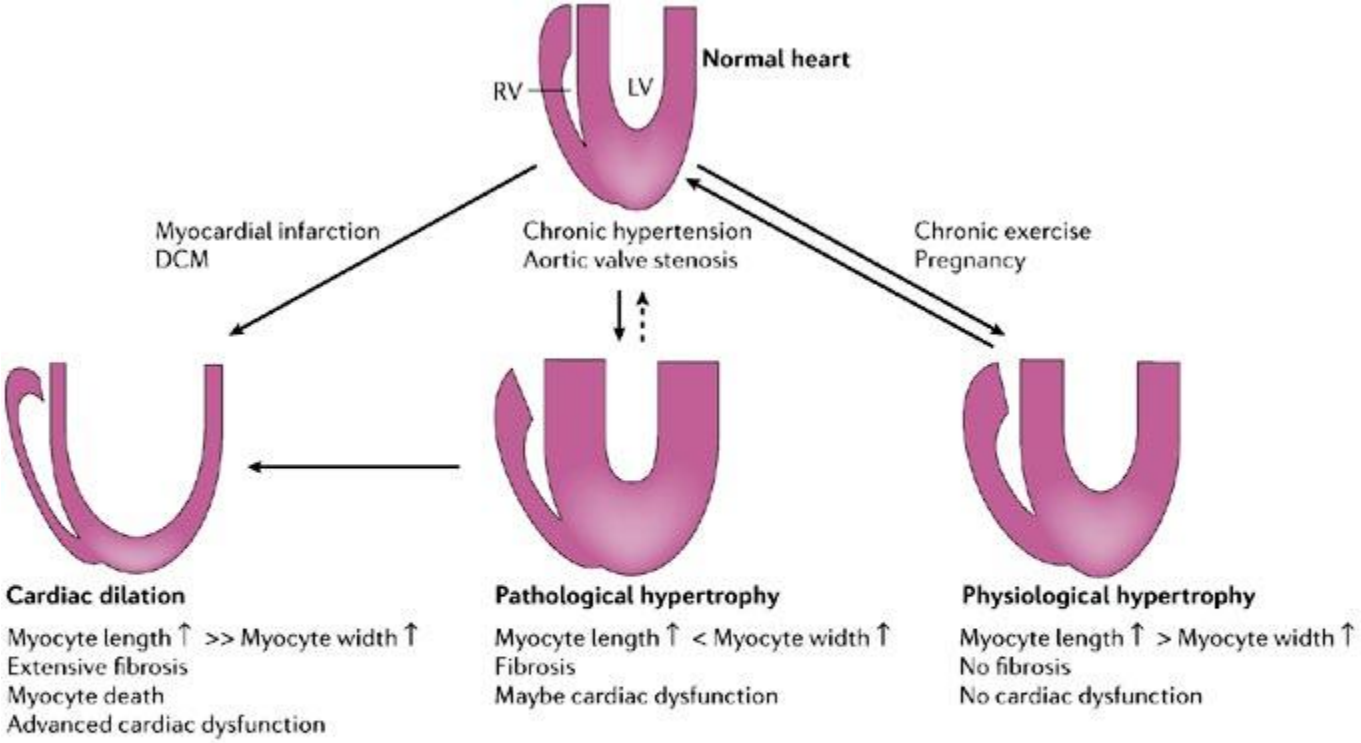
Adaptation

- Hypertrophy of cardiomyocytes
- Concentric left ventricular hypertrophy
  - pressure overload
    - Aortic stenosis
    - Arterial Hypertonus
- Excentric left ventricular hypertrophy
- - Volume overload
    - Mitral valve failure
- Right heart - hypertrophy

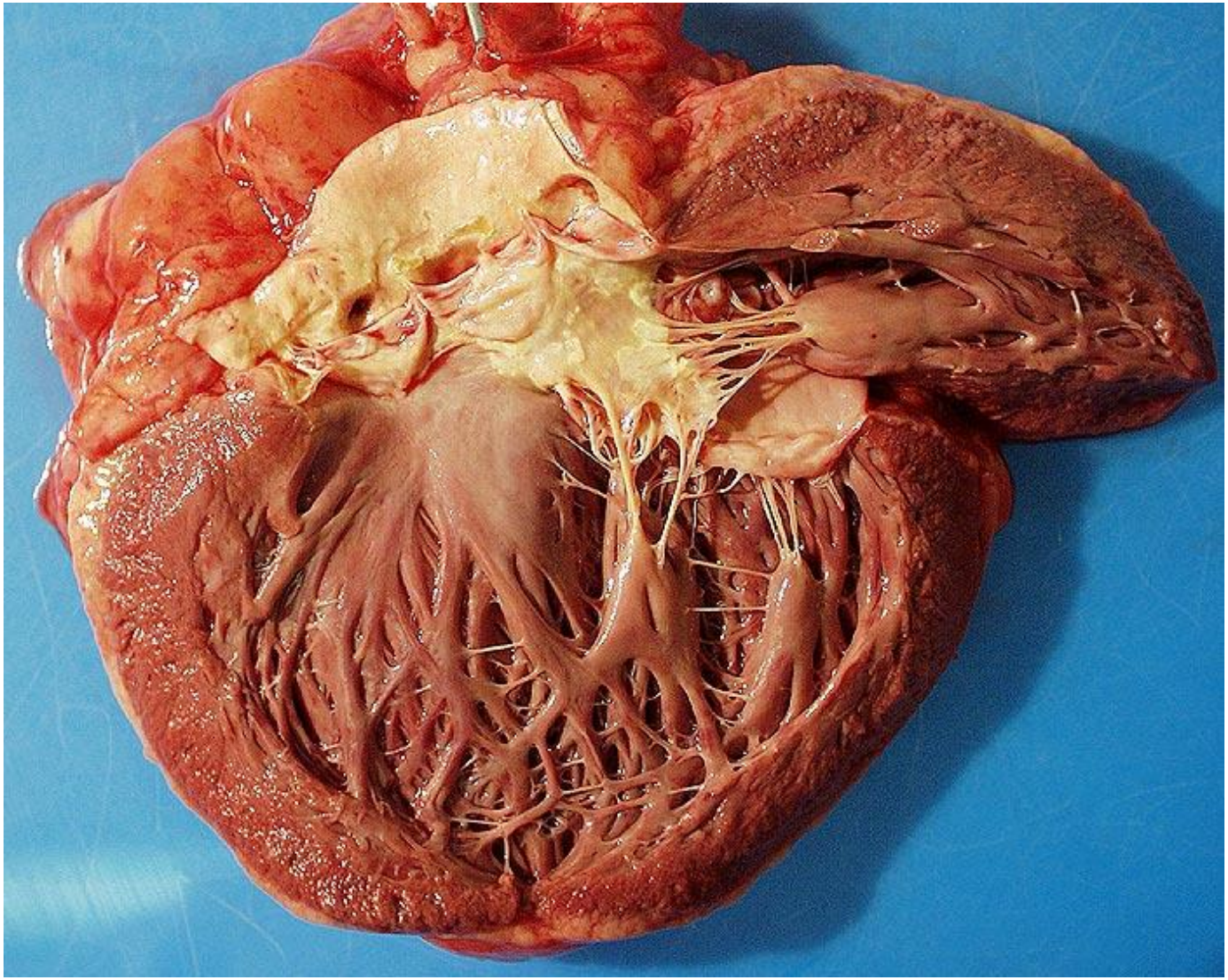
  - Left ventricular decompensation

  - Pulmonal hypertension (Cor pulmonale)

Adaptive vs maladaptive hypertrophy

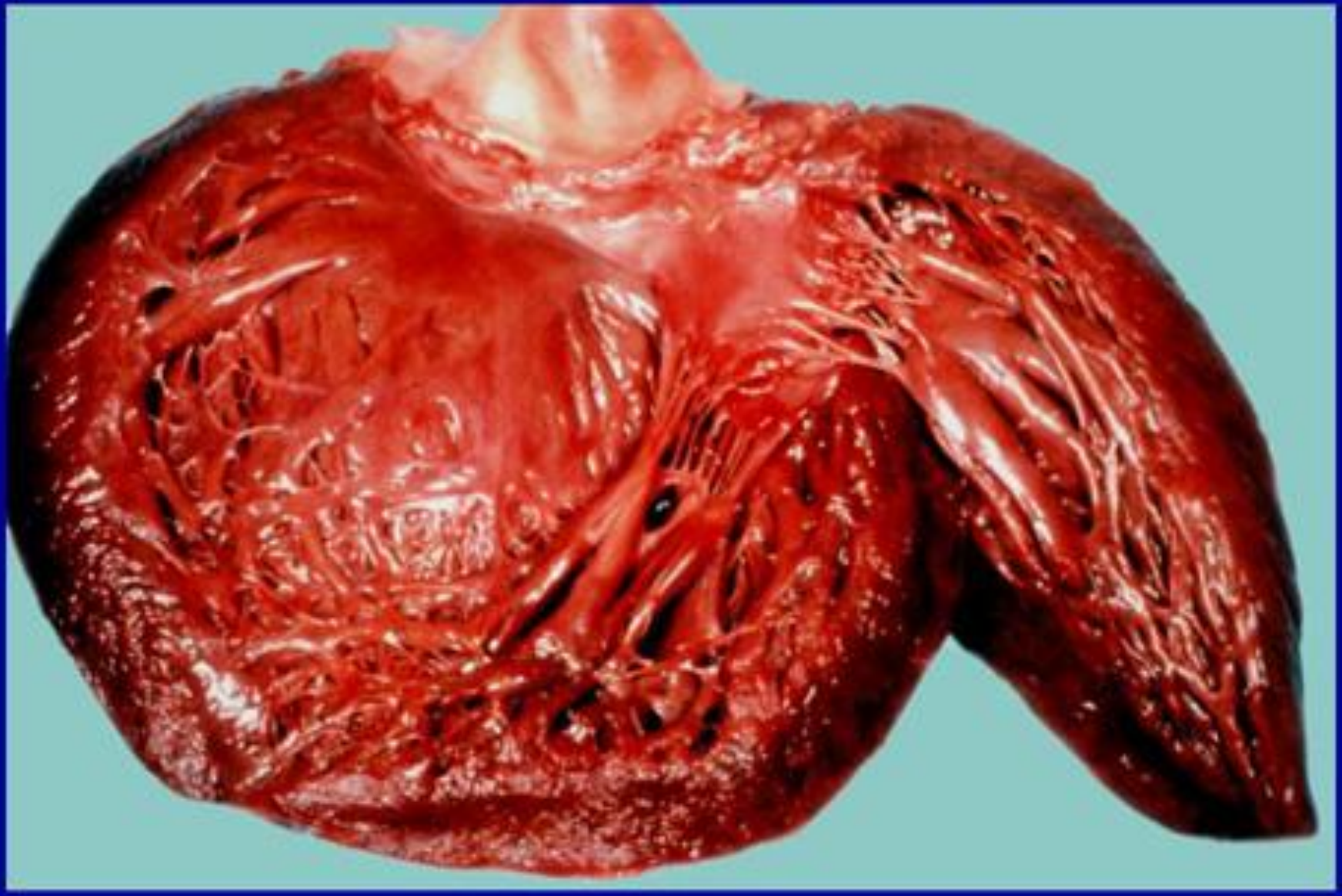


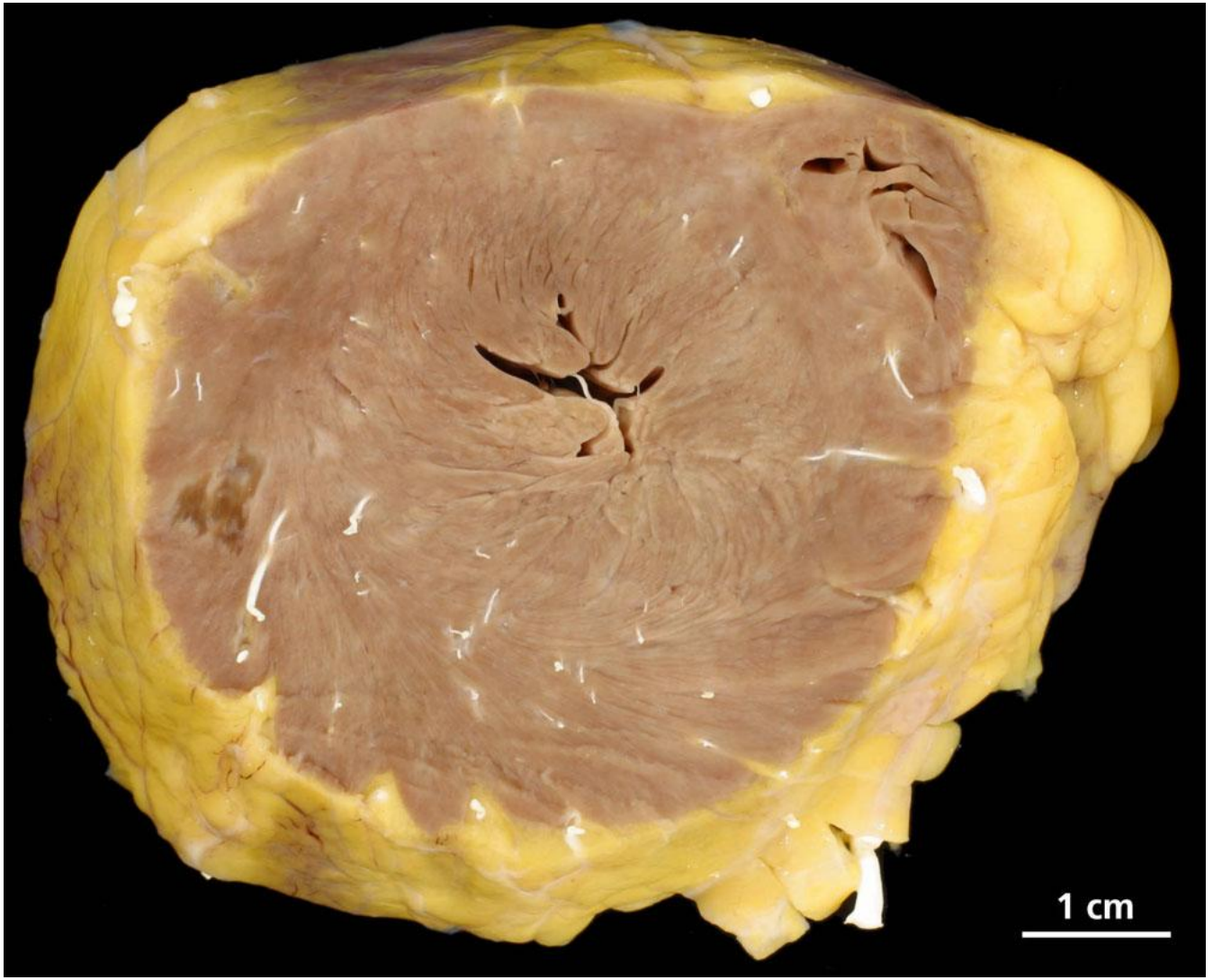
Pathological cardiac hypertrophy can produce concentric hypertrophy in which the ventricular wall and septum thicken with a net decrease in ventricular chamber dimensions (see figure). This remodelling is associated with a greater increase in cardiac myocyte width than length. However, pathological cardiac hypertrophy can also produce a phenotype of eccentric and dilatory cardiac growth. Cardiac dilation, although not typically referred to as hypertrophy, can result from a growth response in which sarcomeres are predominantly added in series to individual myocytes. The molecular underpinnings whereby sarcomeres are either added in series, in parallel or in a combination of both are not entirely understood. DCM, dilated cardiomyopathy; LV, left ventricle; RV, right ventricle.



Diagnosis: Excentric Hypertrophy of the left chamber
Description: enlarged heart, increased wall thickness. Enlarged left heart chamber, round apex
Clinics (anamnesis): Adipositas, coronary heart disease, Diabetes mellitus Typ II

Exzentrische Hypertrophie

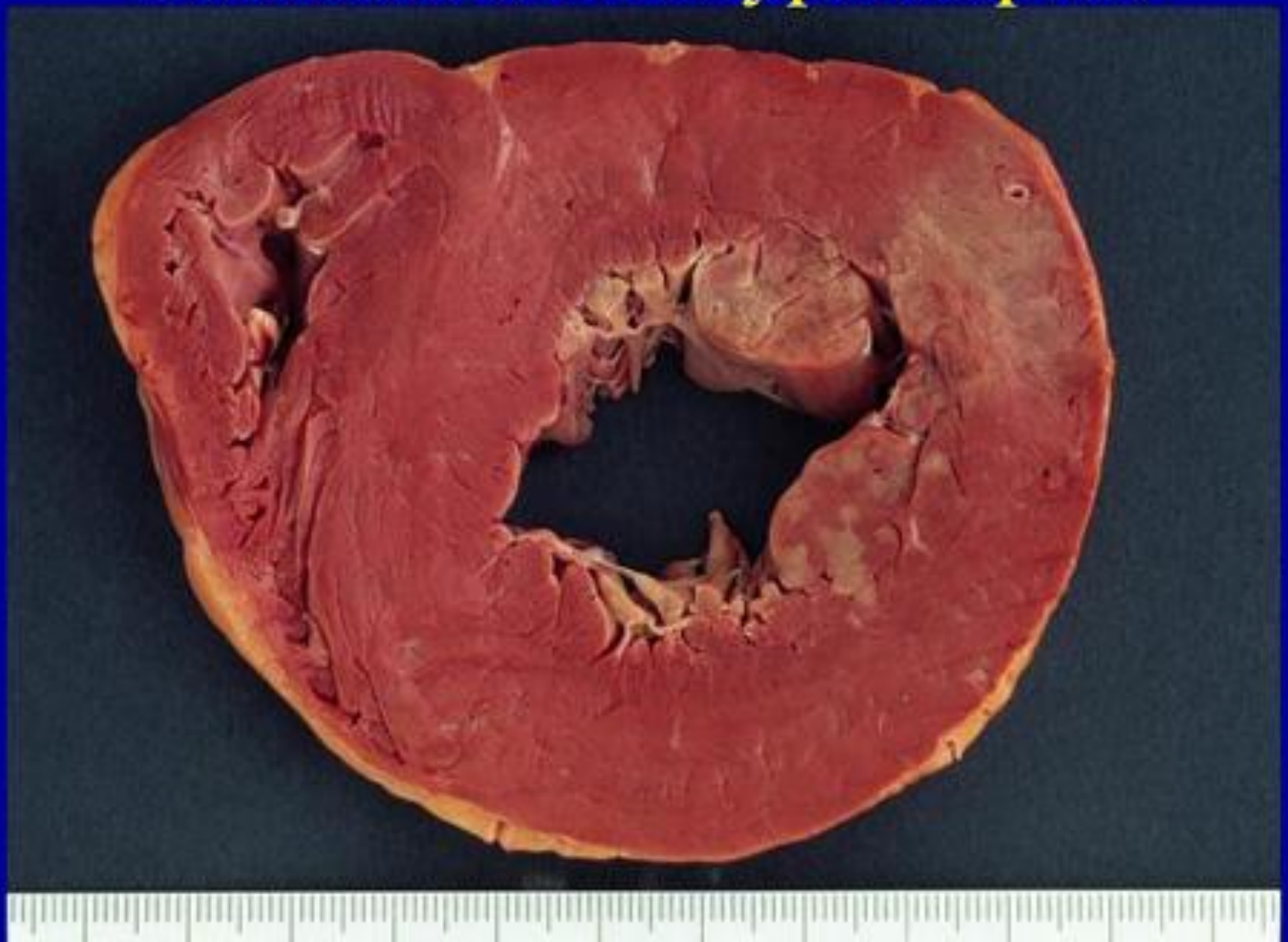




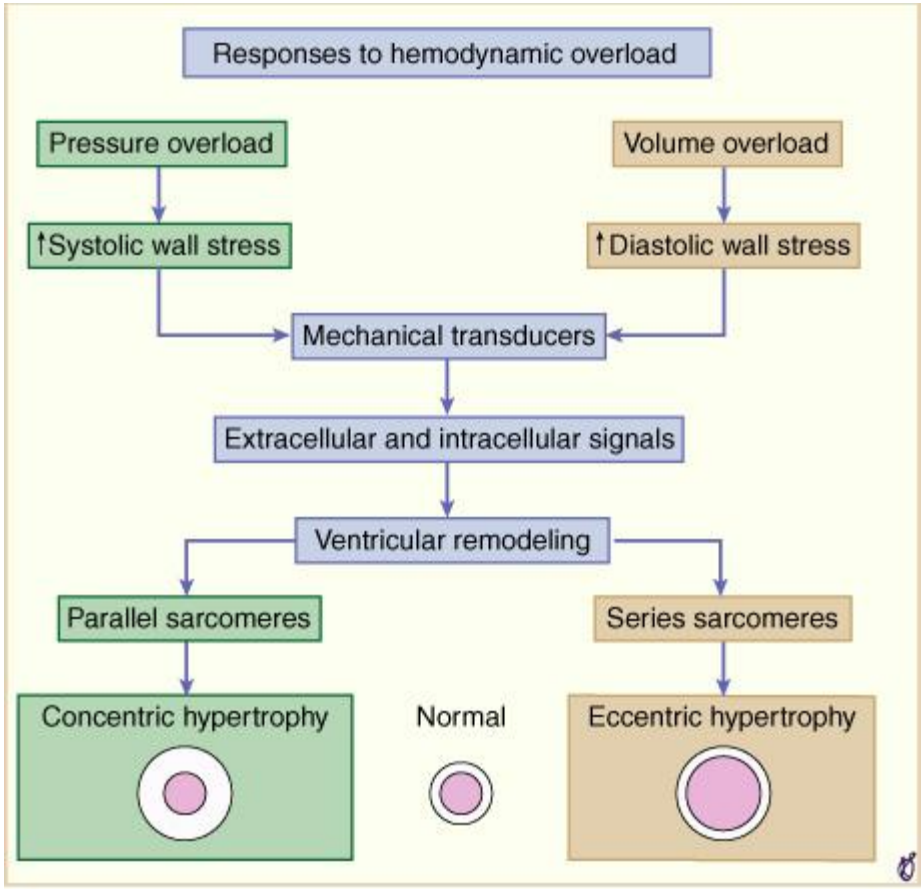
Diagnosis: left heart concentric myocardial hypertrophy, subacute necrosis

Description: Massive thickening of the left and slightly less of the right ventricle. Subacute necrosis lateral.

Konzentrische Hypertrophie



Concentric vs. Eccentric Hypertrophy



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The morphological response to a hemodynamic overload depends on the nature of the stimulus. When the overload is predominantly due to an increase in pressure (e.g., with systemic hypertension or aortic stenosis), the increase in systolic wall stress leads to the parallel addition of sarcomeres and widening of the cardiac myocytes, resulting in concentric **hypertrophy** of the ventricle. When the overload is predominantly due to an increase in ventricular volume, the increase in diastolic wall stress leads to the series addition of sarcomeres, lengthening of cardiac myocytes, and eccentric chamber **hypertrophy**.

Hypertrophy 1

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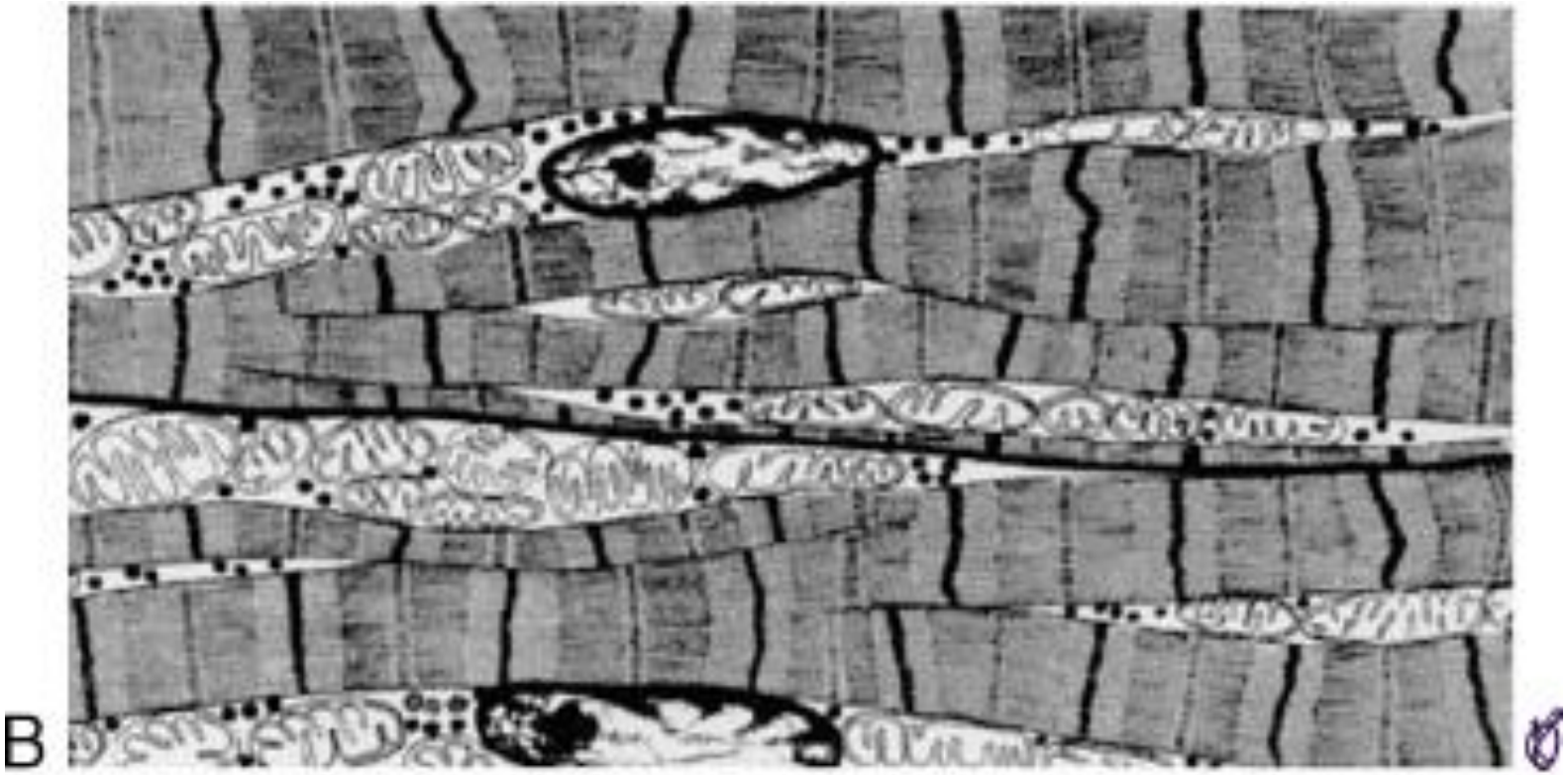
The early stage of cardiac **hypertrophy (A)** is characterized morphologically by increases in the **number of myofibrils and mitochondria** as well as **enlargement of mitochondria and nuclei**. Muscle cells are larger than normal, but cellular organization is largely preserved.

Hypertrophy 2



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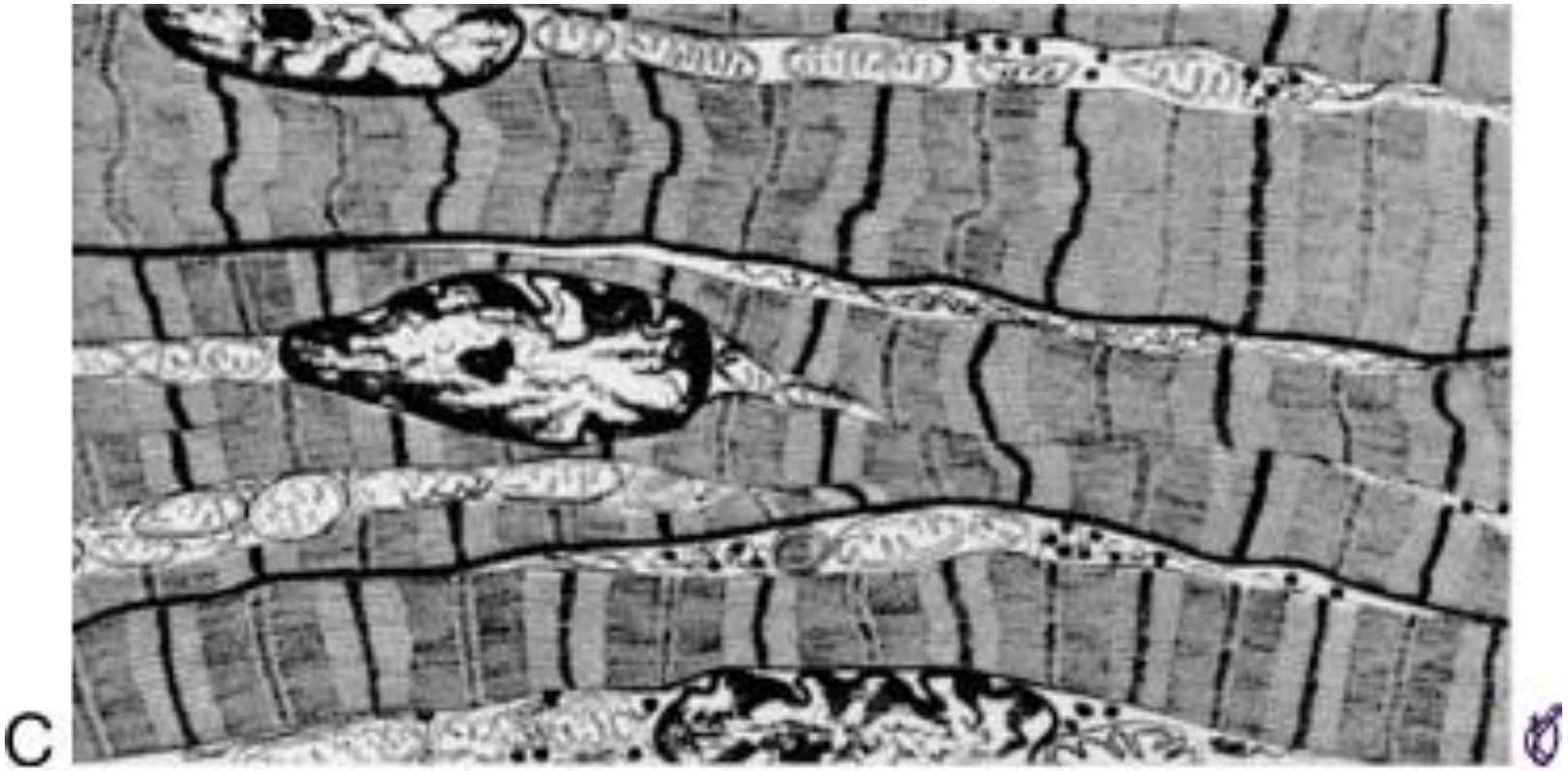
At a more advanced stage of **hypertrophy (B)** , preferential **increases in the size or number of specific organelles, such as mitochondria, as well as irregular addition of new contractile elements in localized areas of the cell,** result in subtle abnormalities of cellular organization and contour. Adjacent cells may vary in their degree of enlargement.

Hypertrophy 3



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Cells subjected to longstanding **hypertrophy** **(C)** show more obvious disruptions in cellular organization, such as **markedly enlarged nuclei** with highly lobulated membranes, which displace adjacent myofibrils and cause **breakdown of normal Z-band registration**. The early preferential increase in mitochondria is supplanted by a predominance by volume of myofibrils.

Hypertrophy 4

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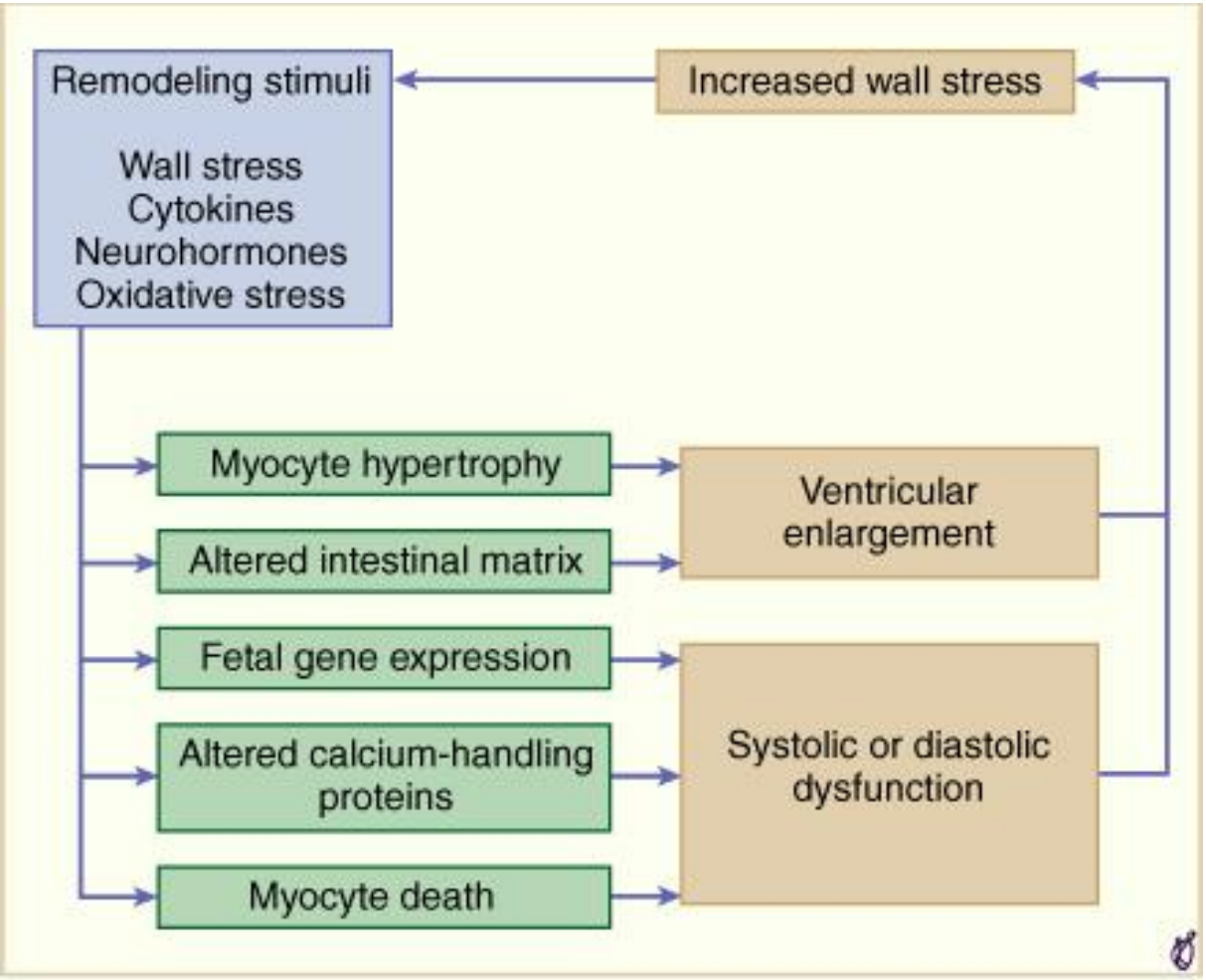
The late stage of **hypertrophy (D)** is characterized by **loss of contractile elements with marked disruption of Z bands**, severe **disruption of the normal parallel arrangement of the sarcomeres**, deposition of **fibrous tissue**, and **dilation and increased tortuosity of T tubules**.

Hypertrophy - Overview



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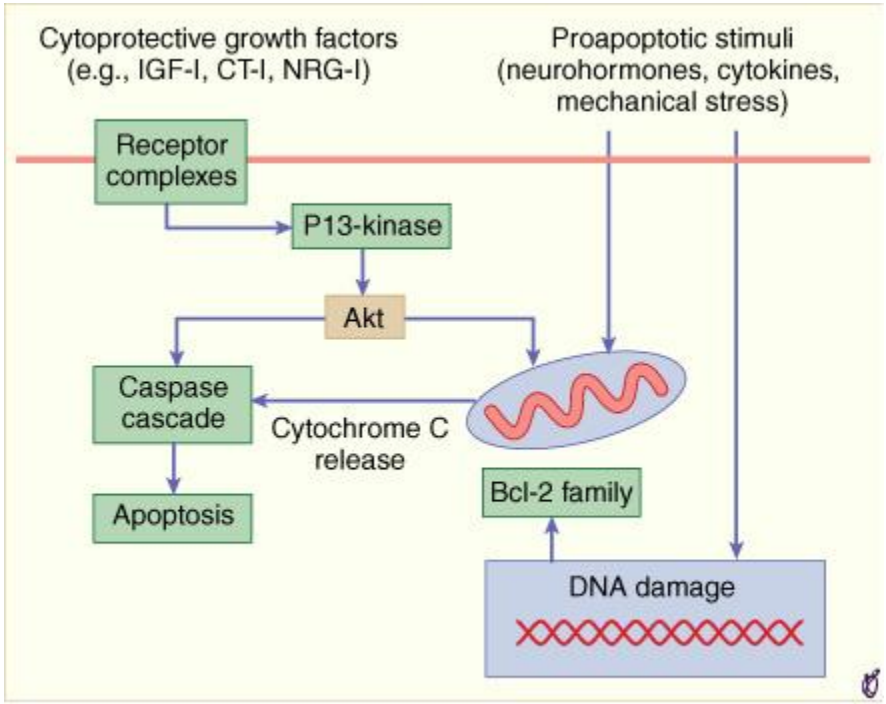
Overview of the pathophysiology of myocardial remodeling. Remodeling stimuli such as increased mechanical wall stress and neuroendocrine activation lead to a complex of molecular and cellular events, including **hypertrophy** of cardiac myocytes, changes in gene expression with a reexpression of fetal programs and decreased expression of adult programs, changes in the quantity and nature of the interstitial matrix, and cell death. These events lead to changes in the structure and function of the ventricle, which may result in further pump dysfunction and increased wall stresses, thereby promoting further pathological remodeling.

Hypertrophy - Apoptosis



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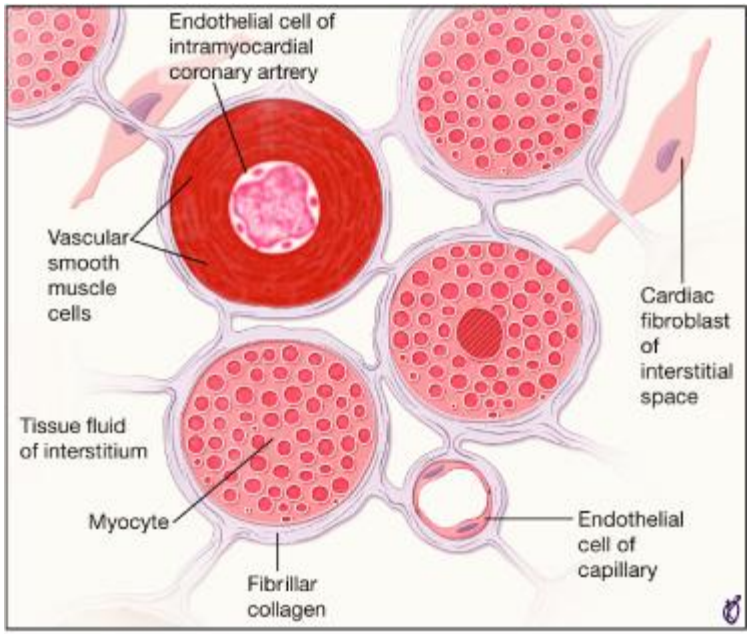
Regulation of myocyte survival in heart failure. The proapoptotic effects of chronic neurohormonal, inflammatory cytokine, mechanical stress, and other stimuli are counterbalanced by prosurvival pathways. The fate of any single myocyte is a function of the *net* effect of these influences. Antiapoptotic influences in the myocardium are mediated in part by cytoprotective growth factors, including insulin-like growth factor-1 (IGF-1), cardiotrophin-1 (CT-1), and neuregulin-1 (NRG-1), that suppress the apoptotic cascade at multiple levels at least in part through the activation of phosphoinositol-3kinase and Akt as depicted.

Hypertrophy - Extracellular Matrix



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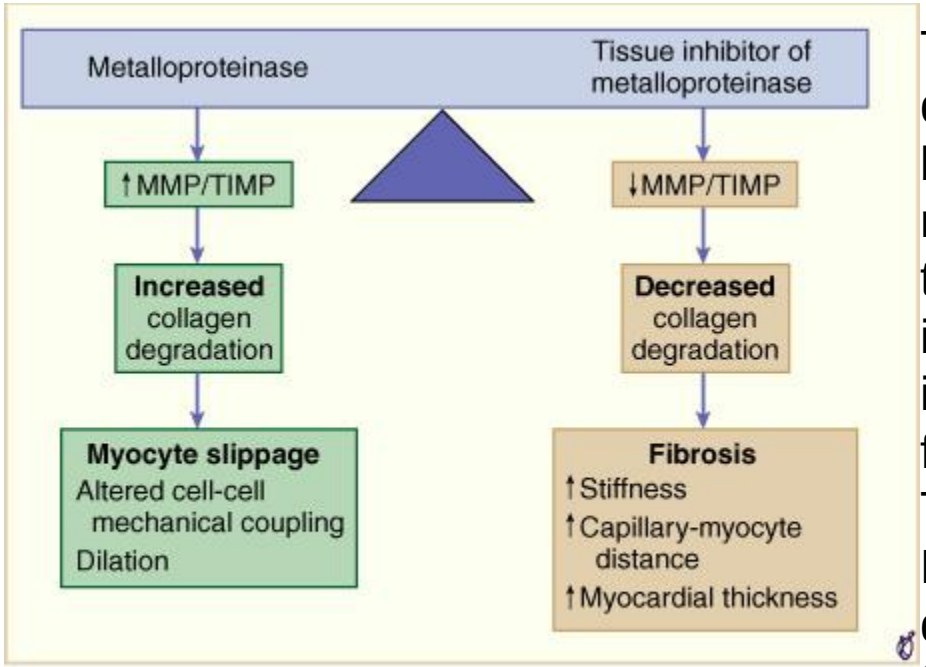
Myocyte and nonmyocyte constituents of the heart. Although myocytes are the major components of the heart on the basis of mass, they represent only a minority of the cells on the basis of number. Nonmyocyte cellular constituents of the myocardium include fibroblasts, smooth muscle cells, and endothelial cells. Myocytes and nonmyocytes are interconnected by a complex of connective tissue and extracellular matrix. Components of the extracellular matrix include collagens, proteoglycans (such as fibronectin), several peptide growth factors, and proteases (such as plasminogen activators). There is increasing appreciation that by regulating the nature and quantity of the extracellular matrix, nonmyocytes in the heart play an important role in determining the response of the myocardium to pathologic stimuli, such as hemodynamic overload.

Extracellular Matrix Turnover



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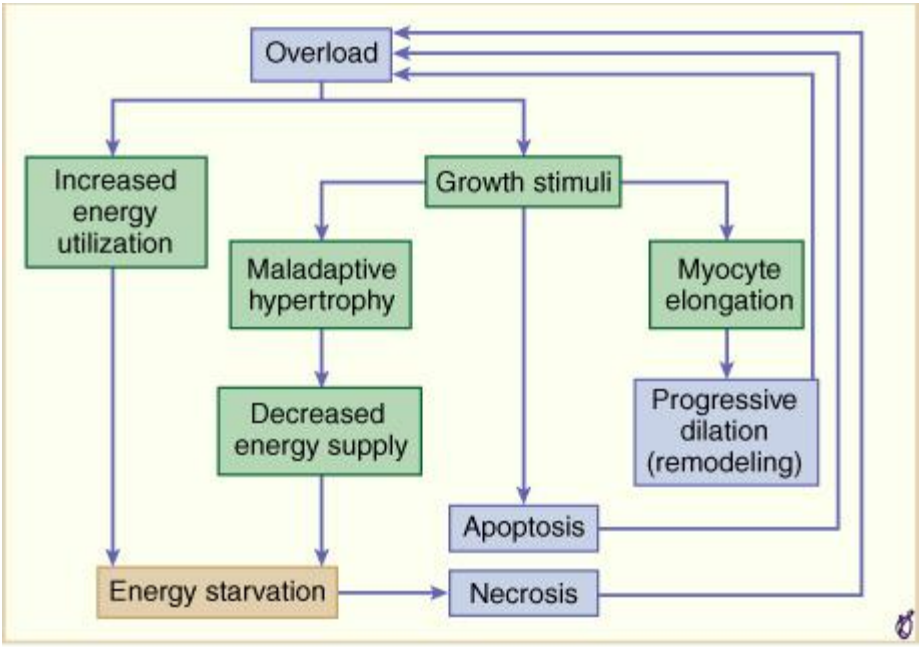
The regulation of extracellular matrix degradation is determined by the balance between the activity of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). Both an increase in MMP activity and a decrease in TIMP activity have been observed in failing myocardium from patients. Theoretically, such an increase in the MMP/TIMP ratio could contribute to depletion of the fibrillar collagen struts that tether myocytes together and might thus contribute to chamber dilation. Conversely, an increase in extracellular matrix accumulation, which might occur as the result of a decrease in the MMP/TIMP ratio or an increase in matrix synthesis, could contribute to chamber stiffness and abnormal relaxation.

Some of the vicious circles that operate in the overloaded heart



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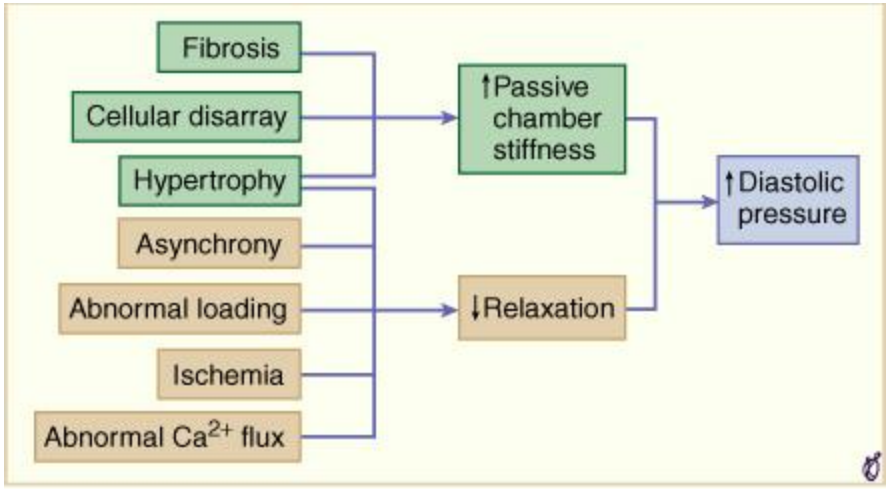
Overload both increases energy utilization and stimulates growth.

- The former contributes directly to a state of energy starvation, which is made worse by several consequences of maladaptive hypertrophy that decrease energy supply.
- The latter include myocyte elongation, which causes remodeling, a progressive dilation that increases wall tension so as to increase the overload.
- Growth stimuli also promote apoptosis, which by decreasing the number of viable cardiac myocytes increases the load on those that survive.
- Hypertrophy also causes architectural changes that reduce the energy supply to working cardiac myocytes.

Factors – diastolic function



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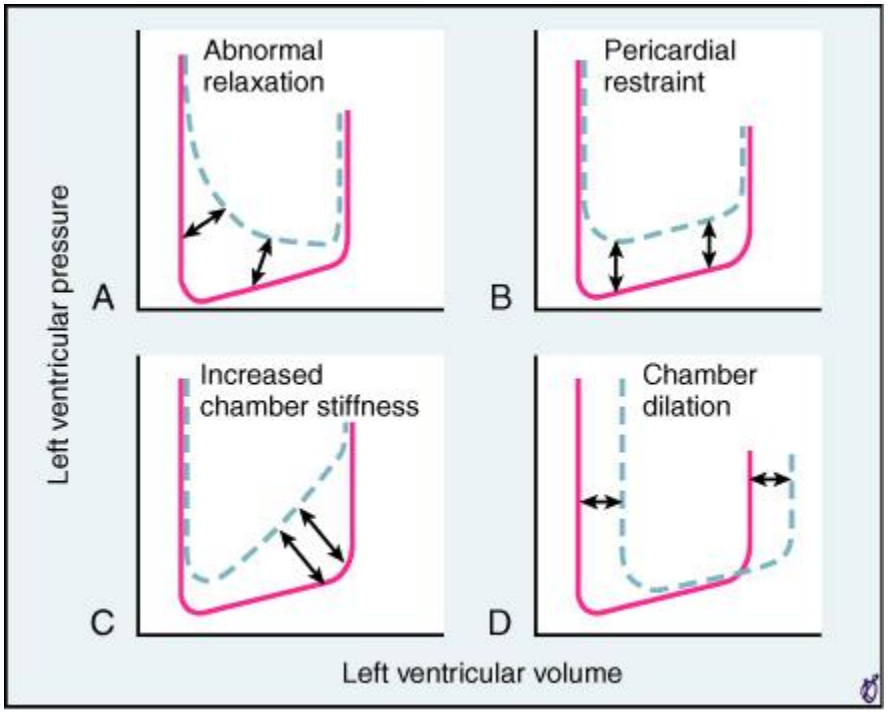
Factors responsible for diastolic dysfunction and increased left ventricular diastolic pressure.

Diastolic Dysfunction



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Mechanisms that cause diastolic dysfunction. Only the bottom half of the pressure-volume loop is depicted. Solid lines represent normal subjects; dashed lines represent patients with diastolic dysfunction.

Short-Term and Long-Term Responses to Impaired Cardiac Performance

TABLE 21–1 Short-Term and Long-Term Responses to Impaired Cardiac Performance

Response	Short-Term Effects*	Long-Term Effects†
Salt and water retention	Augments preload	Causes pulmonary congestion, anasarca
Vasoconstriction	Maintains blood pressure for perfusion of vital organs (brain, heart)	Exacerbates pump dysfunction (after-load mismatch); increases cardiac energy expenditure
Sympathetic stimulation	Increases heart rate and ejection	Increases energy expenditure
Sympathetic desensitization		Spares energy
Hypertrophy	Unloads individual muscle fibers	Leads to deterioration and death of cardiac cells; cardiomyopathy of overload
Capillary deficit		Leads to energy starvation
Mitochondrial density	Increase in density helps meet energy demands	Decrease in density leads to energy starvation
Appearance of slow myosin		Increases force, decreases shortening velocity and contractility; is energy sparing
Prolonged action potential		Increases contractility and energy expenditure
Decreased density of sarcoplasmic reticulum calcium pump sites		Slows relaxation; may be energy sparing
Increased collagen	May reduce dilatation	Impairs relaxation

From Katz AM: Cardiomyopathy of overload: A major determinant of prognosis in congestive heart failure. N Engl J Med 322:100, 1990. Copyright 1990, Massachusetts Medical Society.

*Short-term effects are mainly adaptive and occur after hemorrhage and in acute heart failure.

†Long-term effects are mainly deleterious and occur in chronic heart failure.

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Sarcoplasmic Reticulum Alterations in the Failing Heart

TABLE 21–2 Sarcoplasmic Reticulum Alterations in the Failing Heart

Protein	Change in Human Heart Failure
Sarcoplasmic Reticulum	
Calcium pump ATPase (SERCA)	Normal or decreased
Phospholamban	Normal or decreased
Calcium release channel (ryanodine receptor)	Normal or decreased
Calsequestrin	Normal
Calreticulin	Normal
Plasma Membrane	
L-type calcium channels	?Increased channel opening
Sodium/calcium exchanger	Increased
Sodium pump	Reexpression of fetal isoforms

ATPase = adenosine triphosphatase.

From Katz AM: Heart Failure. Philadelphia, Lippincott Williams & Wilkins, 2000.

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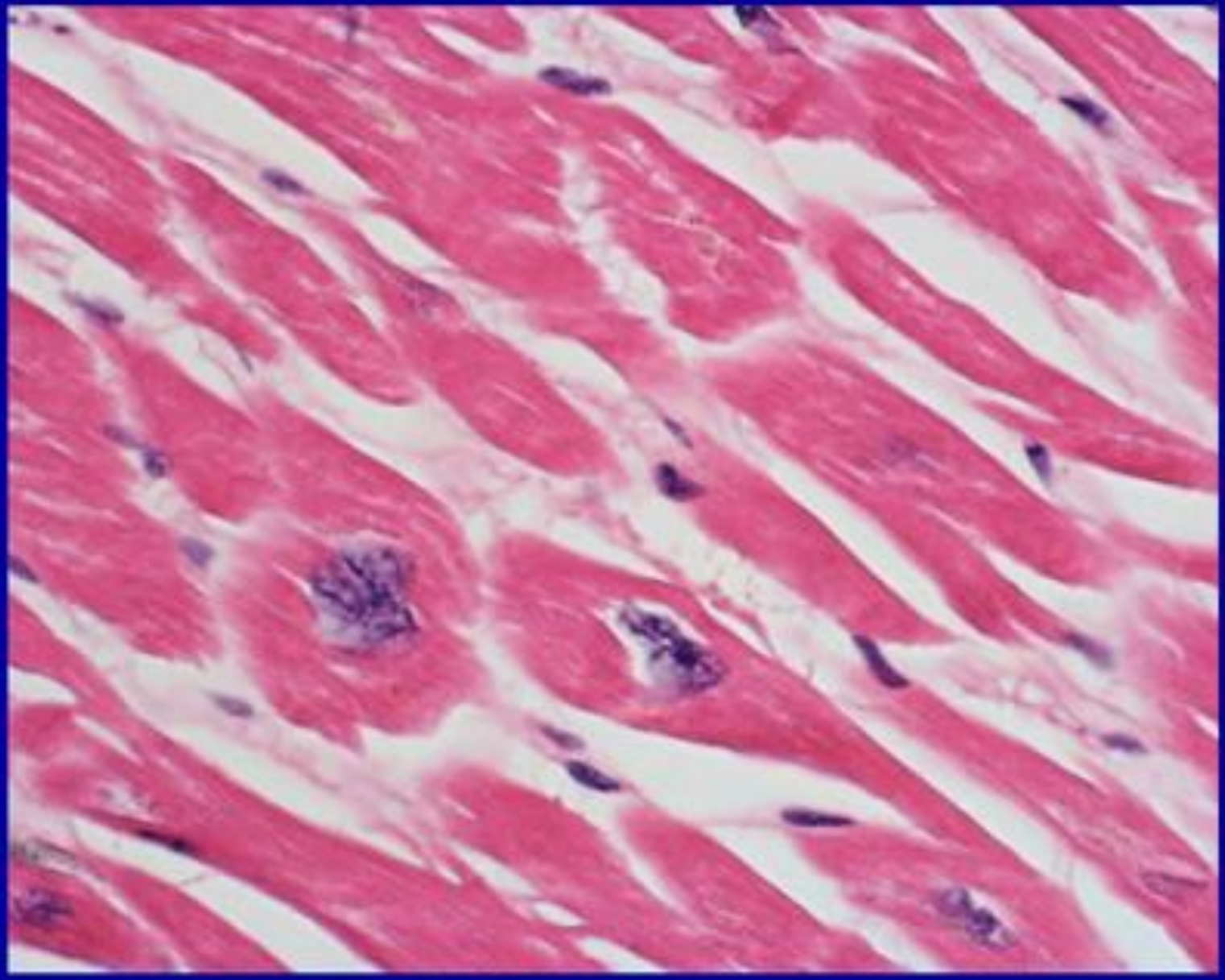
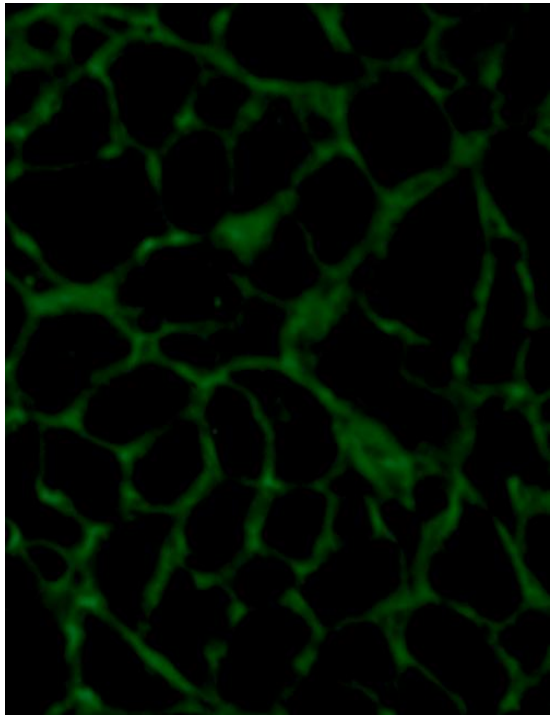
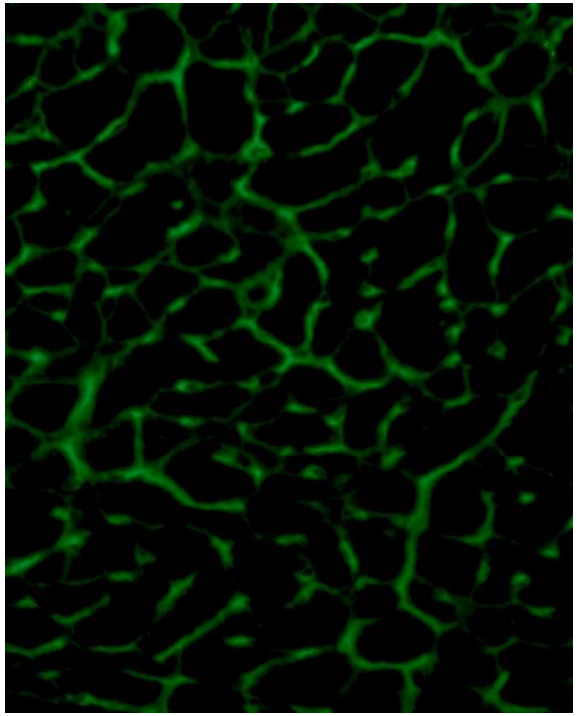
Hypertrophie von Kardiomyozyten



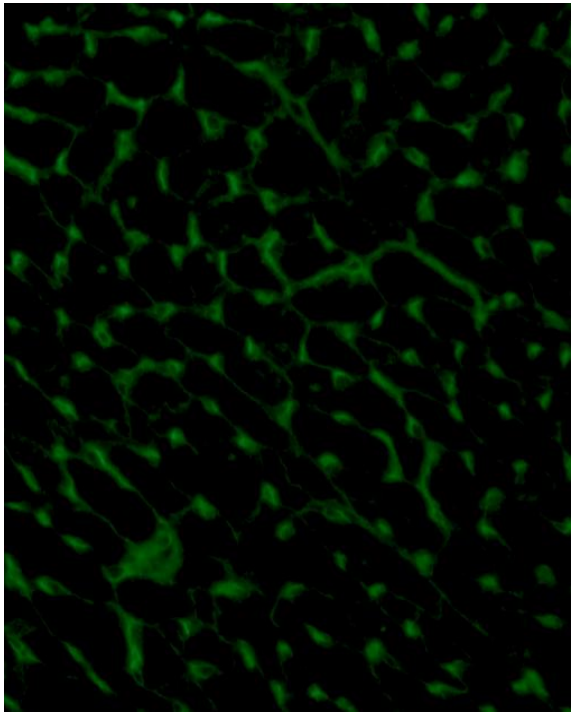
Wheat germ agglutinine



Hypertrophy



Intermediate hypertrophy



Normal

R. Knöll, 2005

Pathogenesis of myocardial hypertrophy

Angiotensin II – (MAP)Kinase
Endothelin 1
Insulin-like growth factor-1 (IGF-1)
Cytokine (IL-1, Cardiotrophin – 1)
Expression of fetal Genes (ß-Myosin), ANF
Proto-Oncogenes (c-myc, c-fos)
Extracellular Matrix - Fibrosis

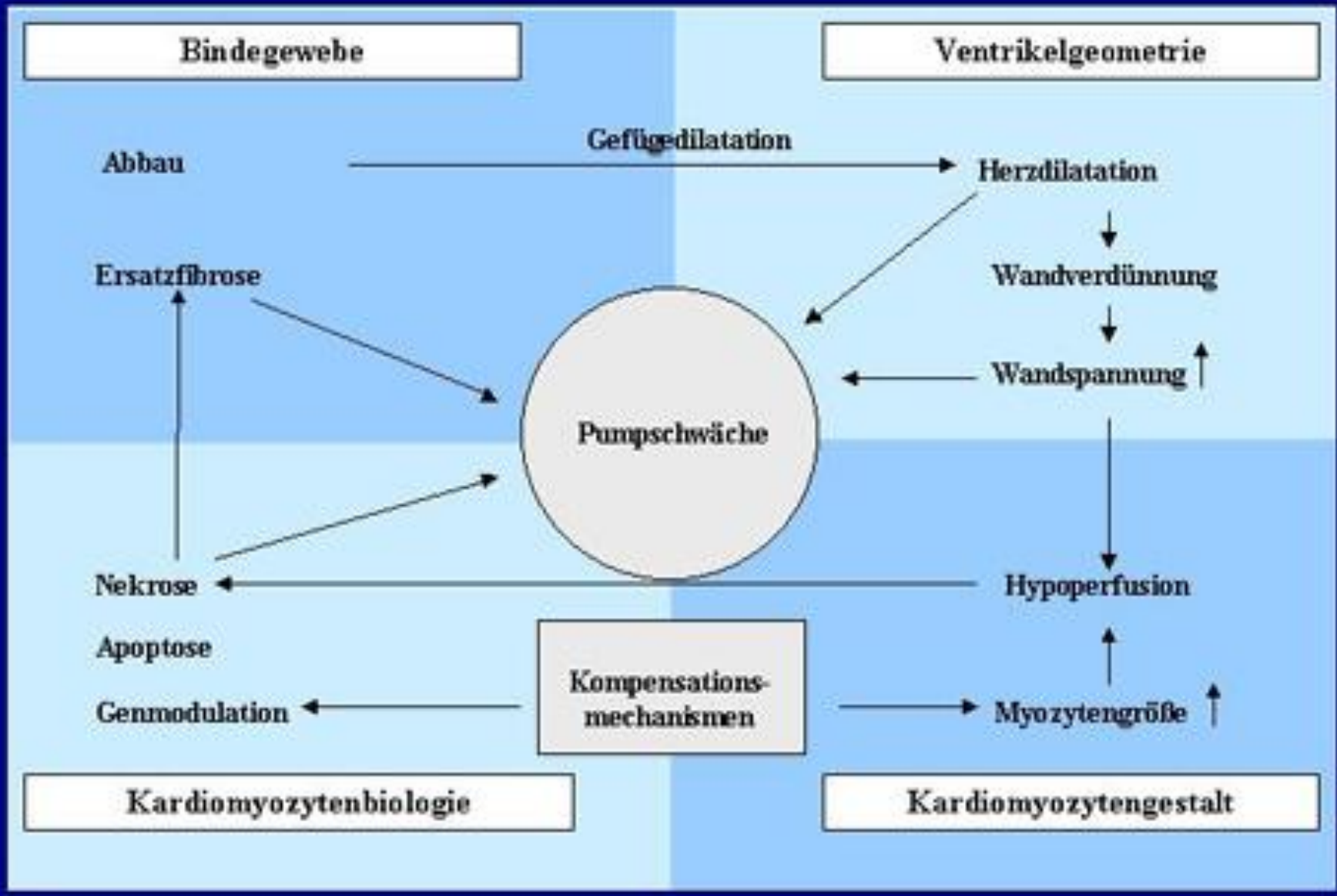

Bindegewebe
Ventrikelgeometrie
Abbau
Gefügedilatation
Herzdilatation
Ersatzfibrose
Wandverdünnung
Wandspannung
Pumpschwäche
Nekrose
Hypoperfusion
Apoptose
Genmodulation
Kompensations-
mechanismen
Myozytengröße
Kardiomyozytenbiologie
Kardiomyozytengestalt

TABLE 21–4 Extracellular Myocardial Remodeling Events During the Progression of Heart Failure: A Summary of Potential Global Extracellular Matrix Changes in the Left Ventricular Remodeling Process

Disease Process	Myocardial Infarction	Hypertrophy	Cardiomyopathy
Early adaptive phase	ECM proteolysis in MI region Activation of MMPs Rapid ECM turnover MI scar formation	ECM turnover to facilitate myocyte growth ECM biosynthesis rates favor accumulation Diminished MMP activity	Biophysical stress induces MMPs Proteolysis of normal ECM
Compensatory phase	Scar maturation ECM accumulation in viable myocardium Persistent ECM turnover in MI border zone	ECM reaches steady state Continued downregulation of MMPs	Induction of "MMP portfolio" and continued ECM turnover Diminished ECM support of myocytes
Transition to failure	Continued ECM proteolysis in MI border and infarct expansion LV wall remodeling and dilation Increased MMPs and acceleration of LV remodeling and dilation	Increased myocardial stiffness due to ECM accumulation and impairment of diastolic function	Increased MMP activation and reduced inhibitory control Accelerated proteolysis of normal ECM structure and loss of structural support LV dilation and diminished transduction of myocyte shortening

ECM = extracellular matrix; LV = left ventricular; MI = myocardial infarction; MMP = matrix metalloproteinase.
From Gunasinghe SK, Spinale FG: Myocardial basis for heart failure. *In* Mann DL (ed): Heart Failure. Philadelphia, Elsevier, 2004, p 66.

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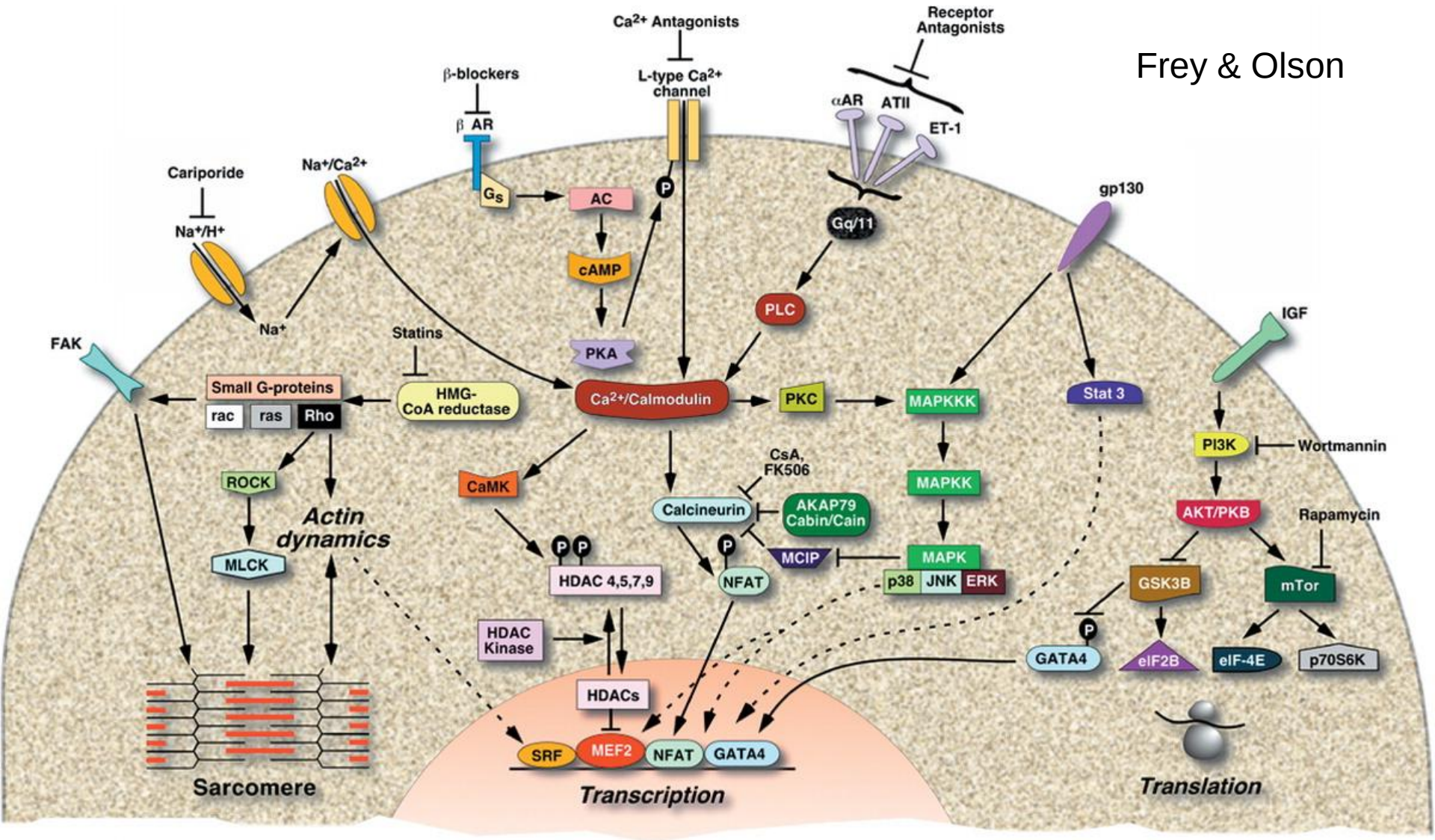
Extracellular Myocardial Remodeling Events During the Progression of Heart Failure: A Summary of Potential Global Extracellular Matrix Changes in the Left Ventricular Remodeling Process

General signaltransduction – cardiac hypertrophy



Responses induced by the activation of a nuclear hormone receptor

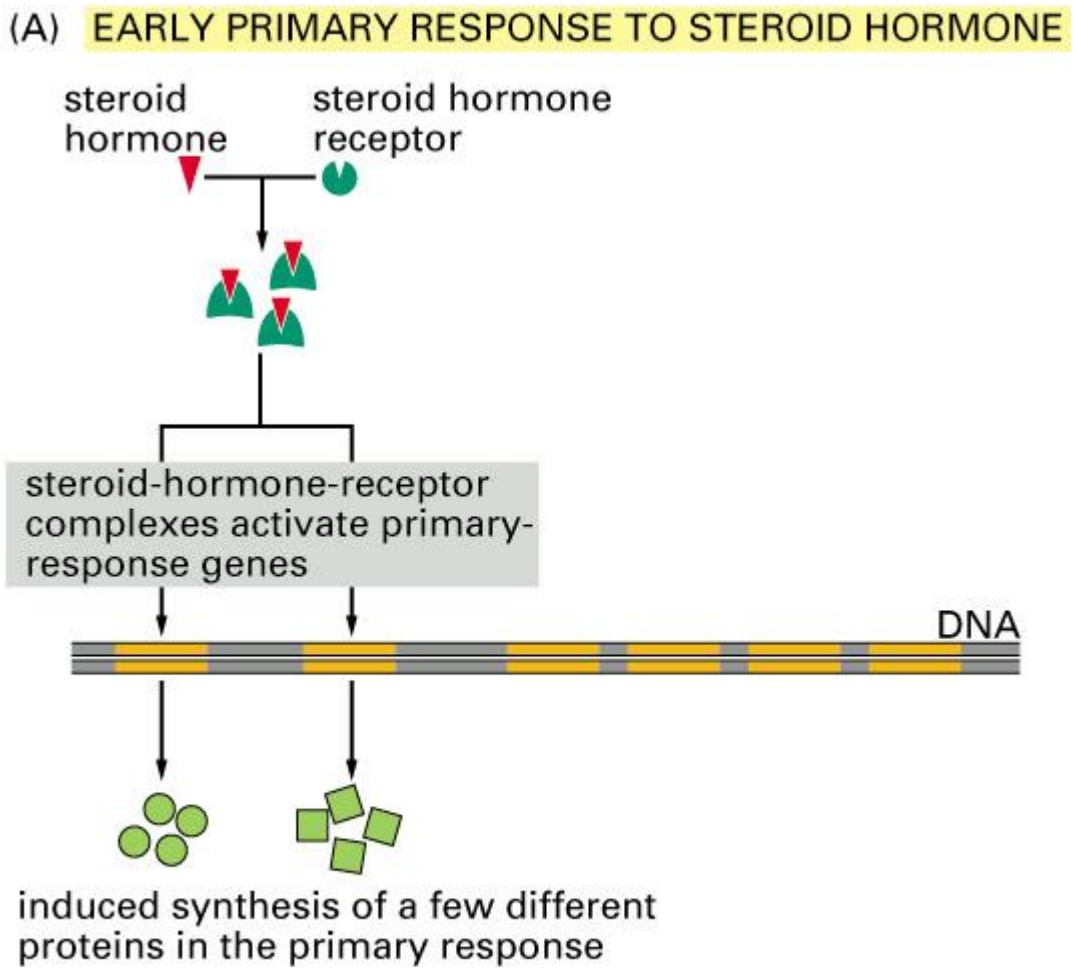
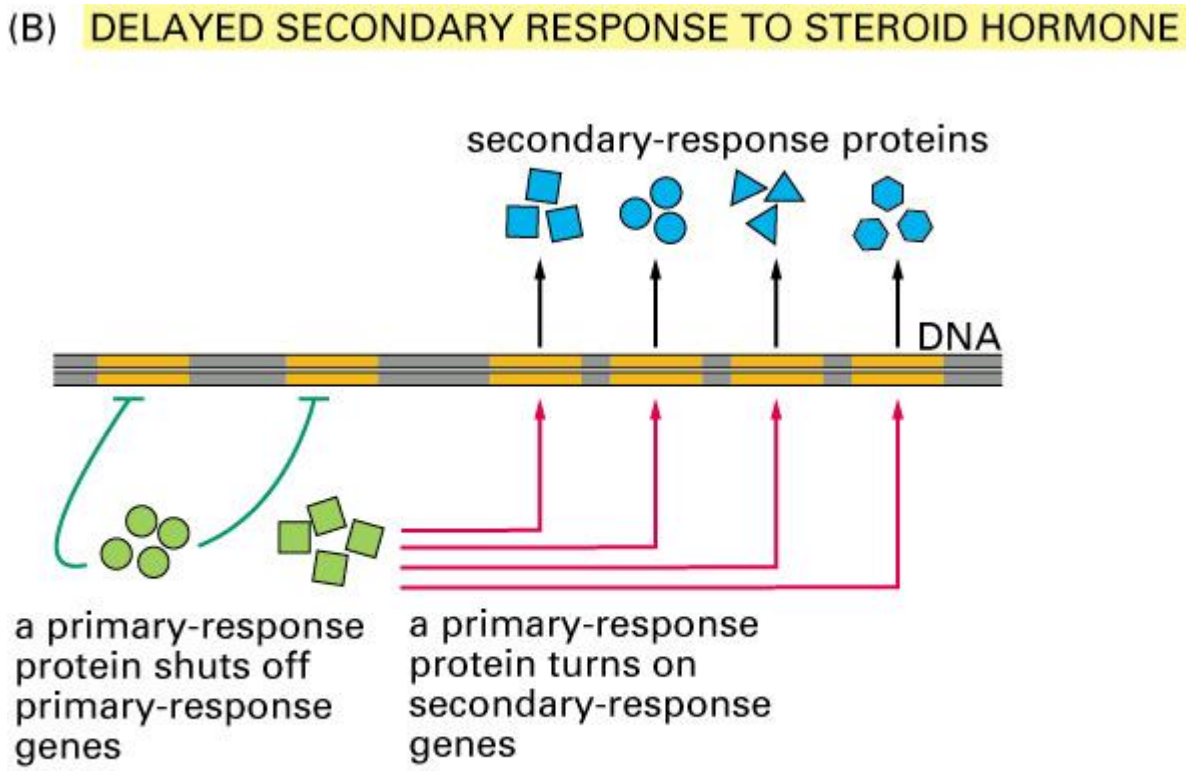


Figure 15–14 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Responses induced by the activation of a nuclear hormone receptor



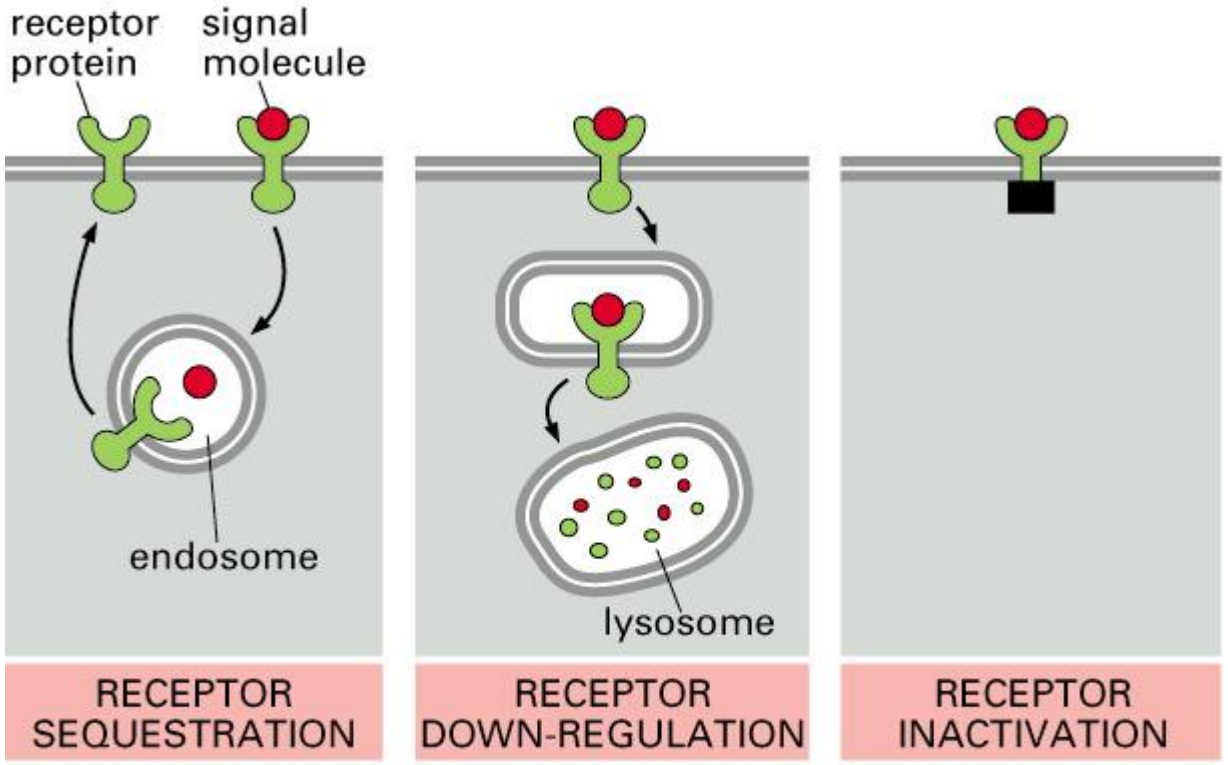
Responses induced by the activation of a nuclear hormone receptor

- Early response genes?
- Early response genes? i. e. c-fos, c-jun, c-myc, AP1 TFs)
- Delayed response genes?
- Delayed response genes? Sarcoplasmic reticulum ATPase (SERCA)
- How to differentiate both?
- Using inhibitors of protein synthesis such as cycloheximide

Beta adrenergic receptors

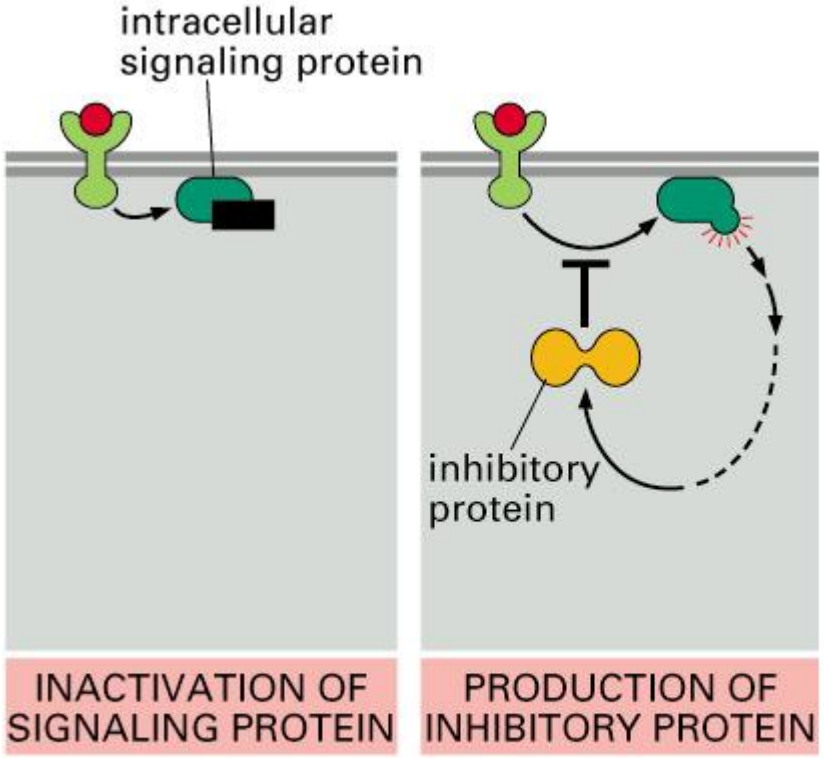
- Beta adrenergic signaltransduction is very important for myocardial hypertrophy.
- Whereas beta adrenergic signaling might be adaptive very soon after an insult, however after weeks, months or years it may cause severe maladaptation.

Five ways in which the target cells can become desensitized to a signal molecule



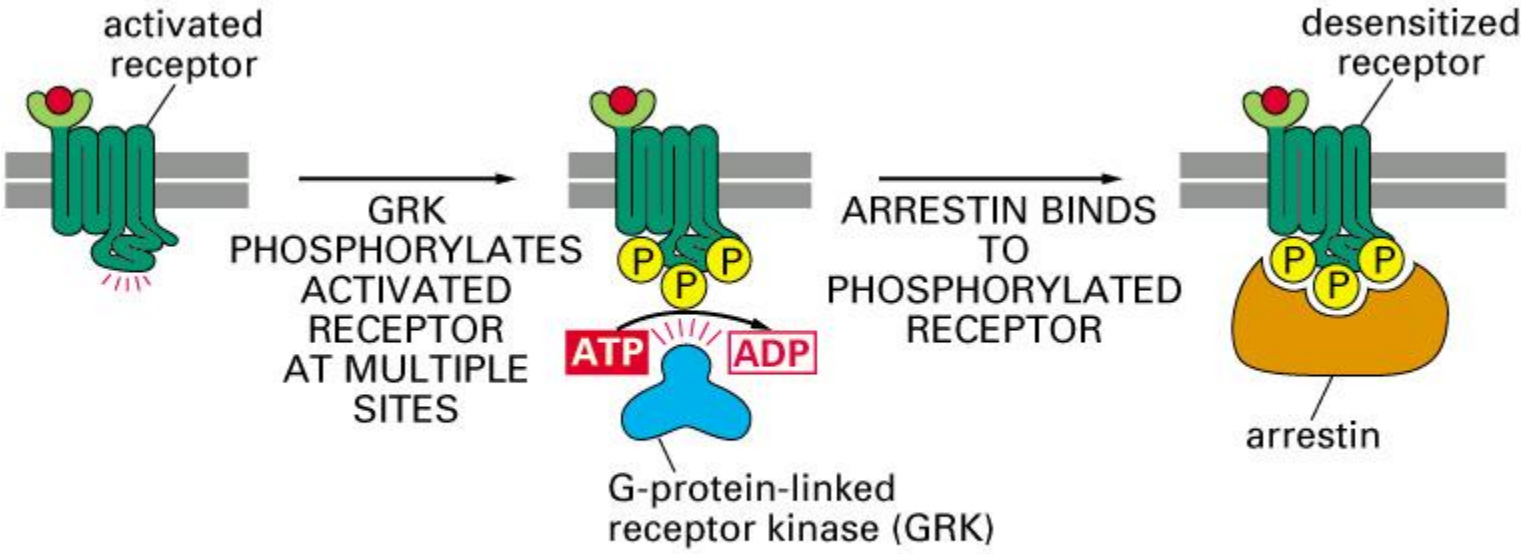
β-receptors

Five ways in which the target cells can become desensitized to a signal molecule



The roles of G-protein linked receptor kinases (GRKs) and arrestins in receptor desensitization

The binding of an arrestin to the phosphorylated receptor prevents the receptor from binding to its G protein and can direct ist endocytosis. Mice that are deficient in one form of arrestin fail to desensitze in response to morphine, for example, attesting to the importance of arrestins for desensitization.



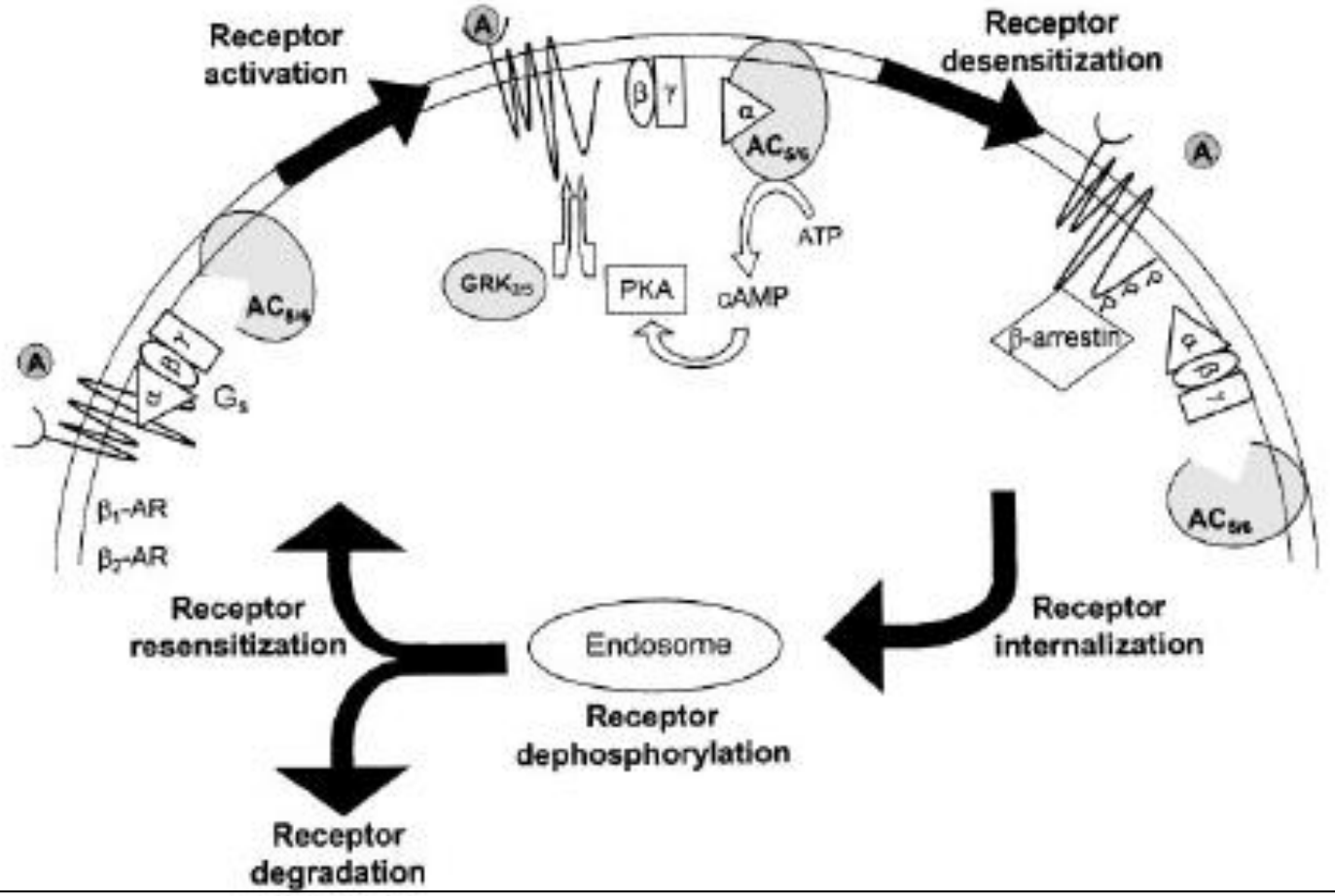
Endosomes

- Endosomes: Many endocytotic vesicles, derived from the plasma membrane, are either transported to a pre-existing endosome and fuse with it or are acidified via proton pump to become an endosome. Some endocytosed material passes through endosomes on its way to lysosomes. Endosomes are, in part, responsible for the sorting of endocytosed material before transport to lysosomes. This allows some material to be returned to the plasma membrane.

Lysosomes

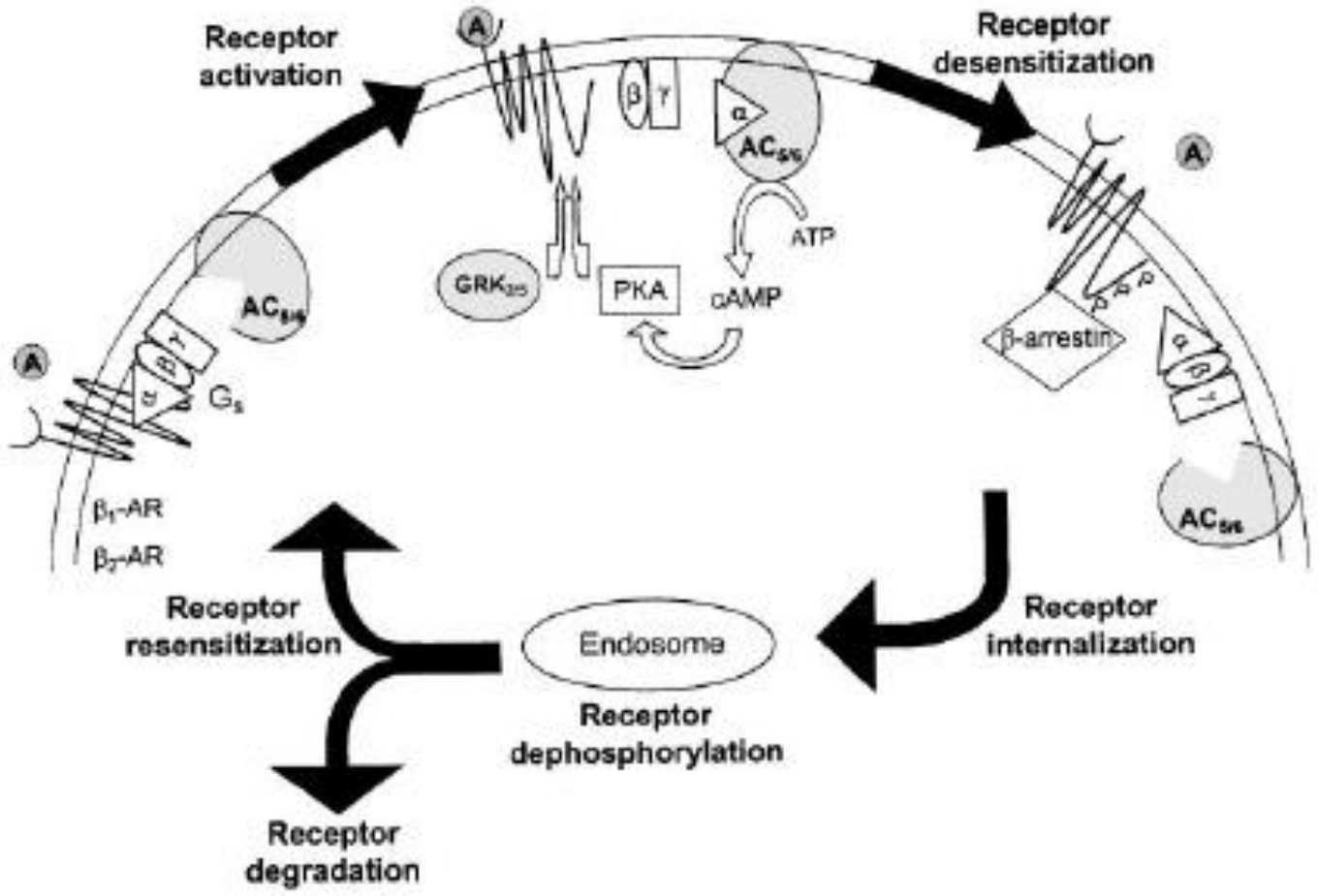
- **Lysosomes** are organelles that contain digestive enzymes (acid hydrolases). They digest excess or worn-out organelles, food particles, and engulfed viruses or bacteria. The membrane surrounding a lysosome allows the digestive enzymes to work at the 4.5 pH they require. Lysosomes fuse with vacuoles and dispense their enzymes into the vacuoles, digesting their contents. They are created by the addition of hydrolytic enzymes to early endosomes from the Golgi apparatus. The name *lysosome* derives from the Greek words *lysis*, which means dissolution or destruction, and *soma*, which means body. They are frequently nicknamed "suicide-bags" or "suicide-sacs" by cell biologists due to their role in autolysis. Lysosomes were discovered by the Belgian cytologist Christian de Duve in 1949.

How gene transcription is activated by a rise in cyclic AMP concentration in the heart



GRK = G-protein receptor kinase, PKA: protein kinase A – both of which are known to phosphorylate b-receptors.

How gene transcription is activated by a rise in cyclic AMP concentration in the heart

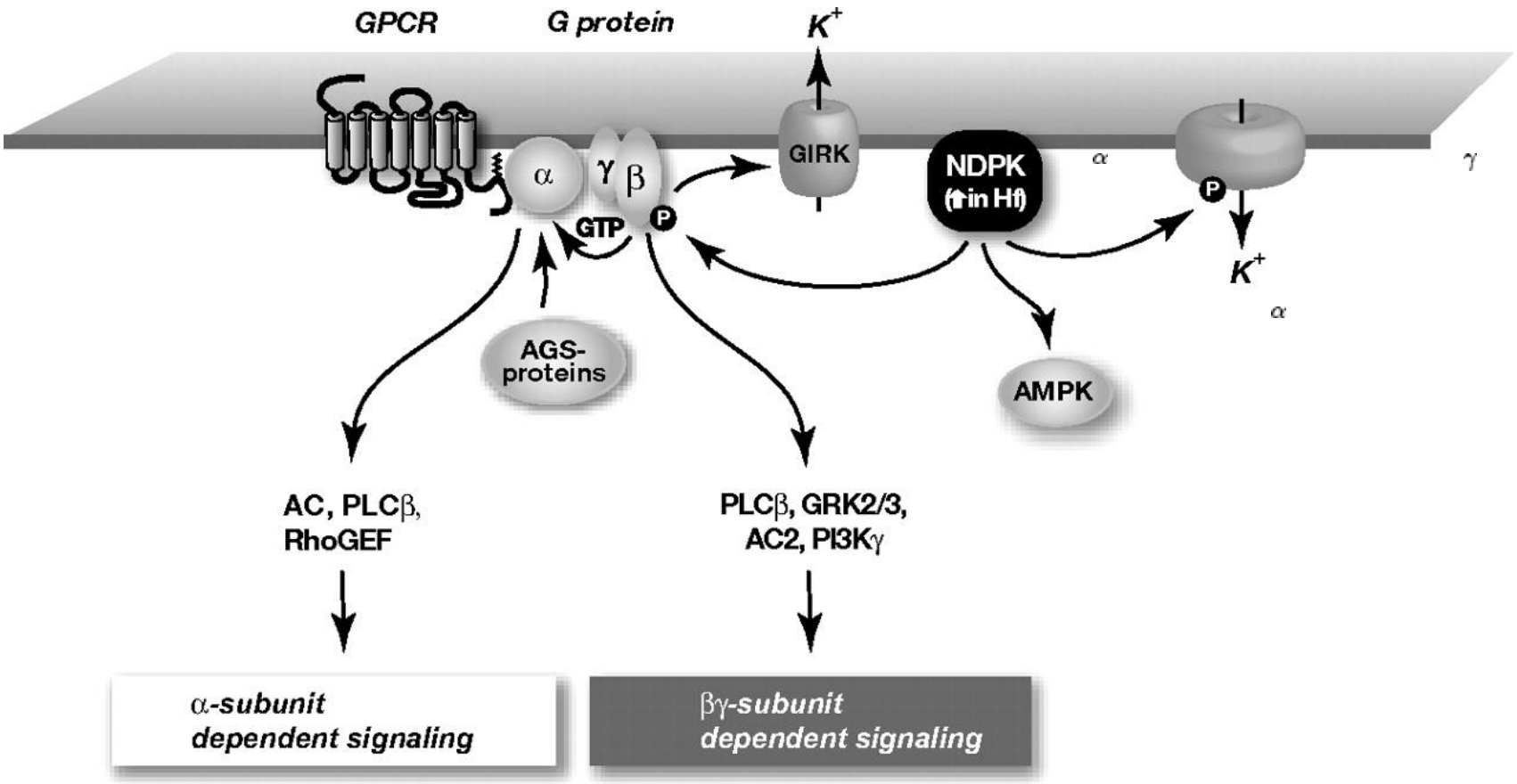


Desensitization or

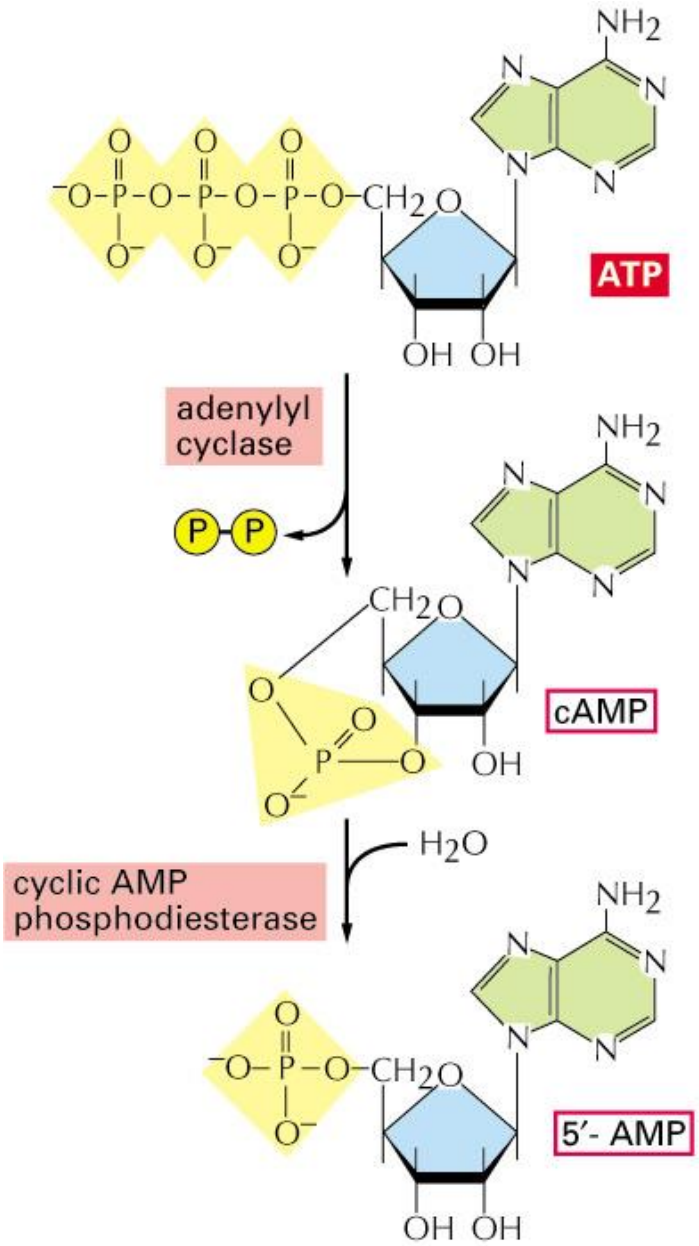
β-receptor downregulation

- An enormously important phenomenon in cardiac biology – beta receptor downregulation – implications:
- First description in the early 1980s (Bristow et al., NEJM) and / or: M. Böhm et al.

G-protein signaling in the heart



Synthesis and degradation of cAMP

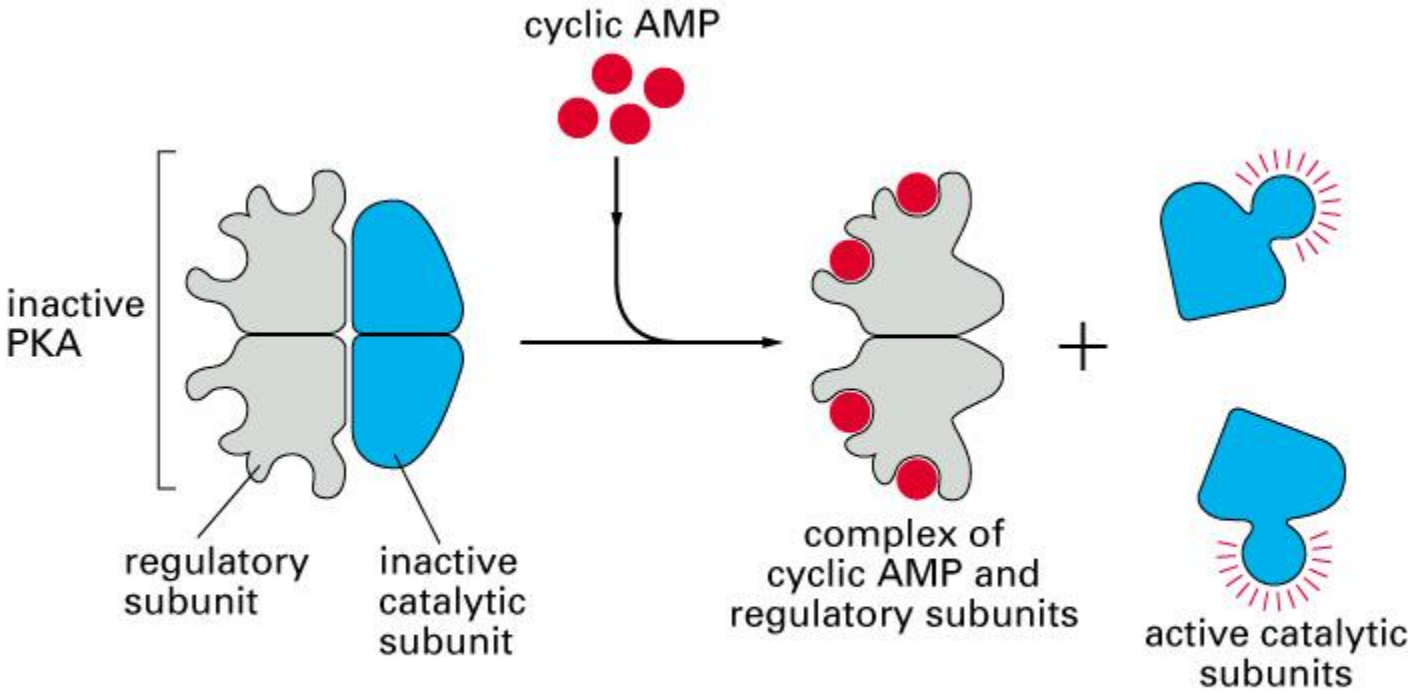


Some Hormone-induced Cell Responses

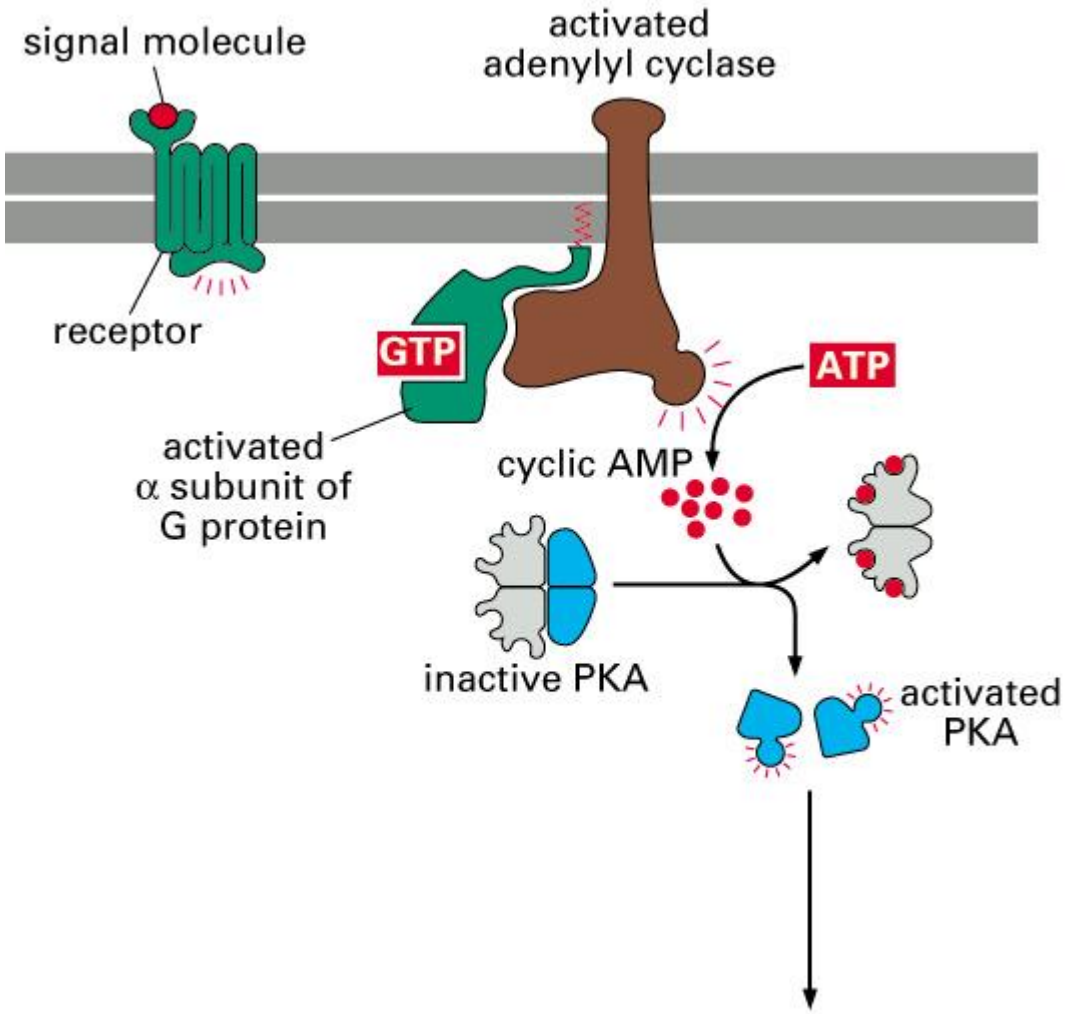
Mediated by cAMP

Target Tissue	**Hormone**	**Major Response**
Thyroid gland	thyroid-stimulating	thyroid hormone synthesis and secretion
Adrenal cortex	adrenocorticotrophic hormone (ACTH)	cortisol secretion
Ovary	luteinizing hormone (LH)	progesterone secretion
Muscle	adrenaline	glycogen breakdown
Bone	parathormone	bone resorption
Heart	adrenaline	increase in heart rate and force on contraction
Liver	glucagon	glycogen breakdown
Kidney	vasopressin	water resorption
Fat	adrenaline, ACTH, glucagon, TSH	triglyceride breakdwon

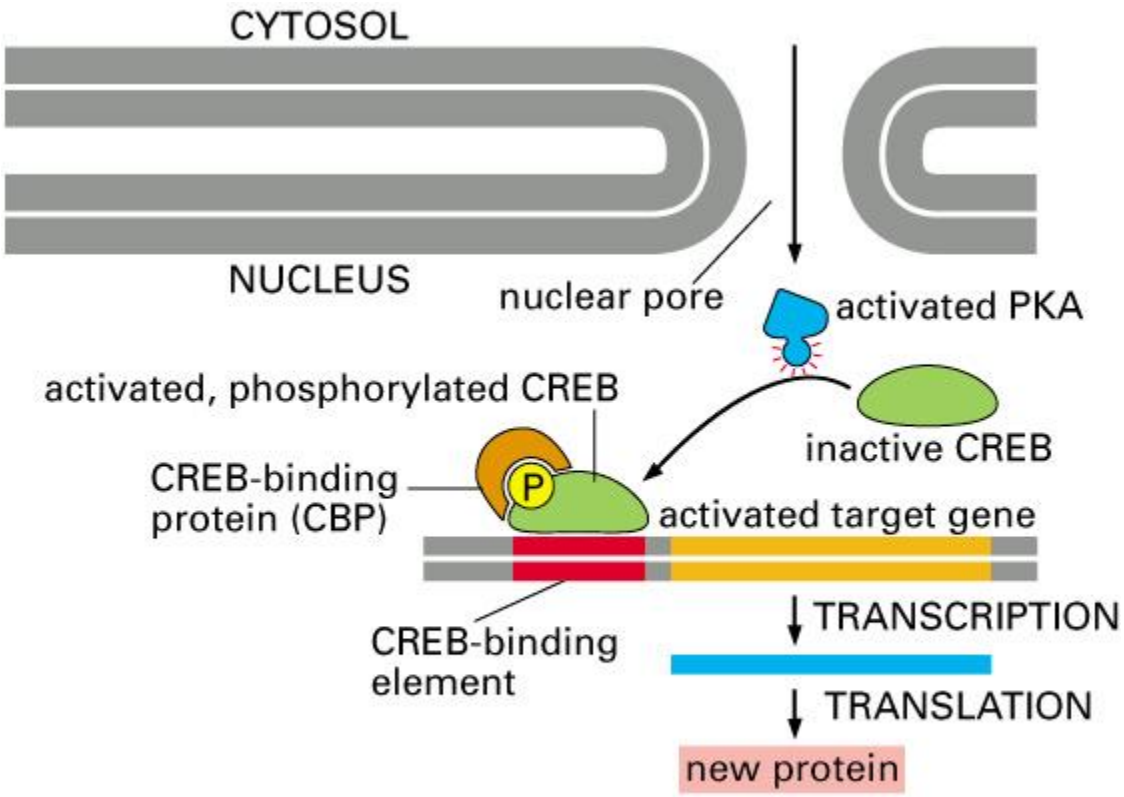
Activation of cyclic AMP dependent protein kinase (PKA)



How gene transcription is activated by a rise in cyclic AMP concentration



How gene transcription is activated by a rise in cyclic AMP concentration



How gene transcription is activated by a rise in cyclic AMP concentration 1

- How about in cardiomyocytes?
- PKA phosphorylates a variety of proteins in the heart, such as:
- Phospholamban – What is the effect?
- L-type calcium channels – Effect?
- The β-receptors – Effect?
- Sarcomeric proteins - Troponin I

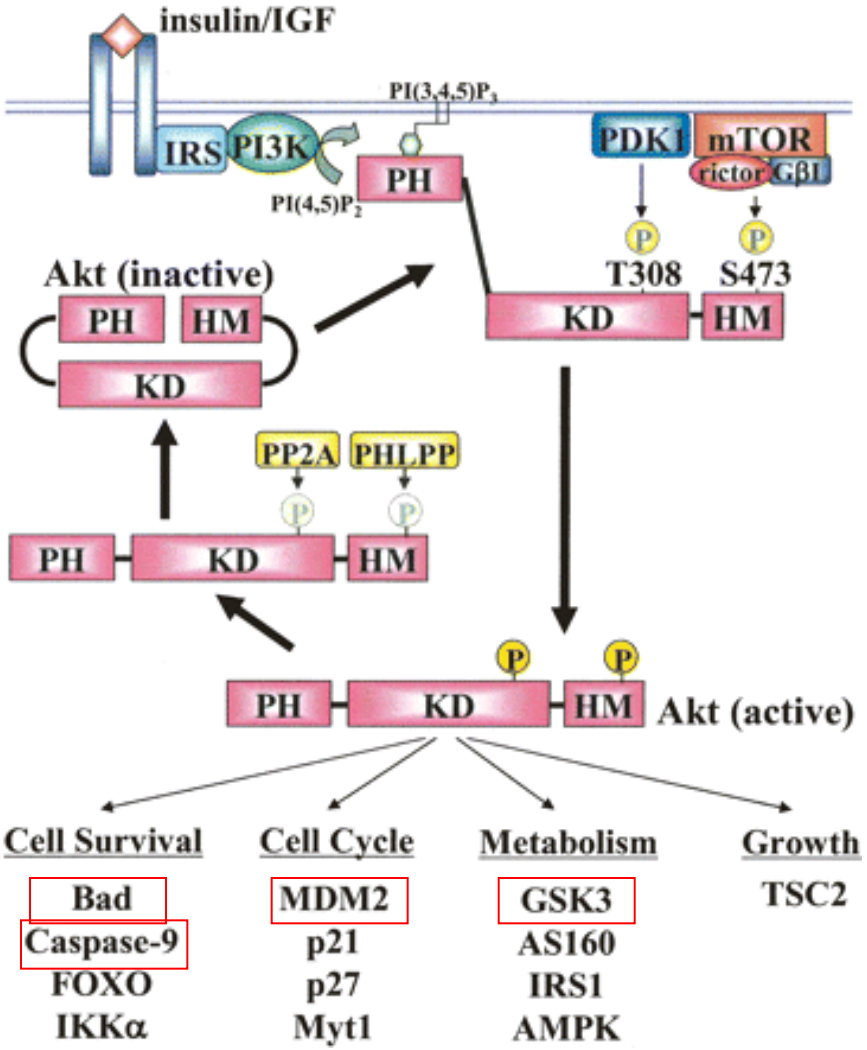
How gene transcription is activated by a rise in cyclic AMP concentration 2

- CREB (cAMP response element binding protein – effect?
- A: enhances activation of transcription

Akt activation & deactivation

The **serine-threonine protein kinase** encoded by the **AKT1** gene is catalytically inactive in serum-starved primary and immortalized fibroblasts.
AKT1 and the related AKT2 are activated by platelet-derived growth factor.
AKT1 is particularly activated by **insulin and IGF1**.
The activation is rapid and specific, and it is abrogated by mutations in the pleckstrin homology domain of AKT1. It was shown that the activation occurs through phosphatidylinositol 3-kinase.
In the developing nervous system **AKT is a critical mediator of growth factor-induced neuronal survival**. Survival factors can suppress apoptosis in a transcription-independent manner by activating the serine/threonine kinase AKT1, which then phosphorylates and inactivates components of the apoptotic machinery.
Multiple alternatively spliced transcript variants have been found for this gene.
AKT1 is animportant survival factor for cardiomyocytes.

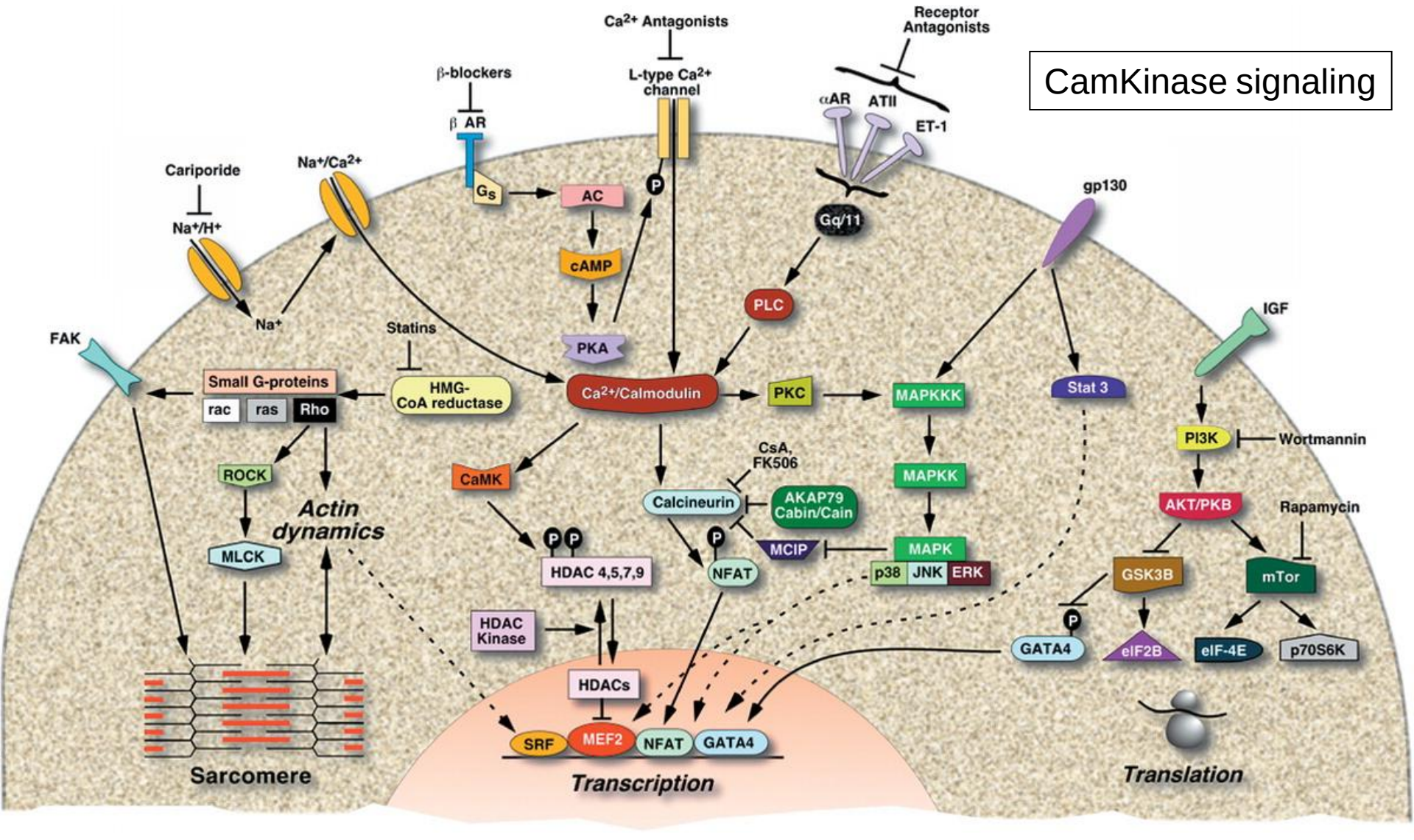
Akt activation & deactivation



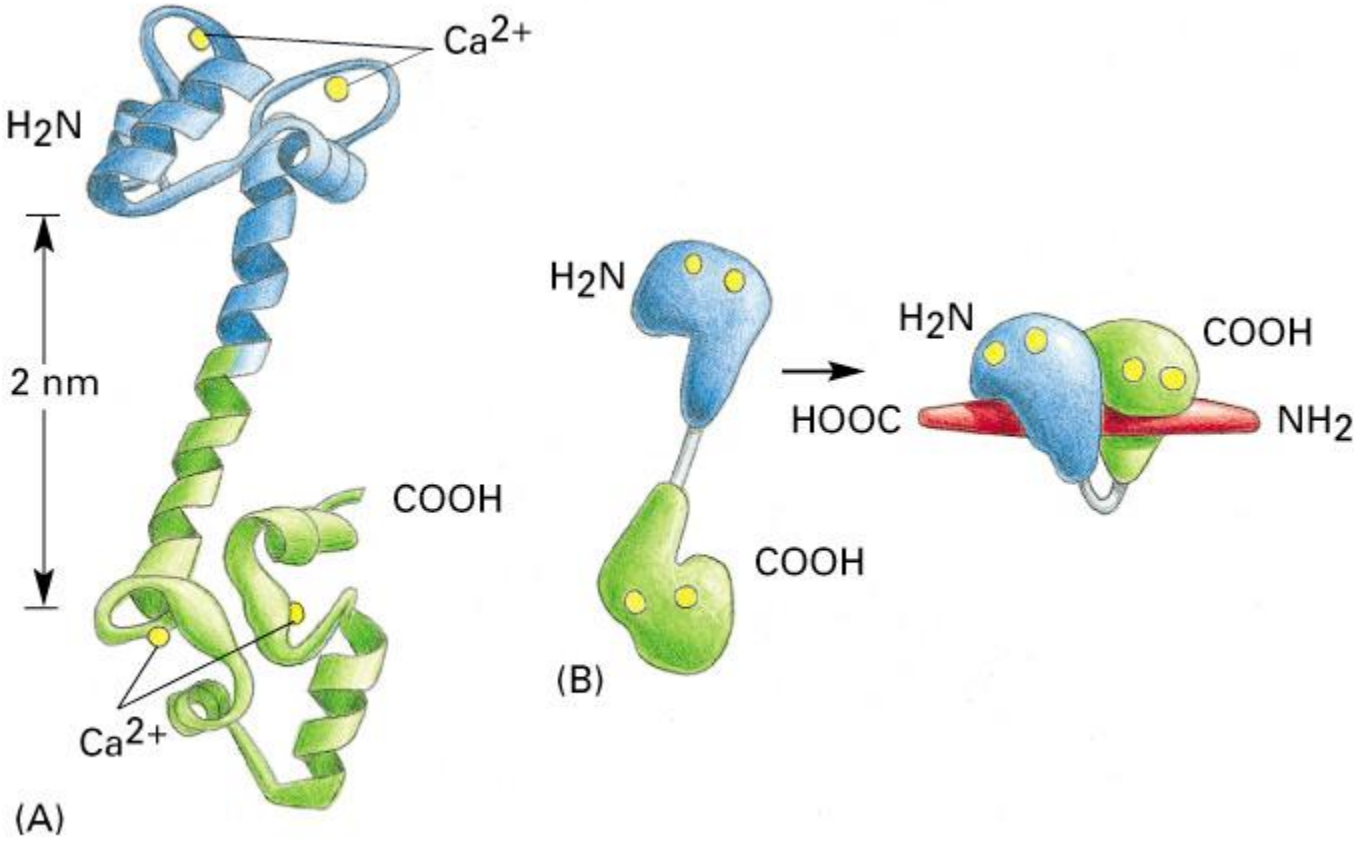
Regulation of Akt kinase activity and downstream Akt substrates

- Upon insulin/IGF stimulation, Akt is recruited to the plasma membrane via its N-terminal PH domain, and activated by phosphorylation at T308 (by PDK1) and S473 (by mTORC2). Active Akt translocates to various sites within the cell and phosphorylates downstream substrates.
- Akt kinase activity is then down-regulated by dephosphorylation of the two regulatory sites by protein phosphatases (T308 by PP2A, and S473 by PHLPP).

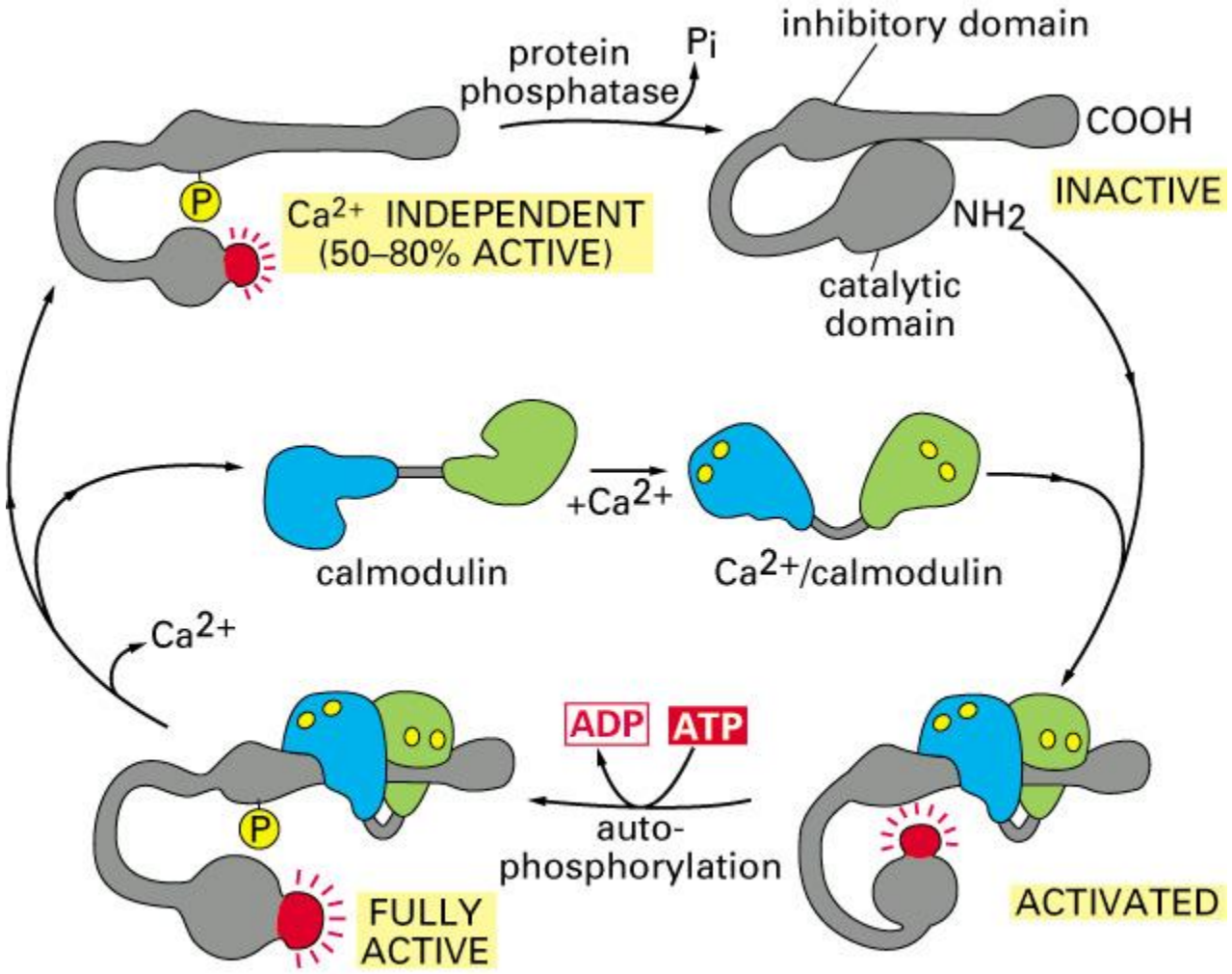
General signaltransduction – cardiac hypertrophy



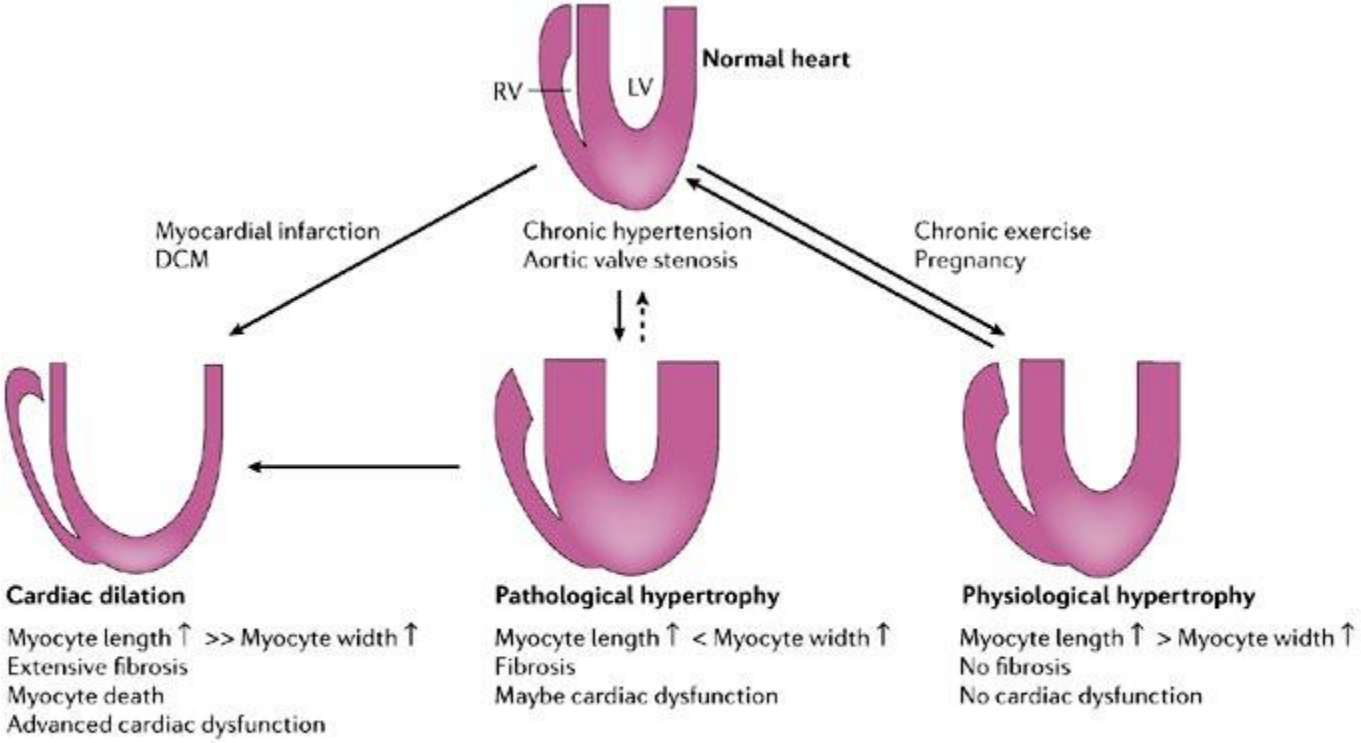
The structure of calcium / calmodulin based on x-ray diffraction and NMR studies



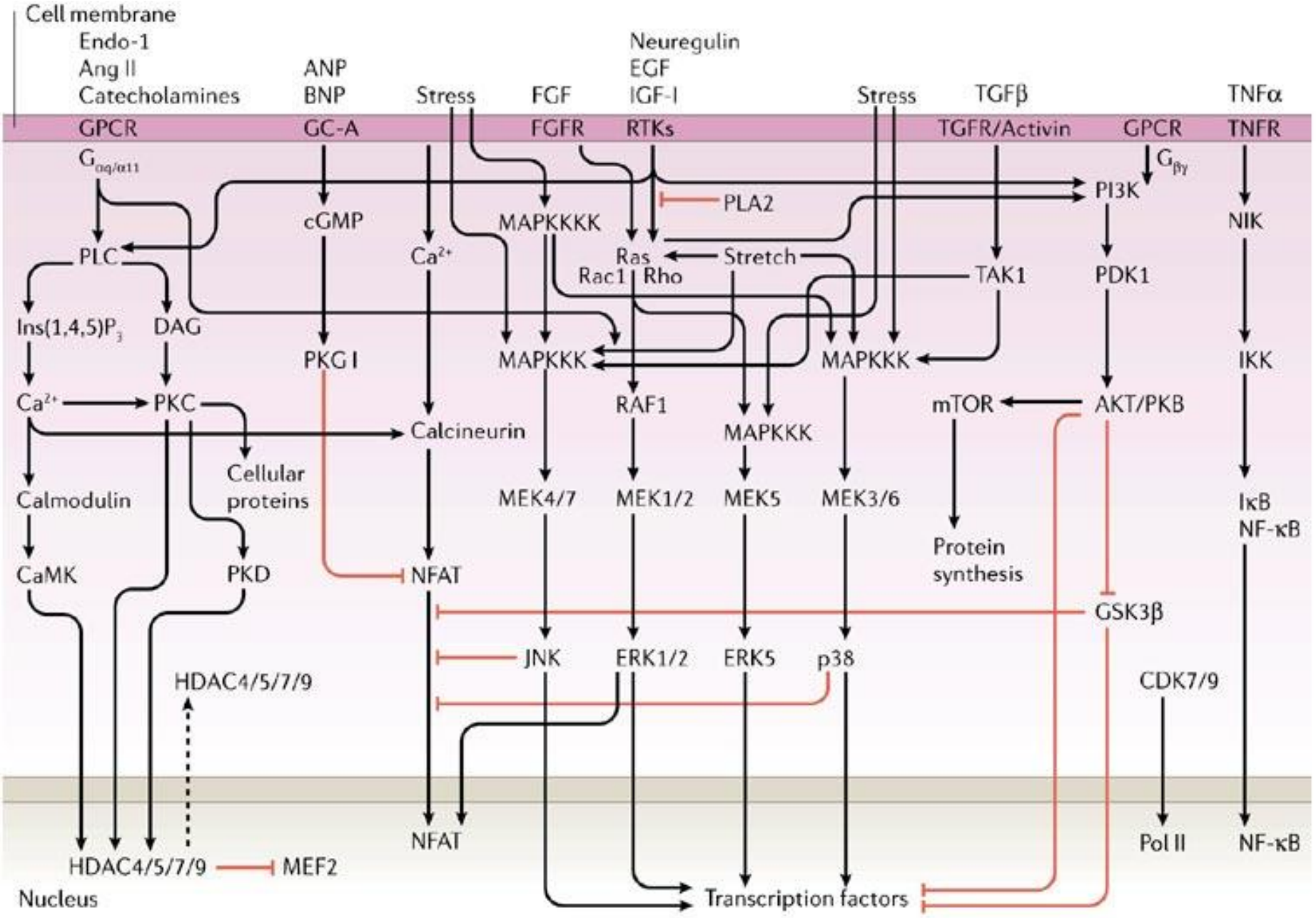
The activation of CaM-kinase II



Adaptive vs maladaptive hypertrophy



Pathological cardiac hypertrophy can produce concentric hypertrophy in which the ventricular wall and septum thicken with a net decrease in ventricular chamber dimensions (see figure). This remodelling is associated with a greater increase in cardiac myocyte width than length. However, pathological cardiac hypertrophy can also produce a phenotype of eccentric and dilatory cardiac growth. Cardiac dilation, although not typically referred to as hypertrophy, can result from a growth response in which sarcomeres are predominantly added in series to individual myocytes. The molecular underpinnings whereby sarcomeres are either added in series, in parallel or in a combination of both are not entirely understood. DCM, dilated cardiomyopathy; LV, left ventricle; RV, right ventricle.



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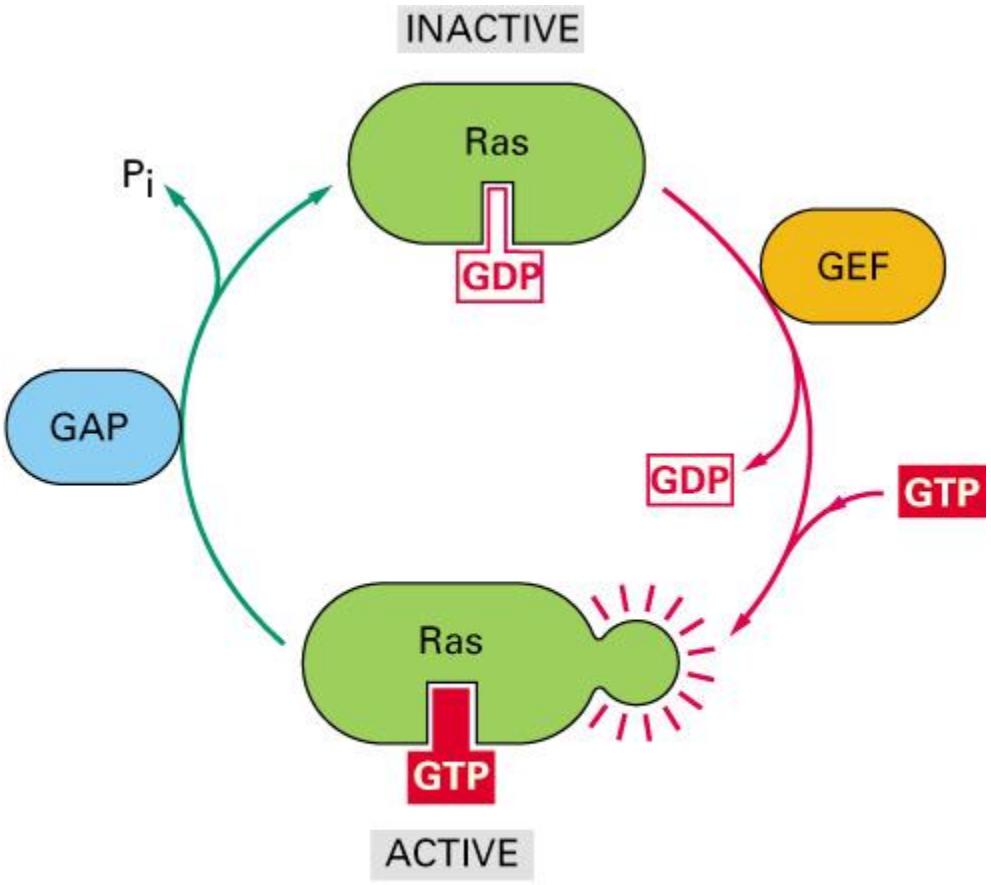
RAS

- ***Ras*** is a family of genes encoding a small GTPases that are involved in cellular signal transduction.
- Activation of Ras signalling causes cell growth, differentiation and survival.
- Ras is the prototypical member of the Ras superfamily of proteins which are all related in structure and regulate diverse cell behaviours.
- Since Ras communicates signals from outside the cell to the nucleus, mutations in *ras* genes can permanently activate it and cause inappropriate transmission inside the cell even in the absence of extracellular signals. Because these signals result in cell growth and division, dysregulated Ras signaling can ultimately lead to oncogenesis and cancer. Activating mutations in Ras are found in 20-25% of all human tumors and up to 90% in specific tumor types

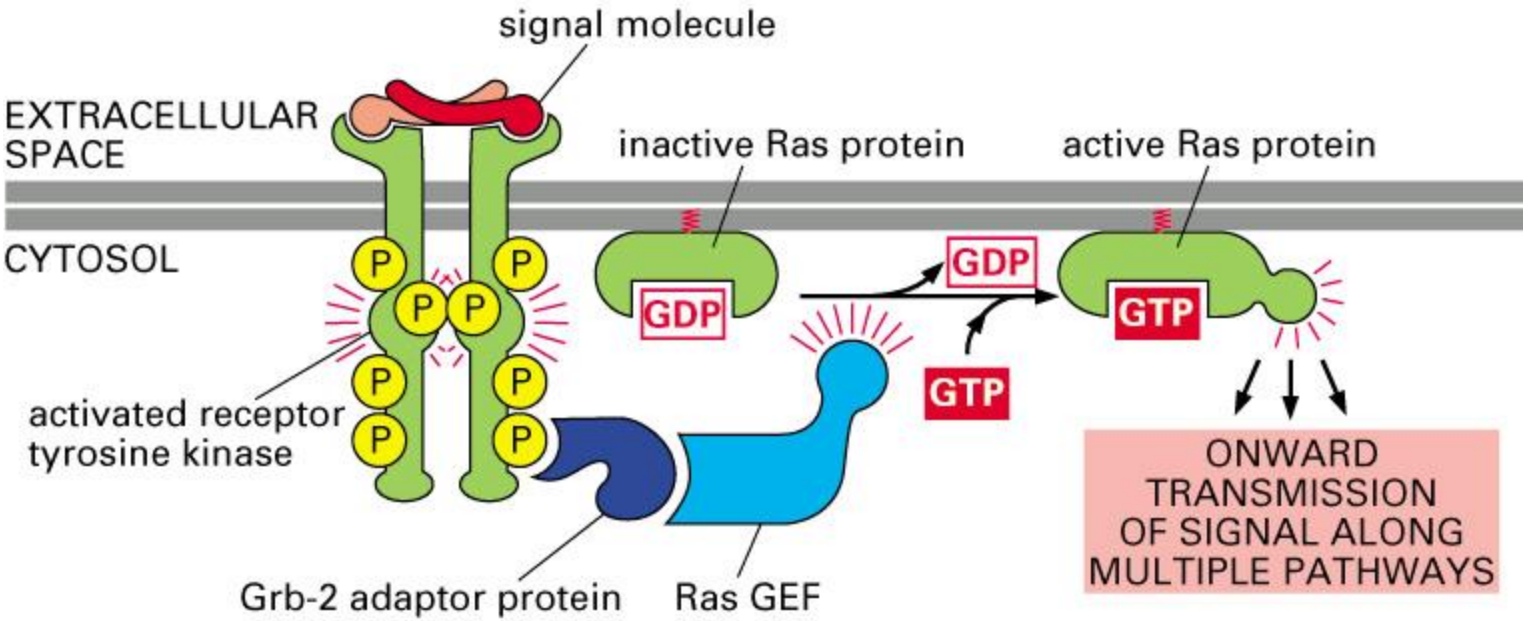
RAS

- Members of the RAS subfamily of GTPases function in signal transduction as GTP/GDP-regulated switches that cycle between inactive GDP- and active GTP-bound states. Guanine nucleotide exchange factors (GEFs), such as RASGRP3, serve as RAS activators by promoting acquisition of GTP to maintain the active GTP-bound state and are the key link between cell surface receptors and RAS activation

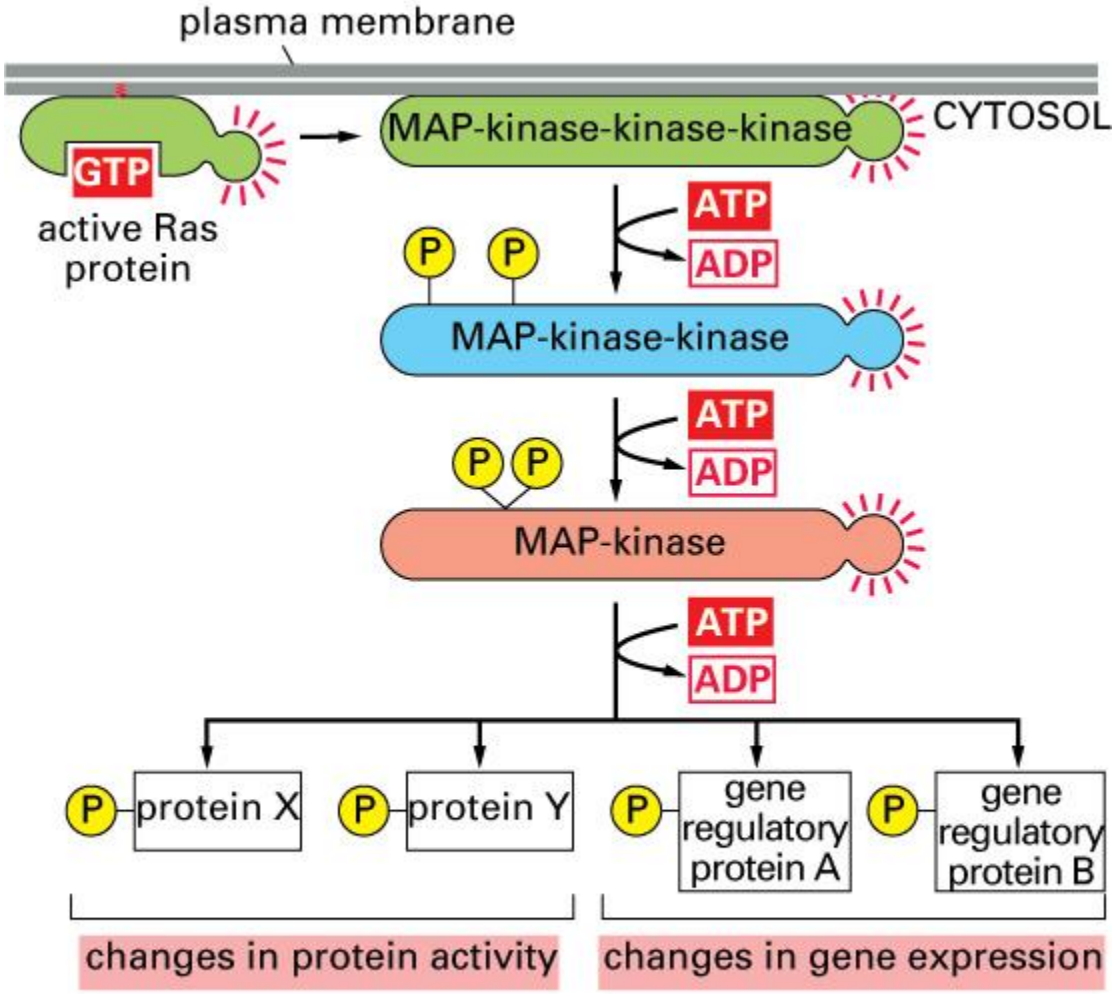
The regulation of Ras activity



The activation of Ras by an activated receptor tyrosine kinase



The MAP kinase serine/threonine phosphorylation pathway activated by Ras (links extracellular stimulus to a variety of cell outputs)

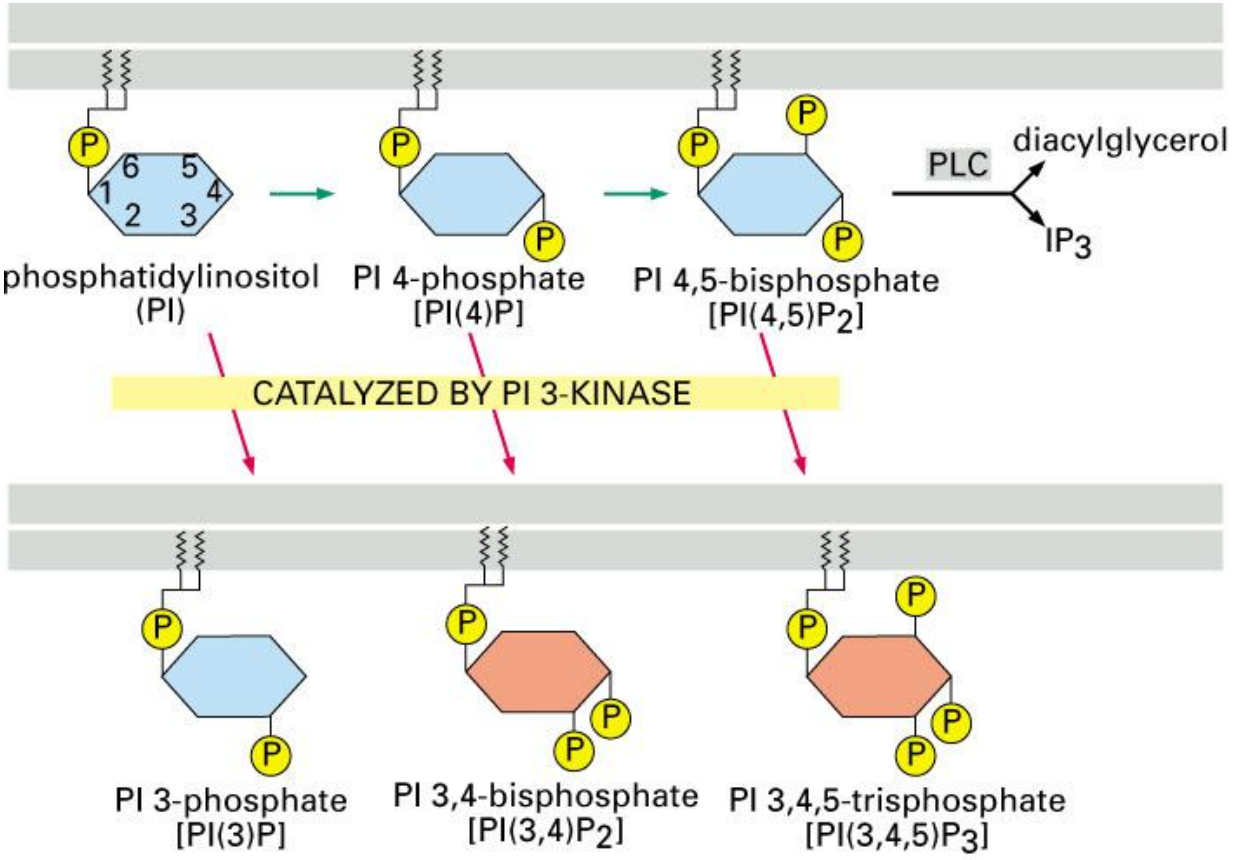


Raf

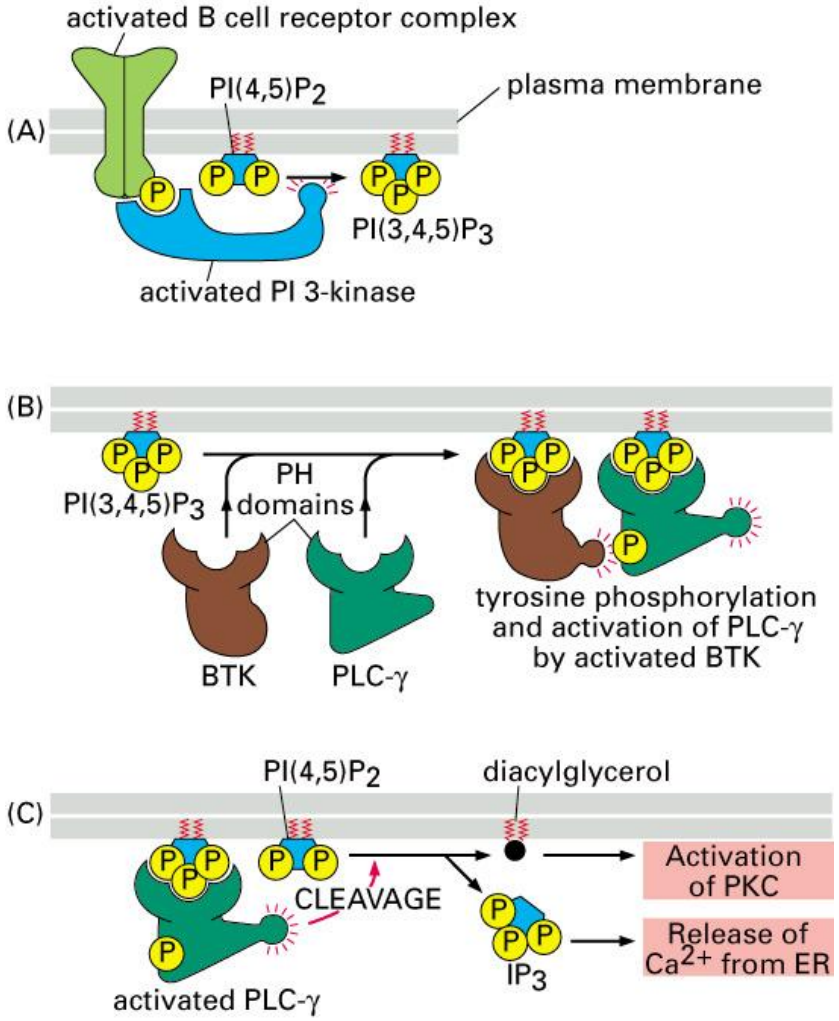
Mek

Erk

Generation of inositol phospholipid docking sites by PI 3-kinase



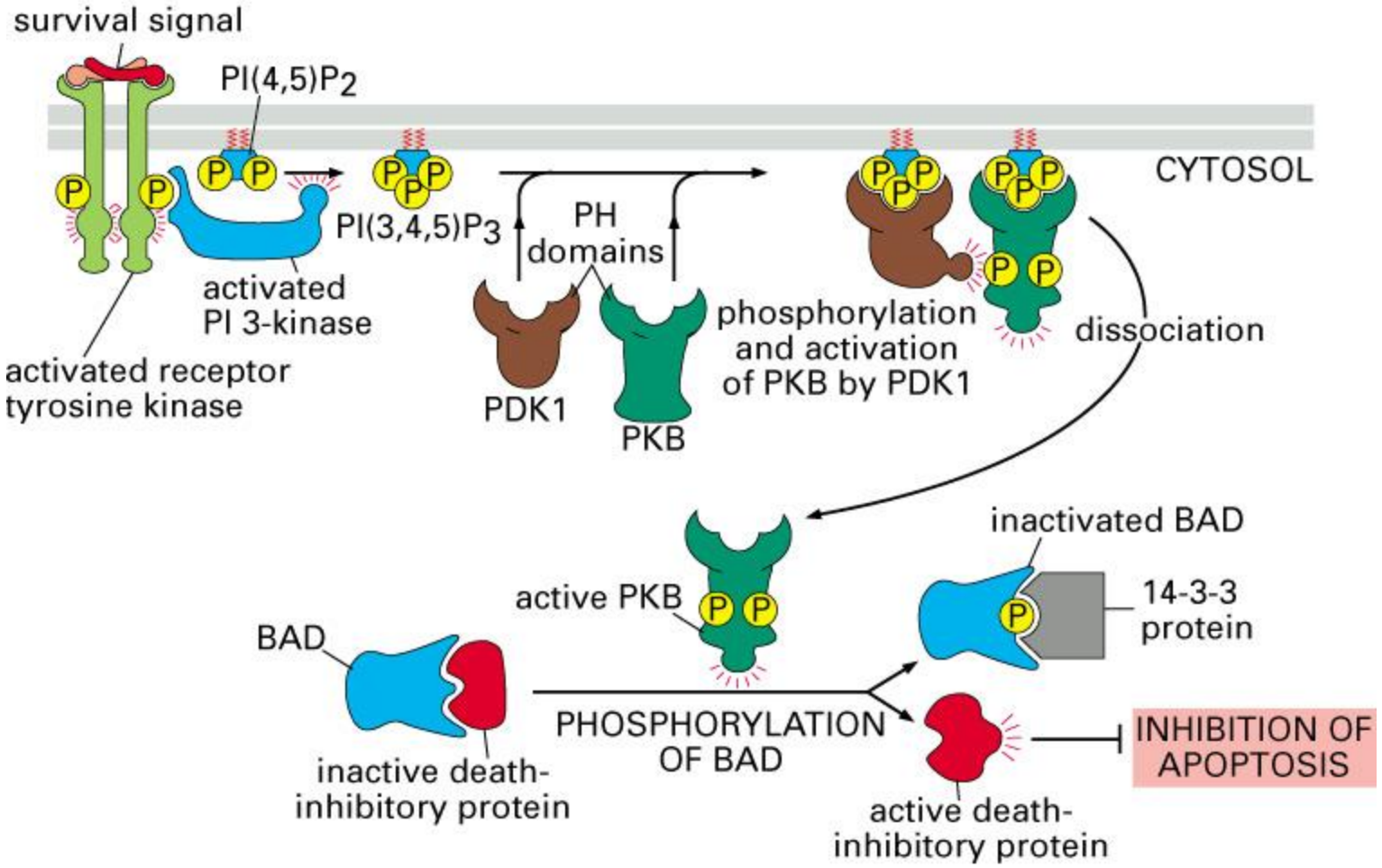
The recruitment of signaling proteins with PH domains to the plasma membrane during B cell activation



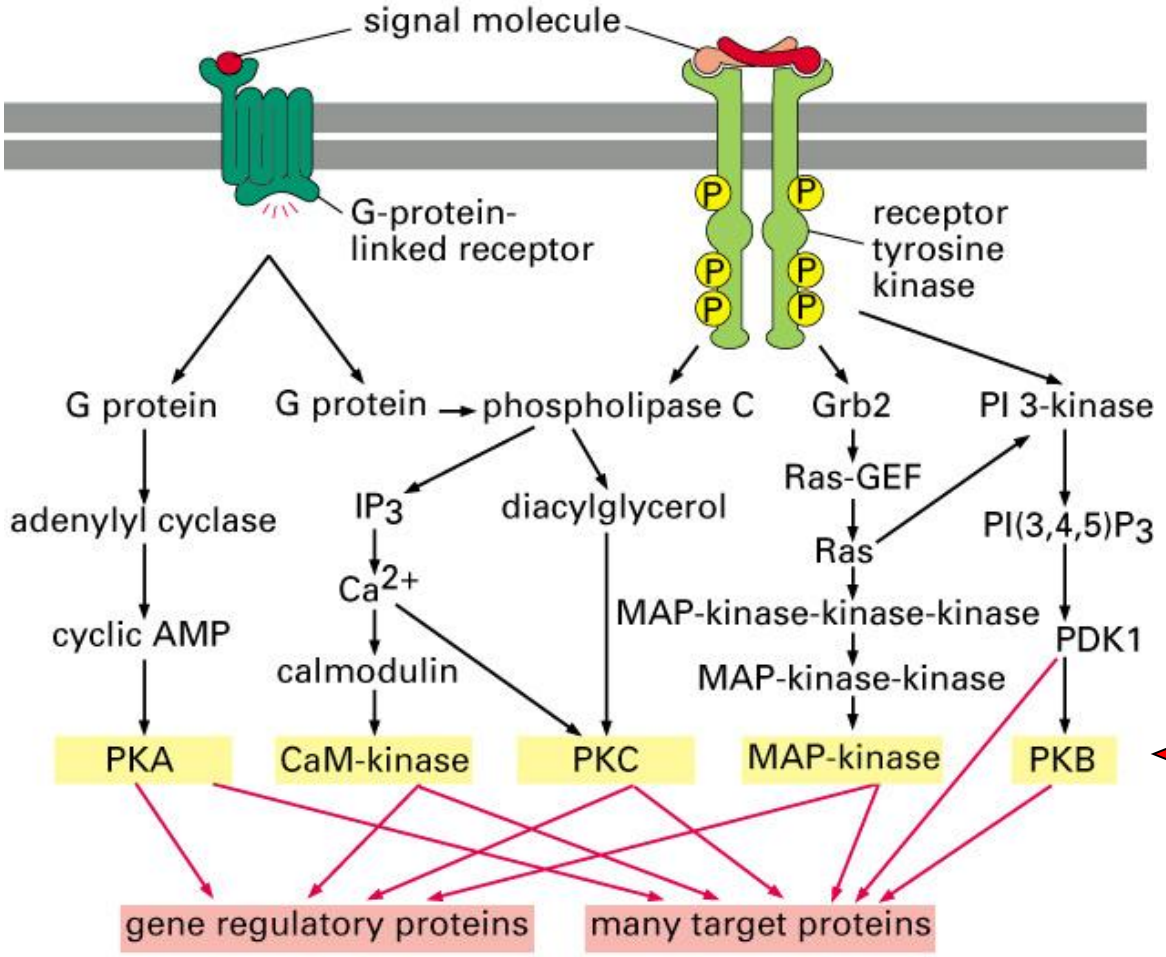
PI 3 – kinase signaling in the heart

- Involved in adaptive (?) versus maladaptive (?) hypertrophy
- Involved in survival pathways as well as those involved in apoptosis

One way in which signaling through PI 3-kinase signaling promotes cell survival



Five parallel intracellular signaling pathways activated by G-protein-linked receptors, receptor tyrosin kinases, or both

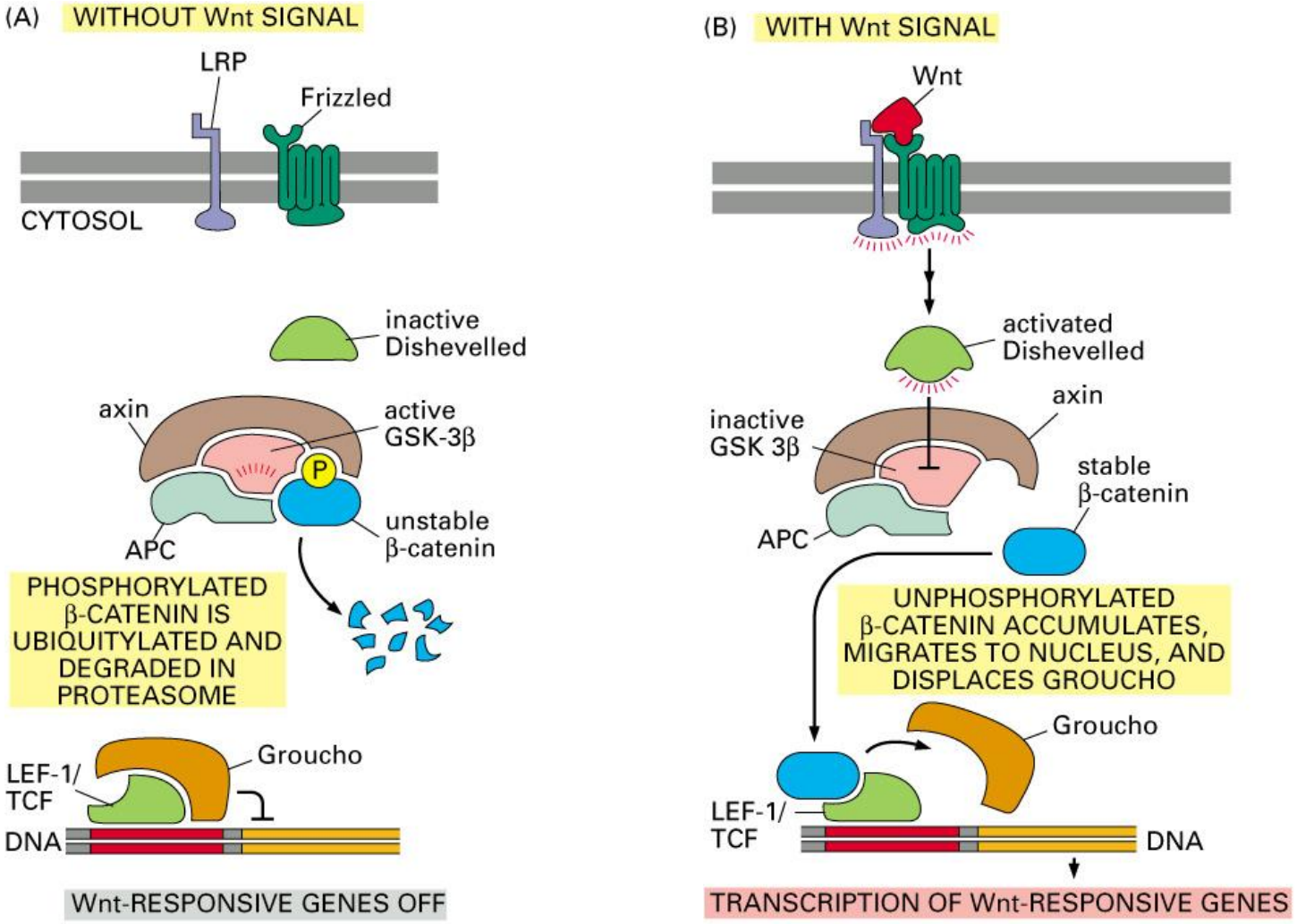


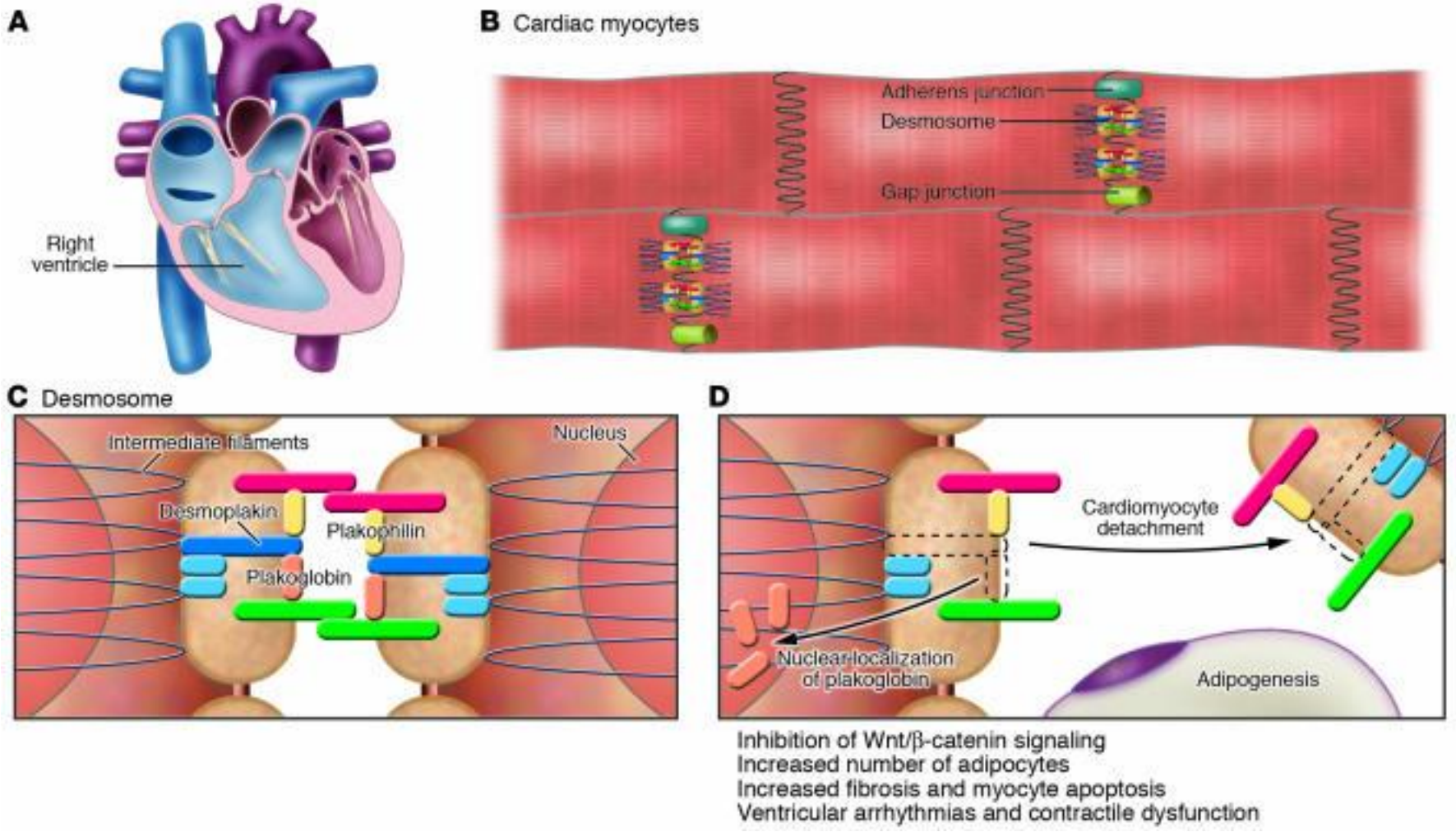
Effects in Cardiomyocytes?

Effects in cardiomyocytes

- PKA?
- CamK?
- PKC?
- MAPK?
- PI3K - PKB?

A model for the Wnt activation of the β-catenin signaling pathway





Cardiac-specific restriction of the desmosomal protein desmoplakin causes nuclear localization of plakoglobin and reduced Wnt/β-catenin signaling, recapitulating human ARVC. (**A**) ARVC predominantly affects the right ventricle of the heart. (**B**) The intercalated discs of cardiac myocytes are characterized by gap junctions, adherens junctions, and desmosomes. (**C**) Cell-cell adhesion is largely dependent on interaction of intracellular components of the desmosomal plaque such as desmoplakin and plakoglobin. (**D**) **Heterozygous cardiac desmoplakin-deficient mice show nuclear localization of plakoglobin and reduced Wnt/β-catenin signaling.** This causes increased expression of adipogenic and fibrogenic genes in vitro, abnormal cardiac adipose tissue and fibrosis in vivo, and ventricular arrhythmias similar to human ARVC. Interactions between signaling defects and mechanical stresses are likely to be involved in the genesis of the final phenotype.

Das waren tolle Zeiten!

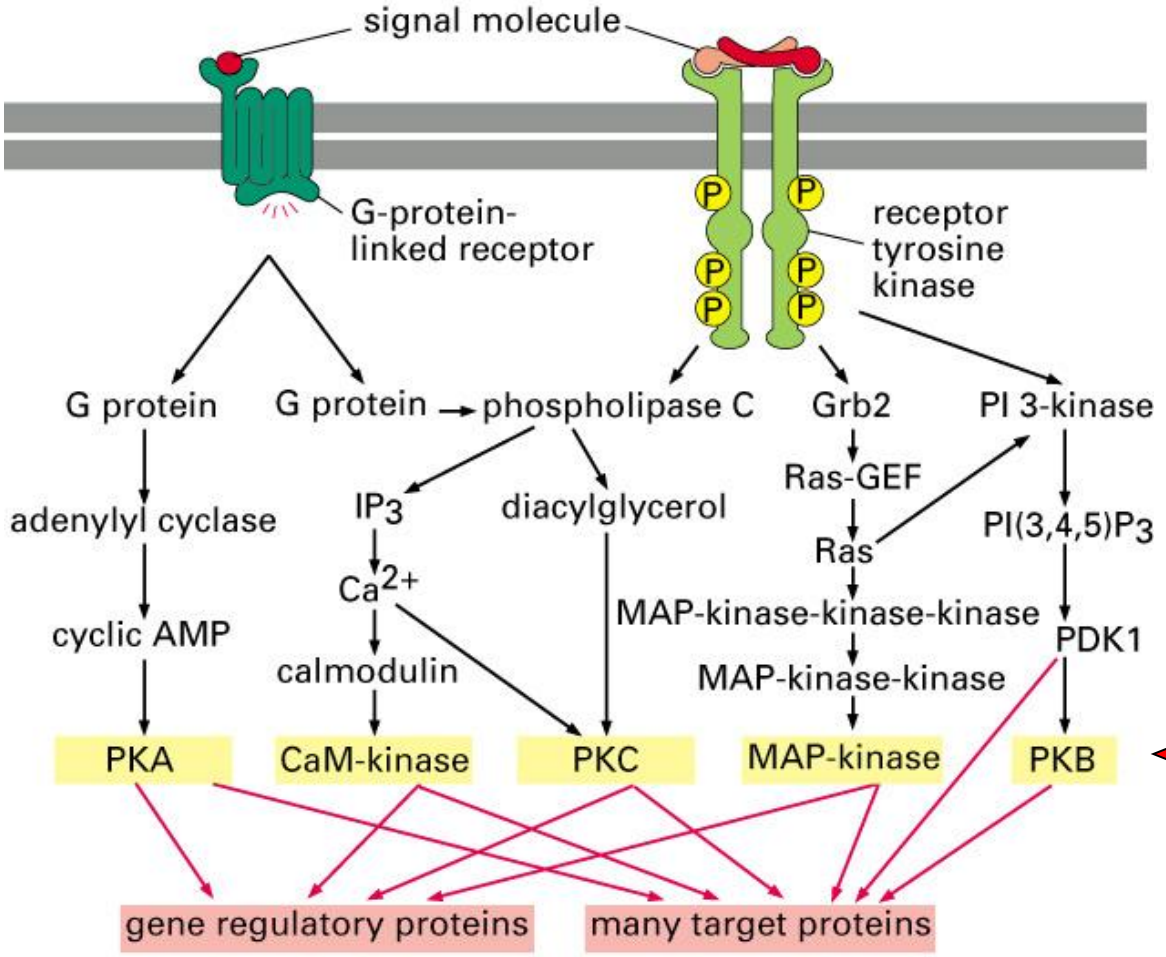
William Harvey, der Erstbeschreiber des geschlossenen Blutkreislaufs, erklärt den politisch verantwortlichen seine Wissenschaft


EXERCITATIO
ANATOMICA DE
MOTV CORDIS ET SAN-
GVINIS IN ANIMALI-
BVS,
GVILIELMI HARVEI ANGLI,
Medici Regii, & Professoris Anatomiæ in Col-
legio Medicorum Londinensi.
FRANCOFVRTI,
Sumptibus GVILIELMI FITZERI.
ANNO M. DC. XXVIII.

Frankfurt, 1628

Harvey explains to the King
Robert Hannah, 1848

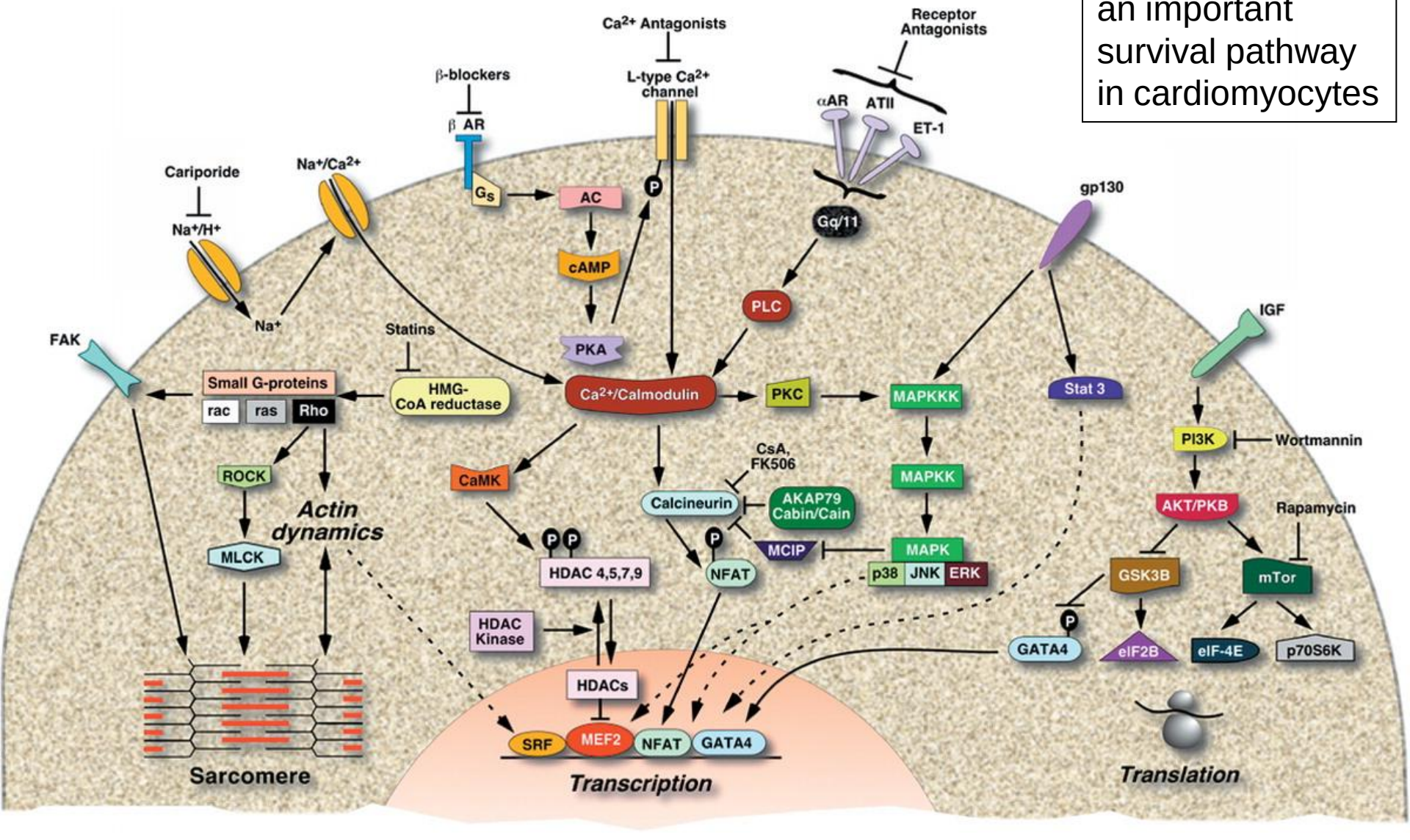
Five parallel intracellular signaling pathways activated by G-protein-linked receptors, receptor tyrosin kinases, or both

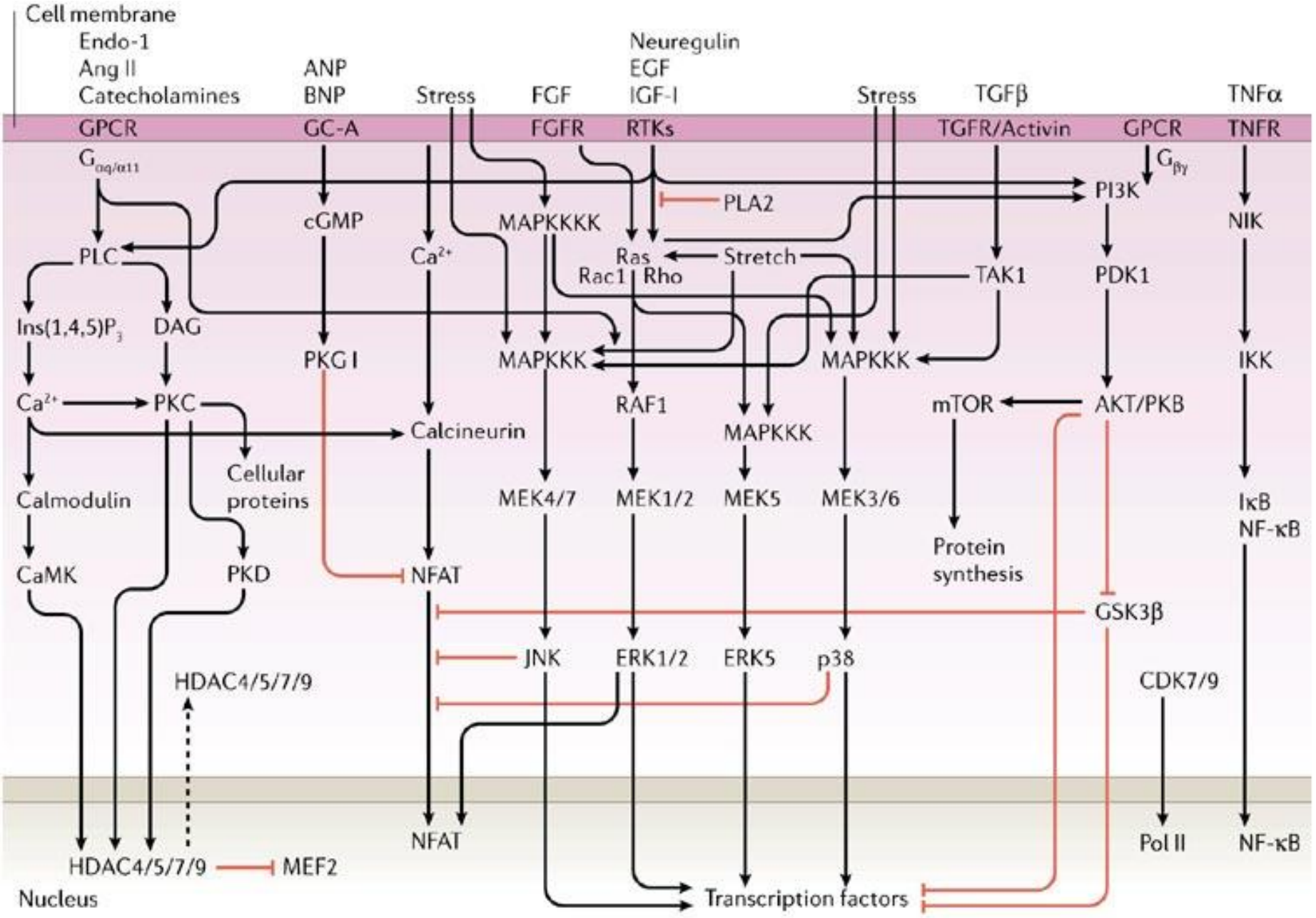


Effects in Cardiomyocytes?

General signaltransduction – cardiac hypertrophy

PI3K pathway: an important survival pathway in cardiomyocytes





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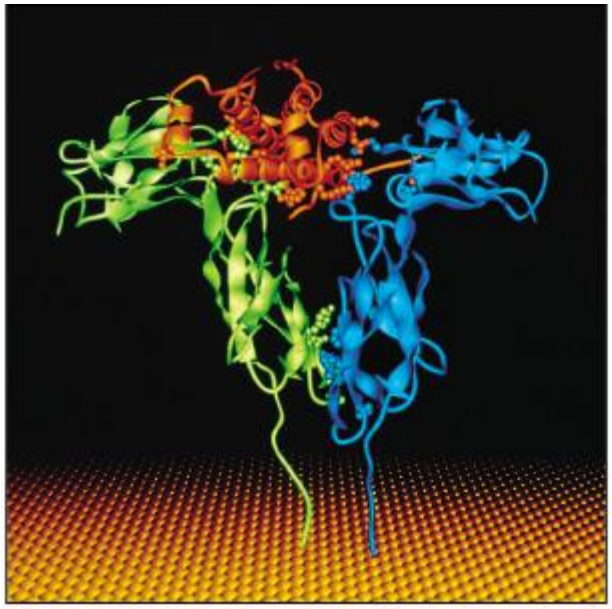
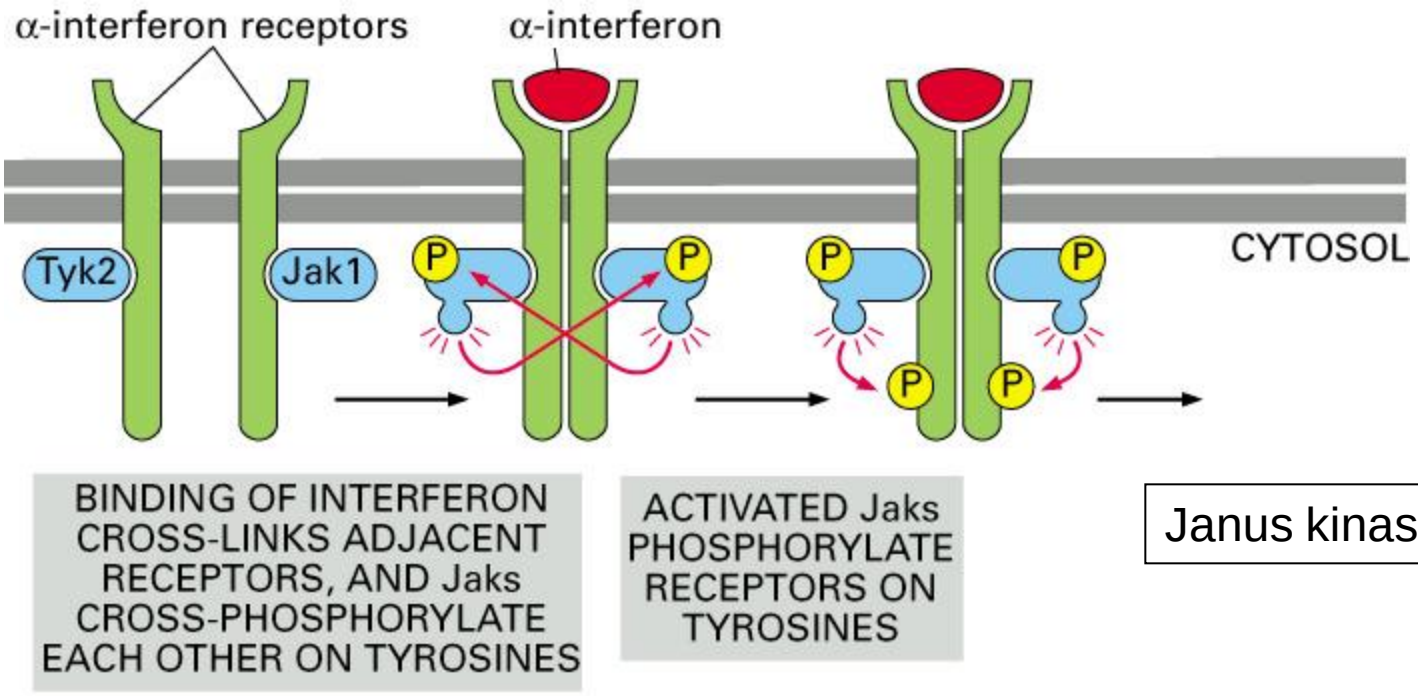
Effects in cardiomyocytes

- PKA?
- CamK?
- PKC?
- MAPK?
- PI3K – Akt / PKB?

Three dimensional structur of human growth hormone bound to its receptor



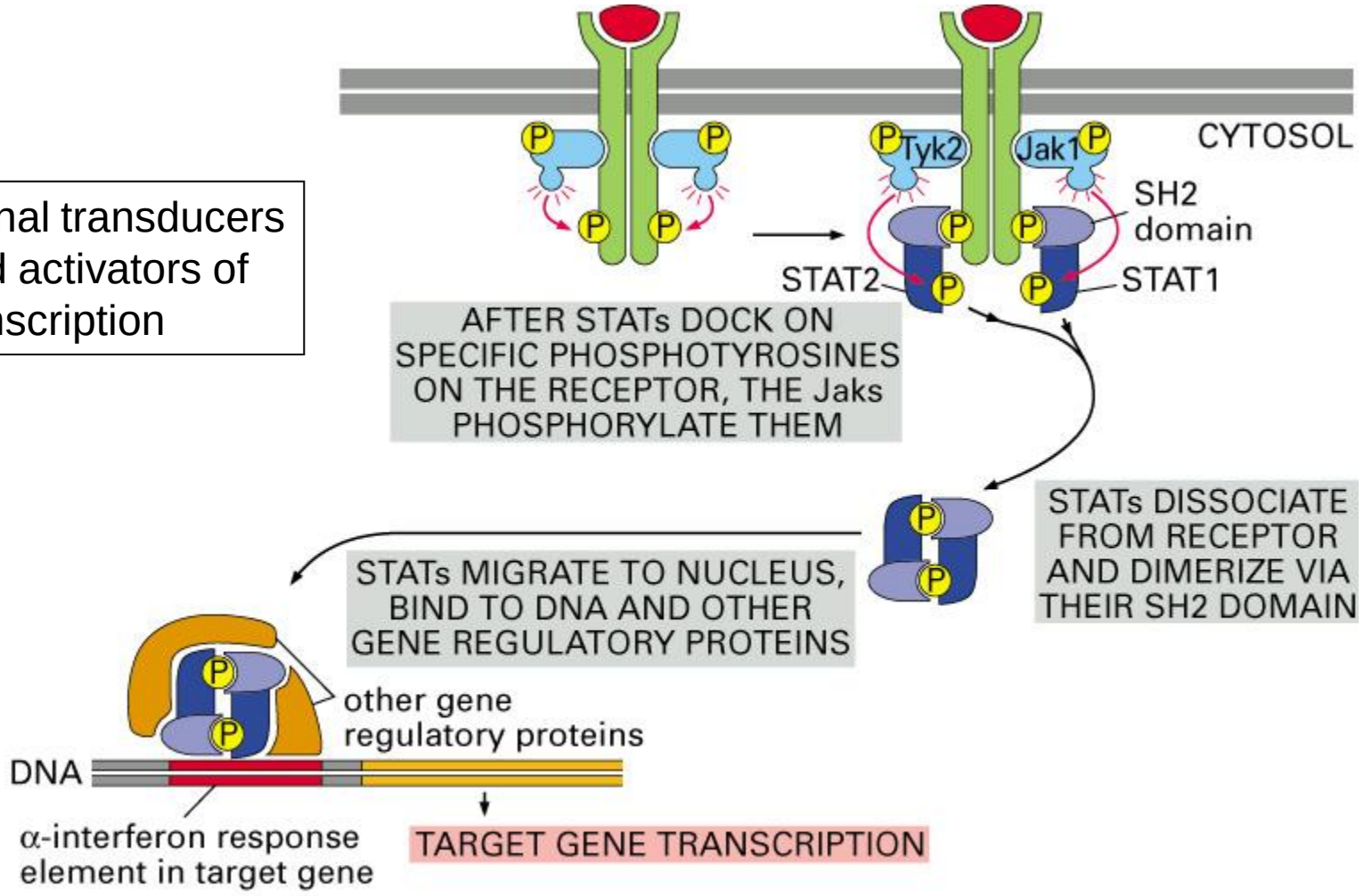
The Jak-STAT signaling pathway activated by alpha interferon



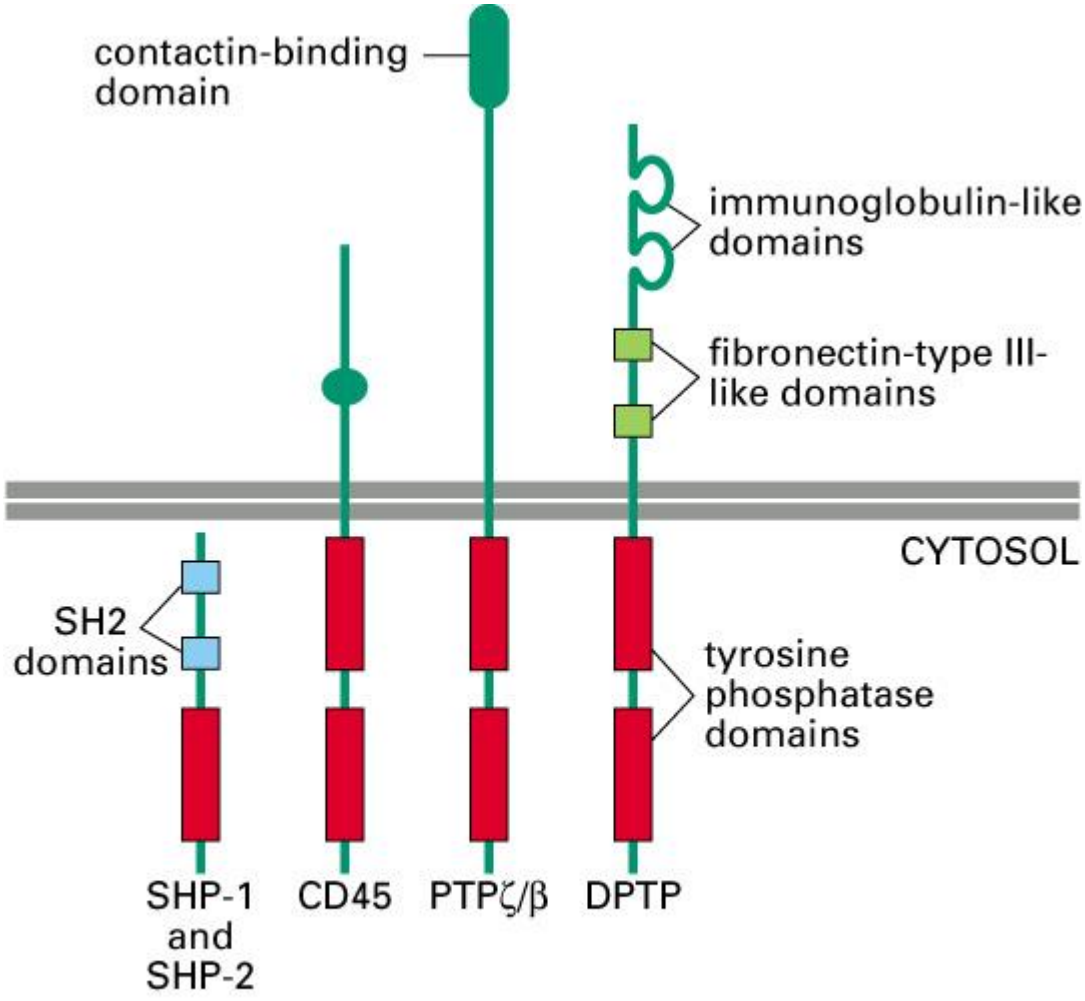
Janus kinases (JAK)

The Jak-STAT signaling pathway activated by alpha interferon

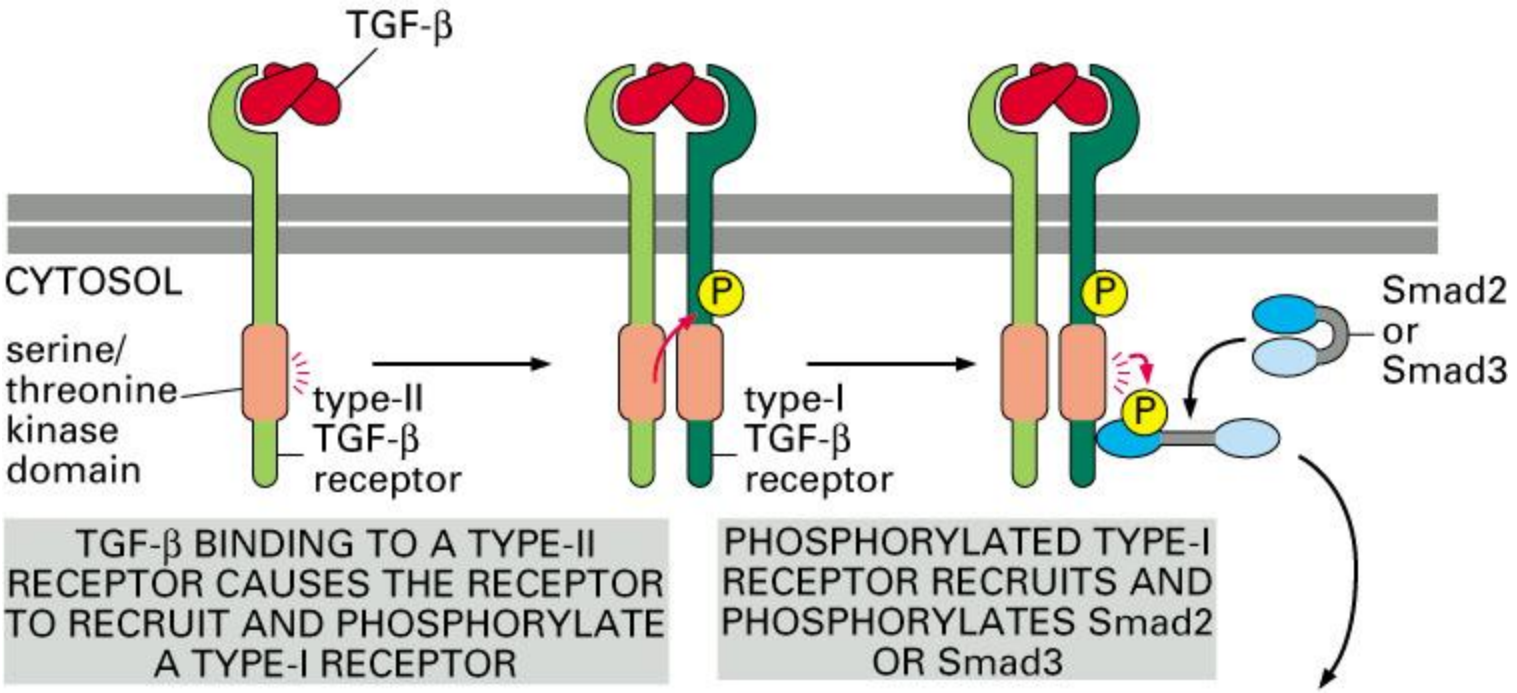
Signal transducers
And activators of
transcription



Some protein tyrosine **phosphatases**



A model for the Smad dependent signaling pathway activated bTGF-β



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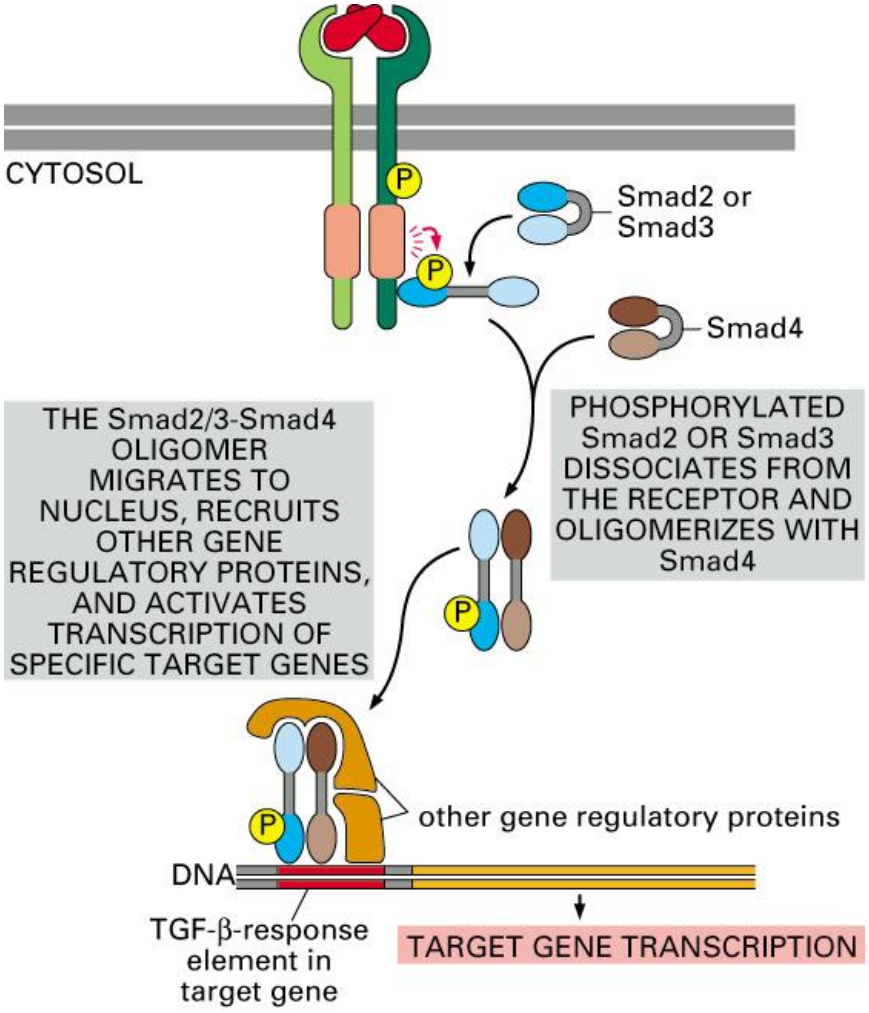
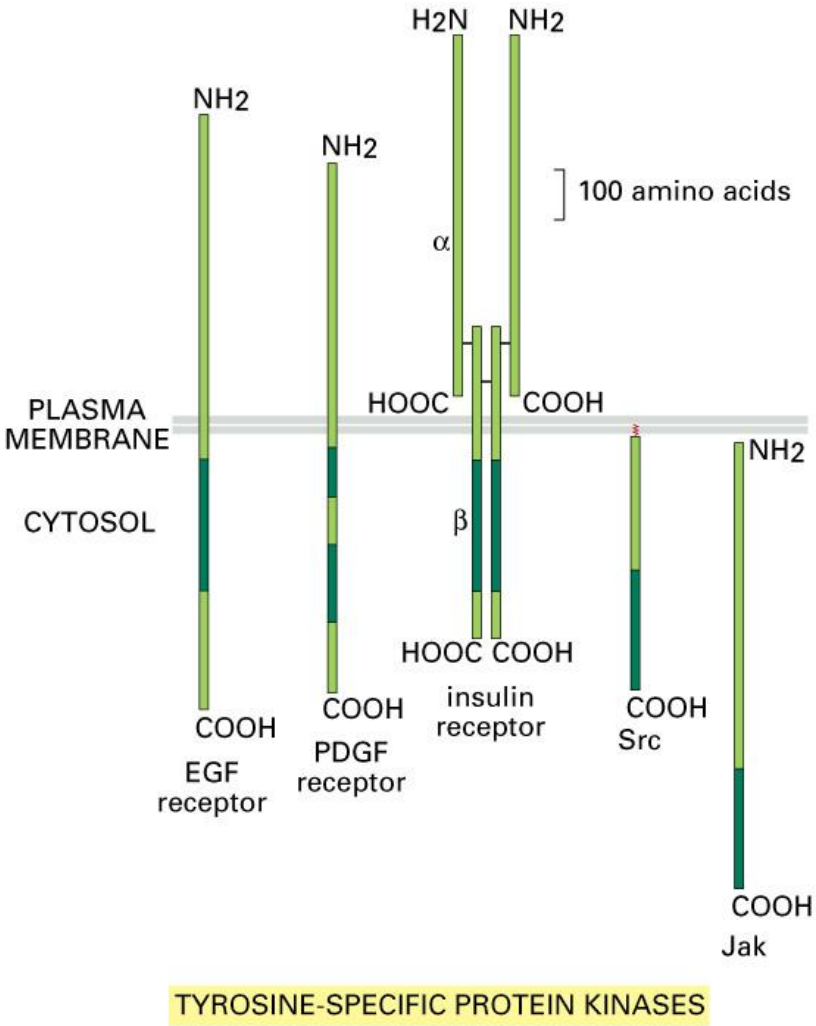
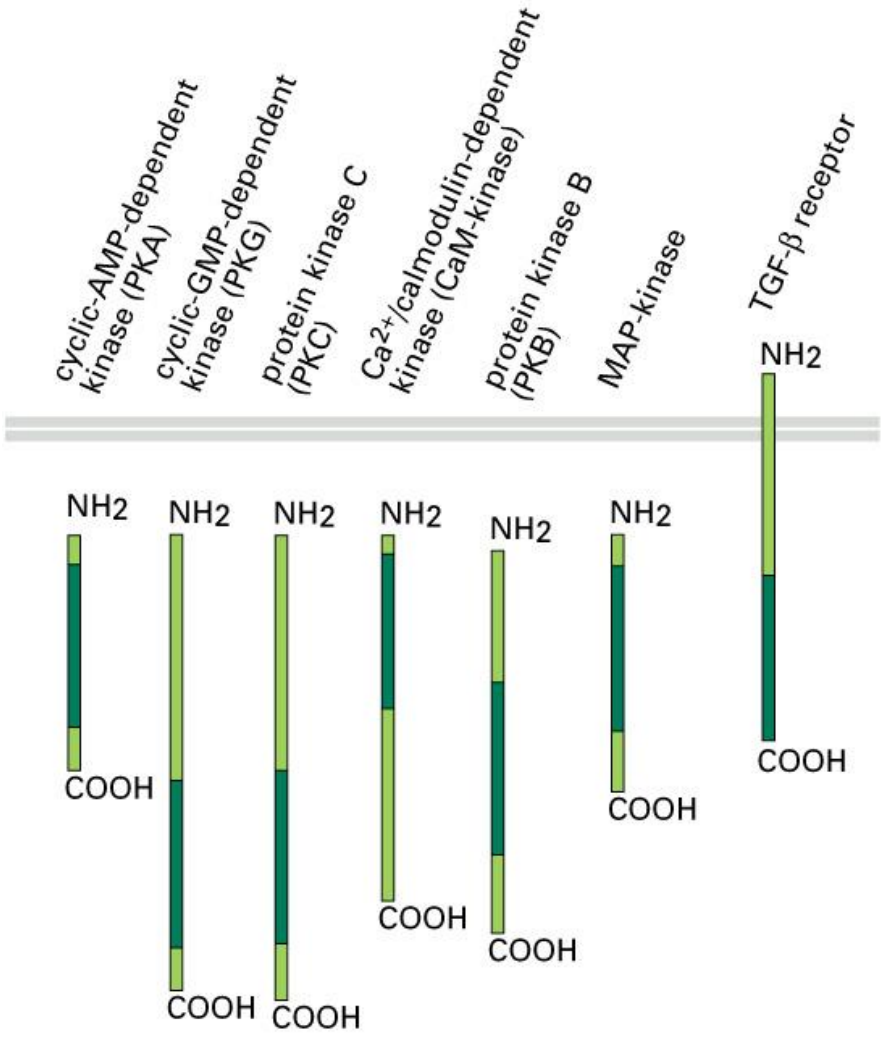


Some of the protein kinases



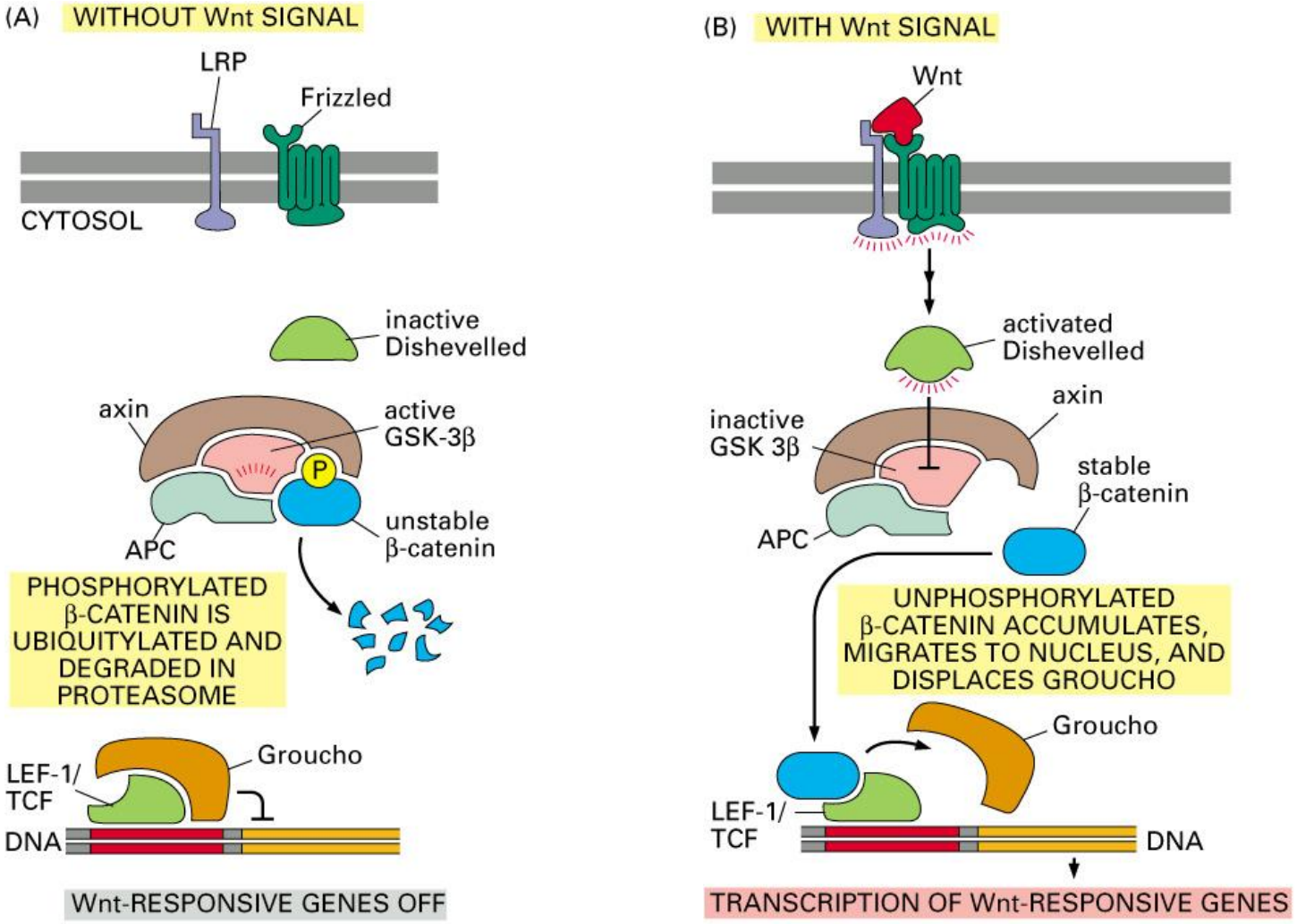
TYROSINE-SPECIFIC PROTEIN KINASES

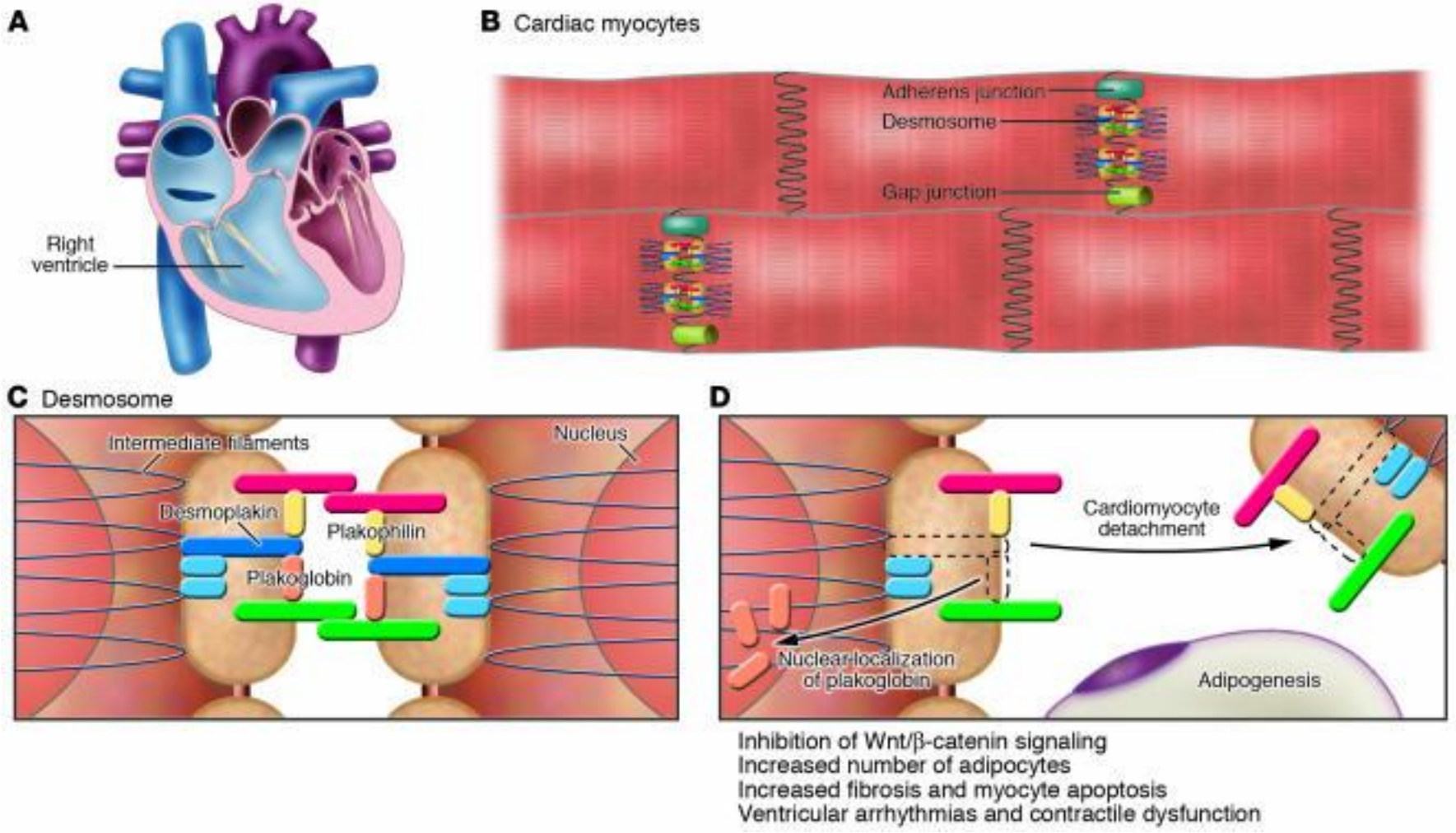


SERINE/THREONINE-SPECIFIC PROTEIN KINASES

Fig

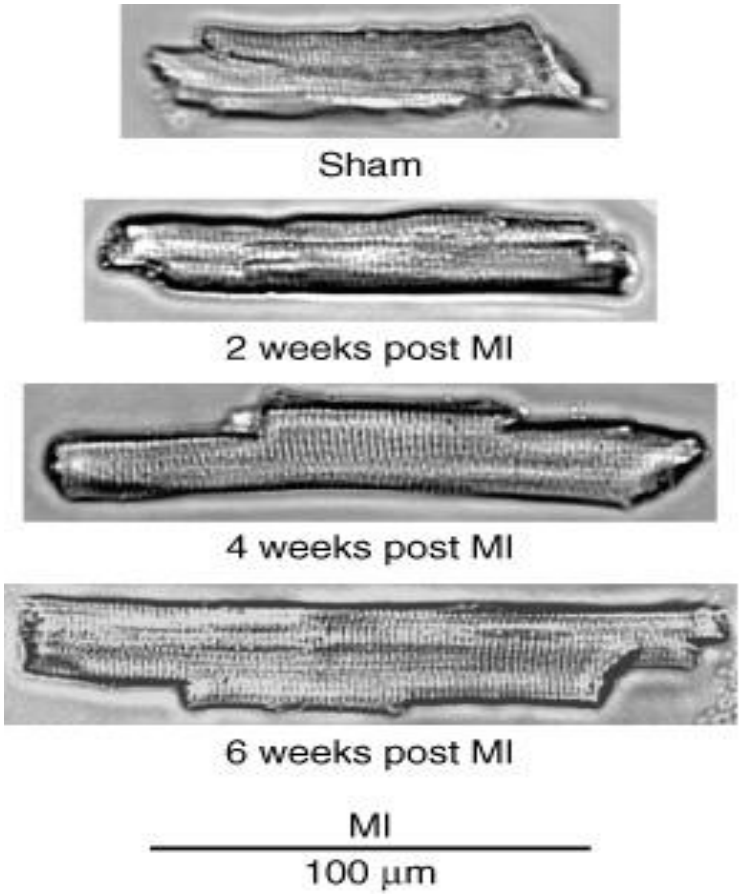
A model for the Wnt activation of the β-catenin signaling pathway

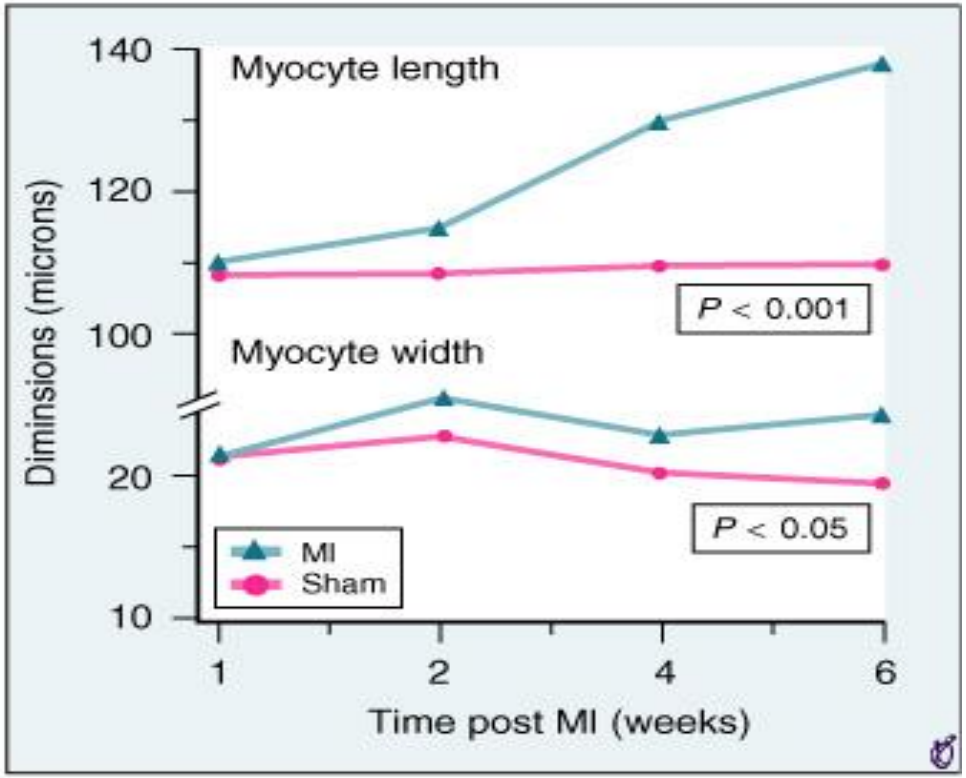




Cardiac-specific restriction of the desmosomal protein desmoplakin causes nuclear localization of plakoglobin and reduced Wnt/β-catenin signaling, recapitulating human ARVC. (**A**) ARVC predominantly affects the right ventricle of the heart. (**B**) The intercalated discs of cardiac myocytes are characterized by gap junctions, adherens junctions, and desmosomes. (**C**) Cell-cell adhesion is largely dependent on interaction of intracellular components of the desmosomal plaque such as desmoplakin and plakoglobin. (**D**) In this issue of the *JCI*, Garcia-Gras et al. (16) report that heterozygous cardiac desmoplakin-deficient mice show nuclear localization of plakoglobin and reduced Wnt/β-catenin signaling. This causes increased expression of adipogenic and fibrogenic genes in vitro, abnormal cardiac adipose tissue and fibrosis in vivo, and ventricular arrhythmias similar to human ARVC. Interactions between signaling defects and mechanical stresses are likely to be involved in the genesis of the final phenotype.

Verlauf einer Hypertrophie nach MI





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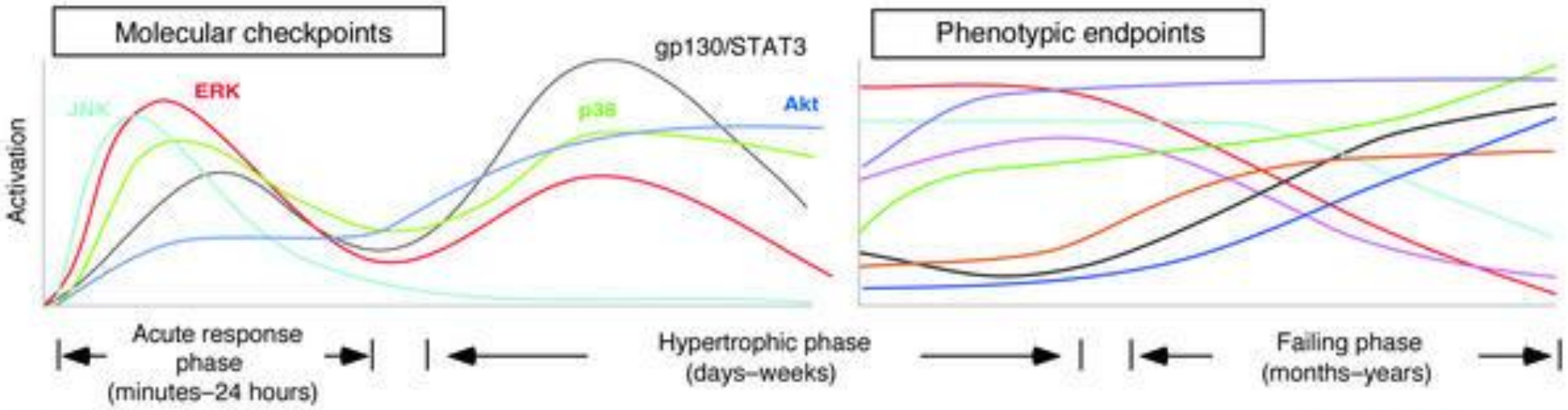

Gene expression profiles

(Acute phase)

Upregulation

c-fos
c-jun
junB
egr-1
nur77
BNP
SOCS3

(Hypertrophic-failing phase)

Upregulation

Secreted proteins
ANF, Lipocortin I, ET-1
HB-EGF, TGF-β1, BNP
Osteoblast-specific factor 2
Cytoskeletal proteins
αMHC, βMHC
MLC1a/v, MLC2a
MLC2v, Tropomyosin
Troponin C, Myomesin
Smooth muscle α–actin
Skeletal α–actin
α–cardiac actin
FHL1 (HCM), Sarcosin
Desmin, Gelsolin,
Extracellular matrix
Fibulin, Fibronectin
Laminin, Collagen
Others
Heat shock 70 kDa proteins 1, 6, 8
Quaking protein, CARP

Metabolism/translation
Ubiquitin, Pyruvate dehydrogenase α
NADH ubiquinone oxidoreductase
Creatin kinase, Myoglobin
Phosphorylase kinase catalytic subunit
Superoxide dismutase 2
Aldose reductase, EF-1a, EF-2, IF-4AII
28S, 60S ribosomal L3
Ion-channels/carriers
Na^+/Ca^{2+} exchanger, Kv1.4
Voltage-dependent anion channel-1
Signaling
Gsα, βARK, Adenylyl cyclase VII
A-kinase, C-kinase inhibitor-1, ILK
Rap1B, SOCS3, Id-1, GATA-4
SP1/3, PGD/D2 synthase

Downregulation

Cytoskeletal proteins
FHL1 (failing heart)
Nonsarcomeric MLC2
Ion-channels/carriers
L-type Ca^{2+} channel
SERCA2
Phospholambam
Kv4.2, 4.3
Kv1.5
KChIP2
Signaling
type-A like Ephrin receptor
Others
α1-Antichymotrypsin
αB-Crystallin
Plasminogen activator inhibitor-1
TIM17

Contractility
Chamber size
Wall thickness
Left ventricular end diastolic pressure
Left ventricular end systolic pressure
Arrhythmia (e.g., AF, VT, AVB)
Myocyte dropout Replacement fibrosis
Embryonic gene program