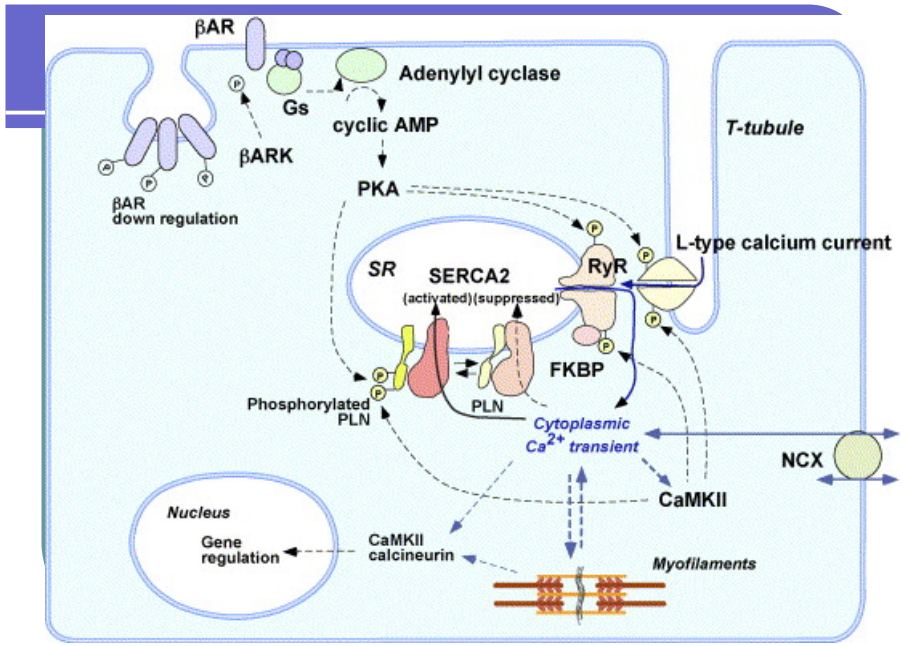
Remodelace srdce a cév za patologických stavů

7. 11. 2007



Cardiac cells

- *Cardiac myocytes* occupy approximately 75% of normal myocardial tissue volume, but they account for only 30–40% of cell numbers. The majority of the remaining cells are non-myocytes, predominantly fibroblasts. Other cell types, such as endothelial or vascular smooth muscle cells, represent comparatively small populations.
- *Fibroblasts* are found throughout the cardiac tissue, surrounding myocytes and bridging 'the voids' between myocardial tissue layers, so that, in essence, every cardiomyocyte is closely related to a fibroblast in normal cardiac tissue.
- Pathological states are frequently associated with *myocardial remodelling* involving fibrosis. This is observed in ischemic and rheumatic heart disease, inflammation, hypertrophy, and infarction. The growth in fibrous tissue content is based on the maintained proliferative potential of fibroblasts (largely absent in myocytes of the adult heart, and the synthesis of extra-cellular matrix (ECM) proteins, predominantly by fibroblasts.

Structural and functional characterisation of cardiac fibroblasts

- Cardiac fibroblasts form one of the largest cell populations, in terms of cell numbers, in the **heart.**
- They contribute to
- structural,
- biochemical,
- mechanical and
- electrical properties of the myocardium.

Fibroblasts

- Fibroblasts are traditionally defined as cells of mesenchymal origin that produce interstitial collagen (in contrast to myocytes that form collagen type IV as part of their basement membrane, fibroblasts also produce types I, III and VI).
- Fibroblasts are principally ***motile*** cells that contain actin (mainly α-smooth muscle actin) and myosin.
- Fibroblasts are ***pleiomorphic***, and their actin or myosin content and arrangement are affected by the environment, in particular mechanical parameters. An increased contractile filament content does not necessarily transform a fibroblast into a new cell type, but may merely represent a distinctive phenotype.

Origin of cardiac fibroblasts

The mesenchymal cells that form the cardiac fibroblast population are believed to be derived from two principal sources:

(1) the *pro-epicardial organ*, and

(2) the *epithelial–mesenchymal transformation* during the formation of cardiac valves.

- Little connective tissue is observed in the early embryonic heart. Most of the connective tissue is involved, at that stage, with the formation of the cardiac skeleton and the various valvular structures. The three-dimensional collagen network begins to form in late foetal development. It is largely laid down during neonatal growth, accompanied by rapid proliferation of fibroblasts and substantial deposition of collagen. Following neonatal development, fibroblast cell division returns to a very low level, unless stimulated by either physiological or pathological signals.

Origin of cardiac fibroblasts

Fibroblast content increases with normal development and aging. During early human development, myocyte and connective tissue cell numbers increase at a similar rate, from about 0.5×10^9 at 28 weeks of foetal development to $2–3\times10^9$ several weeks post partum. Thereafter, myocyte cell numbers remain stable, while the connective tissue cell count rises with cardiac weight to 7×10^9 at 2 months of age. This is mirrored by an increase in the volume fraction of connective tissue, which reaches about 5–6% in normal adult myocardium.

- A further progenitor population may lie ***in the intima of vascular walls*** These cells have the potential to form a variety of cells including fibroblasts, smooth muscle and endothelial cells.
- Fibroblasts are more than just collagen producing cells of the stroma. They have been termed “sentinel cells” that function as ***local immune modulators***. They may also contribute to cardiac ***electrophysiology***.

Collagen in heart

- Thus, fibroblasts form a majority cell population in the normal adult heart (up to two-thirds), which is largely interspersed in the collagen network.
- Net collagen deposition in adult hearts is normally very low. Aging is associated with increased cross-linking of collagen, contributing to tissue stiffening.
- In disease states, however, such as cardiac hypertrophy, heart failure, and infarction, collagen deposition is dramatically increased. The associated proliferation of fibrous tissue has been divided by Weber and colleagues into two categories:
- (1) *reparative fibrosis*, which occurs dispersed through the myocardium, and
- (2) *reactive fibrosis*, which occurs initially associated with capillaries, and then spreads to the myocardium.
- Fibroblasts are sensitive to circulating hormones which affect their proliferative response to pathological stimuli.
- It is conceivable that the proliferating, perivascular fibroblast population in the heart stems origin from bone marrow-derived circulating progenitors.

Structural and biochemical function of fibroblasts

- Fibroblasts are involved in the maintenance of myocardial tissue structure, including ECM homeostasis and production of factors involved in maintaining a balance between synthesis and degradation of connective tissue components, for example cytokines, growth factors and matrix metalloproteinases (MMPs).
- In cardiovascular diseases, fibroblasts play a central and dynamic role in the ***myocardial remodelling*** process, which includes hypertrophy of cardiomyocytes, migration and proliferation of fibroblasts, and changes in the extent and composition of the cardiac ECM.
- Excessive fibroblast proliferation and increase in ECM protein content (fibrosis) induce myocardial stiffening—an important pathophysiological facet of cardiac dysfunction.
- Fibrotic tissue remodelling is associated with increased expression of MMP and humoral factors, such as transforming growth factor TGF-β, angiotensin II, endothelin-1 and tumour necrosis factor-α.

Structural and biochemical function of fibroblasts

- MMP are not exclusively expressed by fibroblasts, but also other cardiac cells (like myocytes and endothelial cells) and by inflammatory cells. They are also involved in the regulation of cell growth and migration, cell survival/death and angiogenesis.
- Angiotensin II, TGF-β and tumour necrosis factor-α are involved in autocrine and paracrine regulation of myocyte hypertrophy, fibroblast proliferation and ECM protein turnover. Angiotensin II further stimulates collagen gene expression and collagen synthesis, and it reduces collagen degradation (by attenuating MMP activity in cardiac fibroblasts), while endothelin-1 induces hypertrophy in myocytes and stimulates collagen synthesis.
- Myocardial tissue remodelling may also be promoted by chronic adrenergic stimulation, which is an important feature of heart failure.
- Statins, normally prescribed for lowering cholesterol, have recently been shown to directly inhibit fibroblast proliferation, an effect that may contribute to the prevention of adverse cardiac remodelling.

Electrical signalling

- Fibroblasts can affect electrophysiology ***passively***, for example by acting as obstacles to the orderly spread of electrical excitation (e.g. fibroblasts, separating groups of muscle cells, may reduce regional electrical coupling, causing slow or discontinuous conduction). Interstitial fibrosis and collagen accumulation are furthermore an important source of local anisotropy in myocardial ischaemia and hypertrophy, which in turn enhances predisposition to cardiac arrhythmogenesis.
- The possibility that fibroblasts may ***actively*** contribute to cardiac electrophysiology has been considered only recently.
- Cardiac fibroblasts are electrically 'non-excitable' cells (i.e. they do not respond to an electrical stimulus with generation of an action potential), but they are efficient mechanoelectrical transducers. Fibroblasts respond to mechanical stimuli, such as imposed by the contractile activity of the surrounding myocardium, or by external stretch, with changes in their membrane potential. These mechanosensitive potentials are attributed to stretch-activated ion channels, permeable to Na+, K+ and Ca2+.

Electrical signalling

- The mechanisms that link changes in fibroblast electrophysiology to cardiomyocyte activity are only beginning to emerge. One hypothesis involves direct gap-junctional coupling of fibroblasts and myocytes.
- After myocardial infarction, right atrial fibroblasts show several electrical abnormalities, such as a negative shift of their resting membrane potential, an increase in membrane resistance, altered mechanically induced potentials, and enhanced sensitivity to mechanical stress. These altered electrical properties of fibroblasts could, if electrically coupled to myocytes, lead to changes in pacemaker activity. Furthermore, heterogeneous coupling of fibroblasts and myocytes in the infarct border zone would affect the spread of excitation in such areas and could contribute to the highly irregular and arrhythmogenic electrical properties of cardiac scar tissue.
- Thus, fibroblasts may affect electrical signalling in the heart passively and, if electrically coupled to cardiomyocytes, actively.

Left ventricular remodeling

- is a complicated process that occurs in the stressed **heart,** and is still not completely understood.
- Several members of the matricellular protein family are up-regulated after cardiac injury. Therefore, this group of proteins may have crucial functions in the **heart** coping with stress.

Matricellular proteins

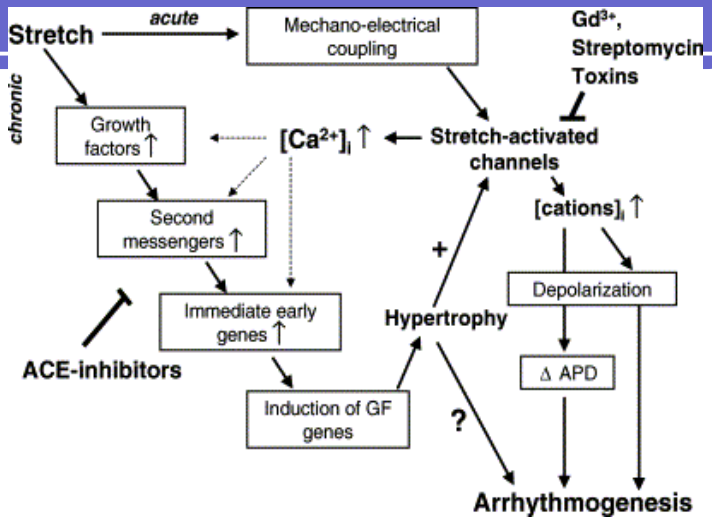
- are extracellular matrix proteins that modulate cell–matrix interactions and cell function, and do not seem to have a direct structural role. The family includes
- tenascin-C (TN-C),
- tenascin-X (TN-X),
- osteonectin,
- osteopontin,
- thrombospondin-1 (TSP1) and
- thrombospondin-2 (TSP2).

Matricellular proteins

- Expression of matricellular proteins is high during embryogenesis, but almost absent during normal postnatal life.
- Interestingly, it reappears in response to injury.

Chronic stress

- Chronic stress on the **heart** activates gene expression in cardiomyocytes and non-myocytes.
- The signal transduction involves atrial natriuretic peptides and growth factors that initiate **remodelling** processes leading to hypertrophy which in turn may contribute to the electrical instability of the **heart** by increasing the responsiveness of mechano-sensitive channels.



Schematic diagram the changes induced by acute and chronic stretch in the heart, that may lead to the genesis of arrhythmias

Fibrosis

- is a complex tissue disease whose predominant characteristic is the excessive deposition of extracellular matrix (ECM) components, especially collagens, the major fibrous proteins in ECM.
- Collagen deposition can take place in various organs, including lungs liver, kidney and skin.
- In most cases, fibrosis is a process involving different pathophysiological events such as the *attraction of blood-borne cells* (e.g., leukocytes, platelets, activated lymphocytes), the *alteration of microvascular cells* (interrupting nonthrombogenic, permeability-regulating, and cell-adhesive functions of the microcirculation), and the *activation of resident mesenchymal cells* (fibroblasts, endothelial cells, pericytes) leading to excessive collagen deposition.
- Thus, the net accumulation of collagen in tissue fibrosis is a result of an ***imbalance*** between the factors leading to enhanced production and deposition, or impaired degradation and removal of collagen. Contributing to the metabolic modulation are cytokines and growth factors.

Collagen I

- The *balance between production and degradation of type I collagen* plays a critical role in the development and maintenance of organ and tissue integrity. It also represents the most crucial element governing the process of tissue repair.
- The synthesis of type I collagen gene is highly regulated by different cytokines at the transcriptional level. Especially, ***transforming growth factor (TGF-β),*** a key player in the pathophysiology of tissue repair, enhances type I collagen gene expression.
- In contrast, tumor necrosis factor (TNF-α), whose matrix-**remodelling**_ function is opposite to that of TGF- β , reduces type I collagen gene expression.

Transcriptional regulation of type I collagen genes by TGF-β

- Transforming growth factor (TGF-β) is a key regulator of ECM assembly and remodeling. Its action is exerted through two complementary pathways, one that
- reduces matrix degradation and the other that
- stimulates matrix accumulation.
- In simplified terms, TGF-β inhibits the synthesis of extracellular proteinases while upregulating the production of their inhibitors and that of structural ECM components. The combined action of TGF-β on the genes implicated in the formation and degradation of the ECM is mostly exerted at the transcriptional level through well-defined intracellular pathways. Therefore, in the context of fibrotic diseases, it appears crucial to understand the molecular mechanisms that cause the transcriptional response of type I collagen genes to TGF-β
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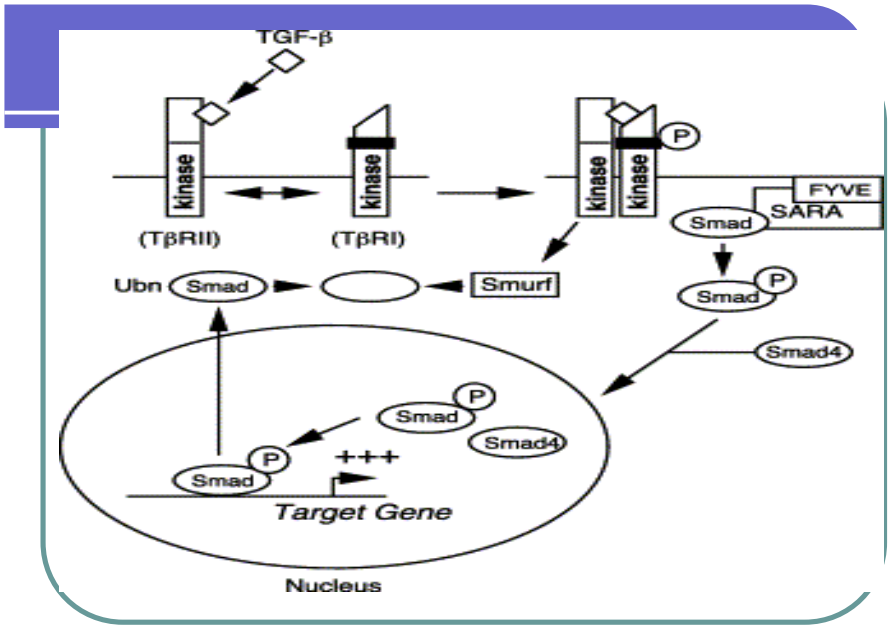
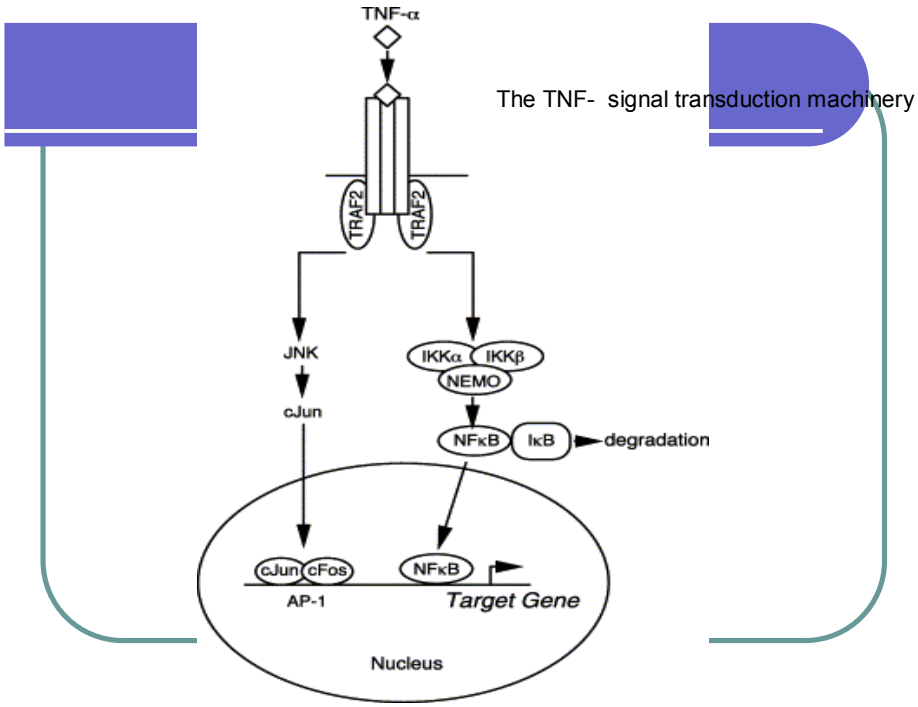


The TGF-β signal transduction machinery

Transcriptional regulation of type I collagen genes by TNF-α

- Tumor necrosis factor alpha (TNF-α) is released by activated macrophages.
- ECM degradation is the hallmark of these conditions and an important component in morphogenesis, organogenesis and tissue remodeling, as well as in wound healing and tissue repair.
- TNF-α reduces ECM deposition either by inducing the production of stromal collagenases or by inhibition of the synthesis of structural components such as the type I collagen, the major structural component of connective tissue.
- TNF-α also counteracts TGF- β stimulation of type I collagen gene expression.
- This finding reflects the functionally antagonistic nature of these cytokines and represent a useful paradigm to study the complex cellular signals that regulate ECM formation and remodeling.



The TNF- signal transduction machinery

Apoptosis in the heart

- During development, apoptosis contributes to the normal morphogenesis of the heart, as it contributes to the morphogenesis of other organs. Apoptotic cardiomyocyte death is known to occur during embryogenesis, while after birth apoptosis is assumed to be involved in the morphogenesis of the conduction system, including the sinus node, atrioventricular, AV node, and His bundle.

Ions during adaptation

- The heart adapts to mechanical overload by
- an increase in cell size and by
- changes in the expression and activity of a series of ion channels and ion transporters.
- This adaptation is, at least in the early stage, compensatory, maintaining contractile function despite increased loading. The changes at the cellular and ion channel level are often called *cellular and ion channel remodelling*.
- In the presence of maintained (over)load, further remodelling can eventually lead to heart failure, characterized by depression of systolic force development as well as diastolic dysfunction.
- Both in (compensatory) hypertrophy and in heart failure, remodelling processes also lead to an increased risk of arrhythmias and sudden death.

The atrial myocardium during atrial fibrillation. Structural remodelling.

- The atrial myocardium undergoes many changes during atrial fibrillation (*structural remodelling*) which is generally characterised by *cardiomyocyte volume increase, loss of sarcomeres, accumulation of glycogen and mitochondrial abnormalities .*
- In patients with AF, both cardiomyocyte dedifferentiation and degeneration occur.
- The adaptive response occurs apart from necrosis and apoptosis or programmed cell death and might actually be considered as programmed cell survival, as it appears to render the cardiomyocytes able to survive stress conditions including ischemia and stretch.

Cardiac hypertrophy

- is characterised by
- an increase in cardiomyocyte size,
- enhanced protein synthesis and
- a higher sarcomere organization,

which are all preceded and accompanied by a ***reactivation of several foetal genes***.

Cardiac hypertrophy

It has been suggested that the ***structural remodelling*** serves as an adaptive response to sustain normal wall tension and cardiac output. Specifically in athletes, it is accepted that this ***exercise-induced*** hypertrophic response is compensatory.

However, ***prolonged hypertrophy*** in response to ***pathological situations*** inevitably leads to ***maladaptive changes***, increasing the risk for arrhythmias or the progression to heart failure.

Cardiac hypertrophy

- Recently, it has been proposed that there is a clear distinction between ***compensatory*** and ***maladaptive*** hypertrophy, of which only the latter leads to heart failure.
- In ***exercise-induced hypertrophy***, the myocardium usually does not exceed a modest increase in ventricular wall thickness and fibrosis is absent.
- At present it is not clear whether ***pathologic-maladaptive hypertrophy*** is first preceded by compensatory hypertrophy and becomes maladaptive when it is prolonged or whether it is entirely maladaptive from the offset.
- Insight into the underlying molecular mechanisms of hypertrophic remodelling may clarify which changes in cellular signalling molecules lead to maladaptive hypertrophy.

Hypertrophic remodelling

- A characteristic consequence of hypertrophic remodelling as a result of pathological stress is the increased risk for fatal ventricular arrhythmias. Alterations in action potential (AP) duration, a disturbed Ca2+ metabolism, and ventricular re-entry circuits arising from regions of slow, inhomogeneous conduction, and conduction block may contribute to arrhythmogenesis.

Hypertrophic remodelling

- The observed alterations in cell-to-cell conduction of electrical impulses may be due to changes in the expression pattern and composition of the gap junctions. Gap junctions are mainly located in the intercalated discs of cardiomyocytes and consist of multiple gap junction channels.
- A ***gap junction channel*** is built of gap junction proteins ***(connexins***); six connexins interact to form a connexon (hemichannel) on one cell surface, which aligns head-to-head with a connexon on the apposing cell surface together forming an intercellular channel.

Hypertrophic remodelling

- In cardiomyocytes, the products of three connexin genes, connexin43 (***Cx43***), -40 (***Cx40***), and -45 (***Cx45***), are expressed.
- The predominant isoform in the ventricles is Cx43, which is expressed at very high levels in all working myocytes and, depending on the species, in the whole (human) or distal (mouse and rat) part of the conduction system.
- Both Cx40 and Cx45 are present throughout the ventricular conduction system.
- However, for Cx45 very low trace amounts have also been detected in focal parts of the ventricular wall.

Hypertrophic remodelling

- A derangement in the intercellular electrical coupling and expression and distribution of connexins may have profound effects on cardiac electrophysiology and arrhythmogenesis.
- Disruption of the side to side cell connections in hypertrophy by interstitial fibrosis, for instance, has been shown to impair cellular impulse propagation.

Hypertrophic remodelling

- Alterations in the amount and distribution of gap junction channels have been frequently correlated with cardiac disease.
- During the initial phase of hypertrophy, connexins are up regulated and that they become down regulated once the hypertrophy becomes prolonged and turns into heart failure.

Hypertrophic remodelling-atria

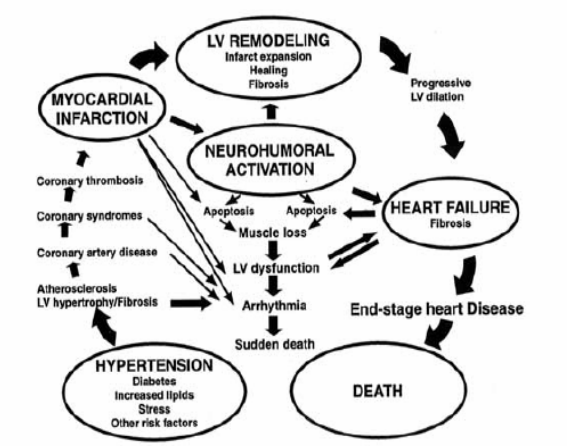
- The reduction of sarcomeric proteins is likely to affect the contractile properties of the atrium. Altered distribution and expression of channel proteins probably interferes with ion handling and excitation–contraction coupling. Likewise, alterations in gap junctions will influence the characteristics of atrial conduction. Calcium overload and stretch appear to be important regulating mechanisms of structural remodelling.

Ions during adapation

- Changes in intracellular Na+, [Na+]i, have not been extensively studied, although they may have important effects on contractile function through modulation of the Na/Ca exchanger.
- In heart failure, e.g. an upregulation of the Na/Ca exchanger is generally considered as a mechanism to compensate for the slowed uptake of Ca2+ from the cytoplasm caused by a defective SERCA2a pump function. This may lead to a loss of cellular Ca2+, but in heart failure, as well as in all other instances of cellular remodelling, changes in [Na+]i will determine the net Ca2+ flux.

Cardiac _remodelling after MI

- Recovery from myocardial infarction is associated with a series of alterations in _**heart**_ structure and function, collectively known as cardiac **remodelling,**_ which play a major role in the subsequent development of **heart**_ failure.
- Early _**remodelling**_ involves infarct scar formation in the ischaemic zone
- ventricular **remodelling** affects mainly the viable non-infarcted myocardium with especially profound alterations in the extracellular matrix.
- There is growing evidence for a role of oxidative stress and redox signalling in the processes underlying cardiac **remodelling.**
- Reactive oxygen species are a group of highly reactive molecules which have the potential to modulate several biological processes as well as cause tissue damage and dysfunction. Their effects can be beneficial or deleterious, depending on the concentrations produced, the site of production, and the overall redox status of the cell. Reactive oxygen species can be generated by all cardiovascular cell types. Under pathophysiological conditions, major enzymatic sources appear to be mitochondria, xanthine oxidase and the non-phagocytic NADPH oxidases.



Remodeling of vascular wall in pathophysiological states

Vascular remodelling

- is both a physiological and pathological process in vessel wall dynamics.
- compensatory enlargement of an artery occurs as the atherosclerotic plaque within the vessel enlarges.
- only when the ability of the vessel to remodel is exceeded does the atherosclerotic plaque narrow the lumen.
- a reduction in blood flow through a vessel is accompanied by constrictive remodelling of that vessel.

Vacular remodelling

- The mechanisms that contribute to remodelling are unknown. Indeed, it is still not clear whether remodelling
- represents primarily a medial or adventitial response to injury, or
- a combination of both.
- In remodelling seen in physiological states, such as flow reduction in arterial circulations after birth, major changes in vessel calibre can be achieved by coordinated cell proliferation/cell death of the arterial media. Such coordinated processes can effectively shrink or enlarge the arterial media, resulting in negative or positive remodelling, or can even cause vessel occlusion.

Vascular remodelling

- Remodelling is a gradual process, with a greater contribution to late loss of lumen at later time points after intervention.
- Remodelling may be either inward (negative/constrictive remodelling) or outward (positive/expansive remodelling). Thus, restenosis may be caused by ***negative remodelling*** of a dilated artery, with little neointima formation.
- In contrast, ***positive remodelling*** of a dilated vessel may accommodate large amounts of neointimal tissue without the vessel becoming stenotic.

Vascular remodelling

- In contrast to neointima formation, remodelling can be defined as a ***relative change in vessel size without necessitating an overall change in tissue volume.*** Although this is seen in the dynamic changes accompanying vasoconstriction or vasodilatation, remodelling describes gradual changes in resting vessel calibre over days to months.
- In early atherosclerosis, there is dilatation of the affected vessel as a compensatory mechanism to the increasing intima. This initial dilatation may be analogous to remodelling seen after physiological changes in blood flow. However, when atherosclerosis becomes severe, the lumen size appears to be reset to an inappropriate calibre.
- Therefore, in a real sense, ***the goal of angioplasty is to prevent the vessel from healing and restoring itself to the inappropriate calibre after dilatation.*** Non-atherosclerotic vessels can remodel sufficiently to accommodate extensive amounts of intima. Thus, we might achieve success, despite intimal hyperplasia, if the vessel were somehow able ***to restore itself to a normal calibre*** by remodelling.

Vascular remodelling

- In addition to changes in the vessel media, a major reaction to arterial injury occurs in the vessel adventitia.
- The adventitia shows the highest cell proliferation rates of any layer after injury, with differentiation of adventitial fibroblasts to myofibroblasts, and accumulation of neoadventitia being the earliest change after injury to otherwise normal porcine arteries.
- Adventitial myofibroblasts are capable of synthesising collagen, and similar to VSMCs, may be capable of contracting collagen gels or networks. This would result in vessel shrinkage by contraction of adventitial scar tissue, effectively constricting the media.
- Indeed, dense caps of collagen fibres are present in the human restenosis lesions.

Vascular remodelling

- Remodelling may also be caused by changes in extracellular matrix properties.
- Angioplasty causes acute changes in extracellular matrix synthesis and degradation, resulting in **increased collagen synthesis** and ***reduced matrix metalloproteinase (MMP) activity*** and, thus, in reduced matrix degradation. The VSMCs seen in restenosis sites show a 'synthetic' phenotype, as demonstrated by an increased volume of organelles within their cytoplasm, compared with primary plaque VSMCs, confirming their increased synthetic capacity.
- Importantly, neointimal collagen density is higher in arteries with negative remodelling than in those with positive remodelling in some animal models, suggesting that increased collagen synthesis directly induces restenosis by constrictive remodelling of the vessel.

Vascular remodelling

- MMP activity is reduced and collagen content increased in human restenosis sites, compared with primary plaques or normal vessels.
- In contrast, MMP inhibition can inhibit restenosis in porcine models by inhibiting negative remodelling, suggesting that MMP activity may be required for medial VSMC migration for remodelling to occur.
- Thus, matrix changes may be as important as changes in cell number in remodelling.

Vascular apoptosis

- Apoptosis (programmed cell death) of vascular smooth muscle cells (VSMCs) has recently been identified as an important process in a variety of human vascular diseases, including atherosclerosis, arterial injury, and restenosis after angioplasty.
- VSMC apoptosis is regulated by
- interactions between the local cell–cell and cytokine environment within the arterial wall,
- the expression of pro- and anti-apoptotic proteins by the cell, including death receptors, proto-oncogenes and tumour suppressor genes.

Mechanisms of restenosis/stent stenosis

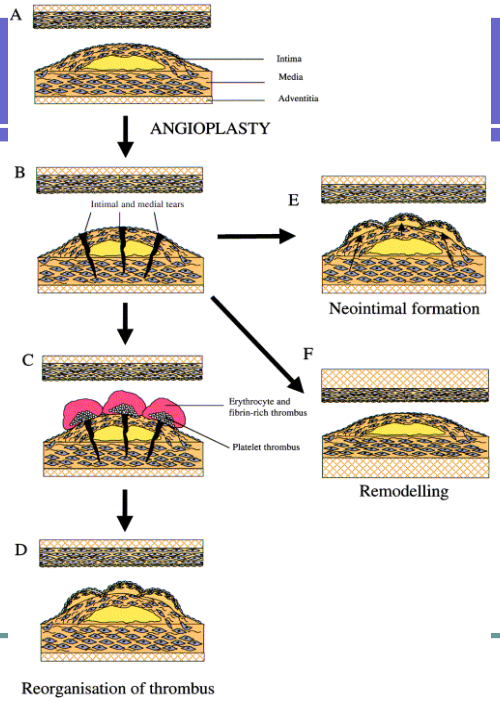
- Overdistension of the diseased vessel by either angioplasty or stent insertion causes endothelial disruption, fracture of the internal elastic lamina, and dissection of the media, often extending into the adventitia.
- Vessel injury also causes adventitial damage.
- Lumen enlargement is due to a combination of *plaque reduction* (compression/embolisation), *axial plaque redistribution* within the lesion (towards the proximal and distal vessel segments outside the stent or angioplasty balloon), *plaque extrusion*, and *vessel expansion*.
- Both angioplasty and stenting cause some loss in overall plaque volume, possibly by micro-embolisation or compression.

Mechanisms of restenosis

- Histologically, arteries that have had successful PTCA (a PTCA site lumen of ≥ 50% of the reference lumen) demonstrate a larger acute lumen, smaller plaque size (normalised to the internal elastic lamina area), and thinner adventitia compared with PTCA failures.

Mechanisms of restenosis/stent stenosis

- Restenosis is the end product of a combination of biological processes, each of which contributes to the final luminal narrowing.
- Although the mechanisms producing restenosis after angioplasty or stenting are different in the proportion of each mechanism that contributes to the final stenosis, the overall mechanisms are similar, and will be dealt with together.



Mechanisms of restenosis/angioplasty

- Arterial injury following coronary intervention induces a number of changes in the vessel wall that would be predicted to promote VSMC proliferation and/or migration into the injury site. Angioplasty induces
- (1) mechanical stretching of the vessel, with rupture of the internal elastic lamina and dissection of the media;
- (2) endothelial denudation, with exposure to circulating mitogens, such as angiotensin II and plasmin; and
- (3) release of mitogens and cytokines from platelets, endothelial cells, VSMCs, and inflammatory cells. VSMCs in the adult artery are normally in the quiescent (G0) phase of the cell cycle.

Mechanisms of restenosis/stent stenosis

- The immediate effect of intervention on the vessel wall may both determine the initial success of the procedure and contribute to restenosis.
- Thus, post-stent plaque burden outside the stent is a good predictor of neointimal accumulation.
- Neointimal thickness usually correlates with the extent of initial injury.

Mechanisms of restenosis/stent stenosis

- In contrast to angioplasty, restenosis after stenting is due mostly to ***neointimal formation***.
- Stenting is associated with an increase in neointimal formation up to 3 months after the procedure, with little change to 6 months. Interestingly, there is gradual reduction in neointima between 6 months and 3 years, suggesting that the neointima itself can remodel over time. Although neointima formation causes in-stent restenosis, again the role of cell proliferation within the neointima remains controversial. Although overall neointima formation after stenting is associated with medial disruption (i.e., extent of injury), cell proliferation indices do not show any relationship to the time of injury. In contrast, most of the proliferating cells appear to be located deep, adjacent to stent struts, apparently as a reaction to the presence of the stent.
- These appearances suggest that VSMC proliferation occurs as a chronic low-grade process after stenting, with the continued presence of the stent acting as a stimulus for cell proliferation. Small amounts of cell proliferation, together with matrix synthesis, therefore, may be sufficient to cause neointimal accumulation.