New concepts In Vascular Calcification

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VC is now considered as an active and finely regulated process similar to osteogenesis that involves cell-mediated processes and complex interaction between the inhibitor and promoter factors of the calcification process.

Biomedicines 2021, 9, 404

VC already develops in the early stages of CKD (25% in stage 3 and 35% in stage 4) and is present in over 50% of patients at the time of starting dialysis ; this also occurs in children with CKD.

Kidney International (2017) 91, 808–817

Patients on dialysis experience, on an average, a 15% annual increase in coronary calcification, likely a significant contributor to cardiovascular death.

Seminars in Dialysis. 2019;00:1–9.

The prominence of VC in CKD can be attributed mainly to the combination of CKD traditional risk factors and the underlying uremic-specific mechanisms that induce the cardiovascular condition.

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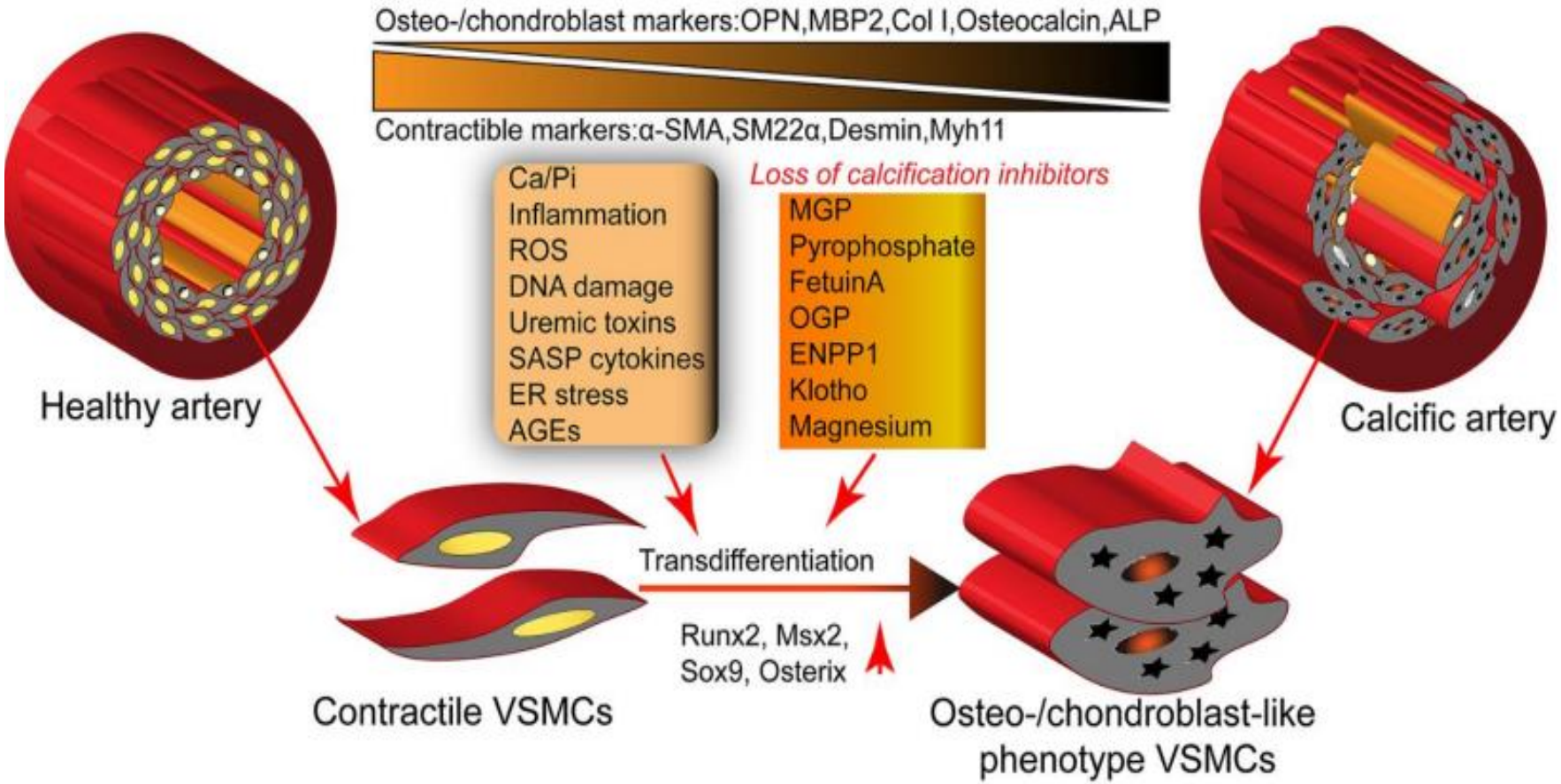

Osteo-/chondroblast markers:OPN,MBP2,Col I,Osteocalcin,ALP
Contractible markers:α-SMA,SM22α,Desmin,Myh11
Ca/Pi
Inflammation
ROS
DNA damage
Uremic toxins
SASP cytokines
ER stress
AGEs
Loss of calcification inhibitors
MGP
Pyrophosphate
FetuinA
OGP
ENPP1
Klotho
Magnesium
Healthy artery
Calcific artery
Transdifferentiation
Runx2, Msx2,
Sox9, Osterix
Contractile VSMCs
Osteo-/chondroblast-like
phenotype VSMCs

Vascular Smooth Muscle Cells (VSMCs)

As we already know, VC is an actively driven process that is regulated by VSMCs.

However, unlike other muscle cells, VSMCs do not terminally differentiate and exhibit phenotypic plasticity .

This allows them to vary their phenotypic expression based on environmental contexts, such as the various

insults found in CKD. Initially, it was thought that once the initial insult was resolved, the VSMCs returned to their original contractile phenotype; however, recent findings suggest that they can continue to express a spectrum of phenotypes , including osteochondrogenic, adipocytic, and foam cell deposition.

CKD is a chronic inflammatory state, and the accumulation of reactive oxygen species and inflammatory cytokines in the vasculature can precipitate RUNX2 and BMP-2 expression, which are known to stimulate osteocytic VSMC expression in the intima and media leading to VC.

They are normally balanced out by anti-calcification markers such as MGP, a BMP-2 inhibitor expressed in VSMCs, which are specifically known to be inhibited in CKD.

Calcium and phosphate both stimulate an osteochondrogenic phenotypic change in VSMCs individually and synergistically.

Phosphate

- The potential mechanisms by which P may cause VC are :

- Stimulation of VSMC transformation to an osteoblastic phenotype,
- Stimulation of VSMC extracellular matrix calcification,
- Promotion of VSMC apoptosis,
- And inhibition of vessel wall macrophage differentiation to osteoclast-like cells.
- Mineral cellular phosphate transport is mediated by sodium-dependent phosphate cotransporters PiT-1 and PiT-2 in VSMCs .Knockdown of PiT-1 has also been shown to decrease osteogenic marker expression such as RUNX2 in VSMCs and decrease calcification.

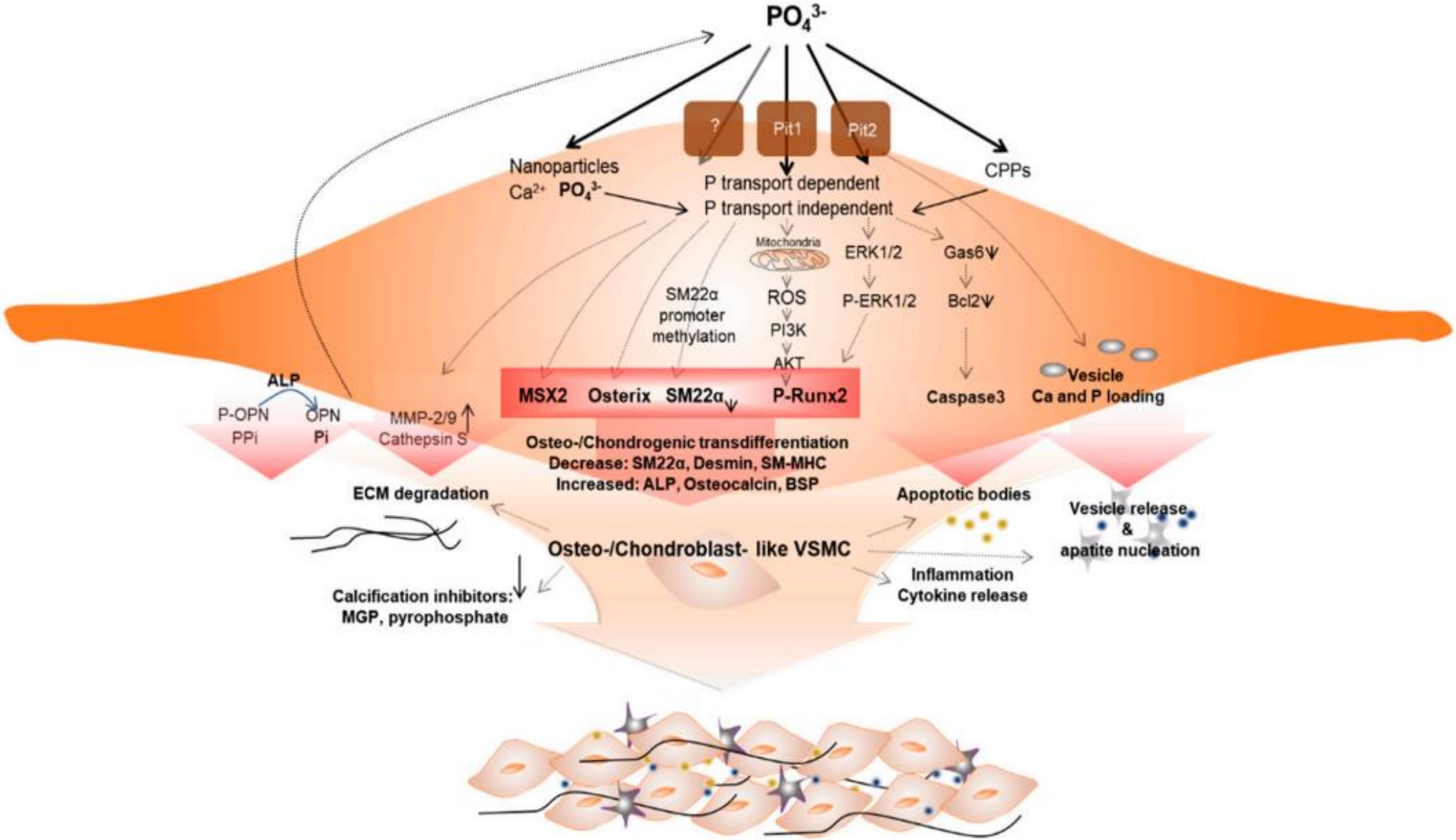
Calcium

Calcium is a key signaling mediator for VSMCs at physiologic levels .Though the exact mechanism of the effect of hypercalcemia on VSMCs is unknown, calcium induces oxidative stress and can directly deposit in the vasculature. Extracellular calcium deposition can also decrease anti-calcification markers such as MGP, leading to increased calcium deposition. VSMCs express a calcium receptor (CaR), which regulates vascular tone. In vitro, calcified tissue had downregulated expression of this receptor, and complete removal in vitro from VSMCs significantly increased VC.

CPPs

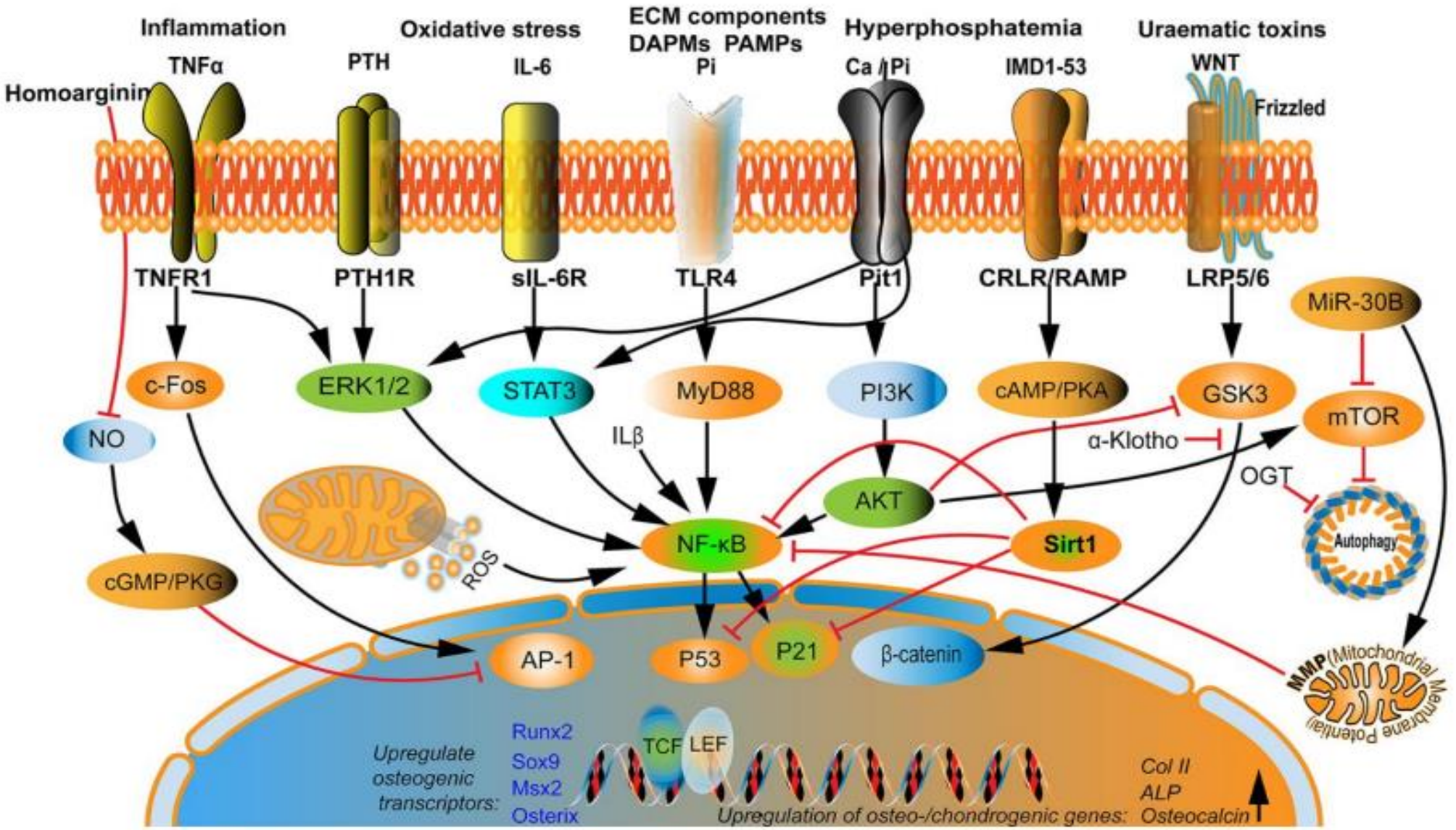
- Serum proteins such as fetuin-A and albumin can chelate nascent calcium-phosphate complexes in circulation, preventing rapid mineral growth. However, as CKD progresses, the resultant calciprotein particles that form from the serum chelation can induce inflammation and promineralization responses in vascular tissues.
- The formation of so called primary calciprotein particles (CPPs) prevents the precipitation of supersaturated calcium and phosphate. These CPPs mainly consist of non-crystalline calciumand phosphate, bound to fetuin-A and other proteins, and are part of the mineral buffering system inherent inblood .Spontaneous rearrangements within these primary CPPs lead to formation of secondary CPPs, which are larger and contain crystalline hydroxyapatite.The half-maximal transformation time from primary to secondary CPPs is called T50 and reflects the capacity of serum to resist crystallization of calcium and phosphate .Importantly, T50 is dependent on various other calcification-related factors such as magnesium, phosphate,calcium, bicarbonate, fetuin-A or albumin. Zawada et al. BMC Nephrology (2023) 24:35
- Novel techniques measuring the maturation of calciprotein particles in patient serum have demonstrated the potential to predict valvular and vascular disease progression. Circulation Research. 2023;132:993–1012

VMSC Calcification



Int. J. Mol. Sci. 2020, 21, 2685

Multifactorial signaling is involved in VSMC osteo/chondrogenic trans differentiation regulation



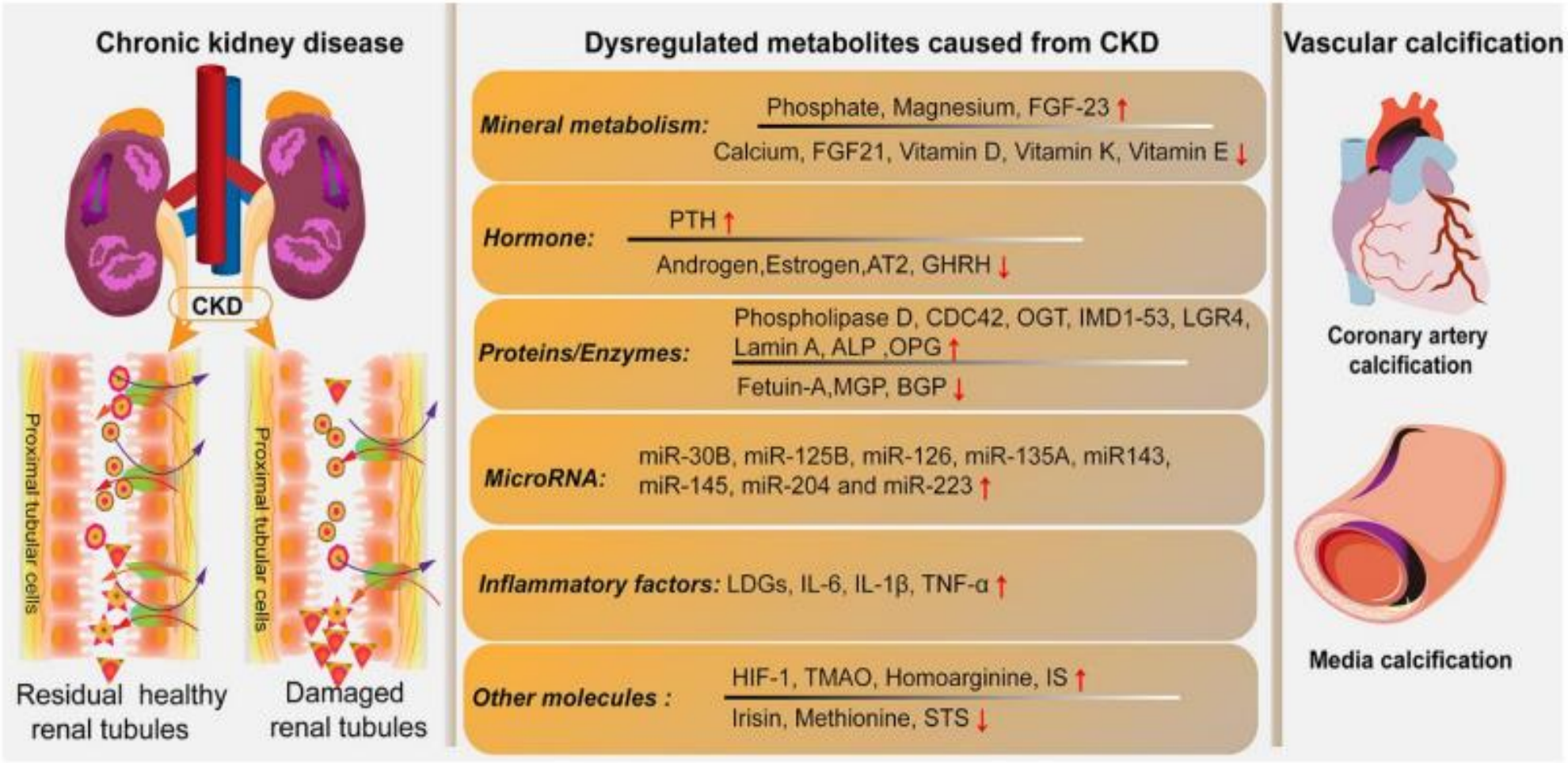
Aging and Disease • Volume 13, Number 3, June 2022

Molecules involved in VC process

Classification	Molecules	Targets	Effects	Involved tissues/cells	Comments	Ref.
Mineral metabolism	Calcium	Pit-1	VC exacerbation	Kidneys, vessels, bones, and intestinal tract	Induces the expression of Pit-1	[43]
	Phosphate	TLR4	VC exacerbation	Kidneys, vessels, bones, and intestinal tract	Activates the TLR4/NF-κB signaling pathway	[32, 113]
	IGF2	Klotho	VC suppression	Kidneys, vessels, and bones	Reduces inflammation and oxidative stress and affects klotho expression	[234, 235]
Hormones	PTH	PTH1R	VC exacerbation	Kidney, vessels, bone, and parathyroid glands	Activates the ERK1/2 and NF-κB signaling pathways	[42]
	AT2	RAS	VC alleviation	Kidneys, vessels, and bones	Stimulates PPAR-γ through klotho expression upregulation	[117, 236]
	Estrogen	HIF-1	VC alleviation	Vessels and bones	Affects BMP-2-p-Smad1/5/8 signaling	[237]
	Growth hormone-releasing hormone	NF-κB, PKA	VC alleviation	Hypothalamus, pituitary, vessels, and bones	Cross talking between the RANKL-NFκB-Runx2 and GHRHR-cAMP-PKA signaling pathways	[238]
Inflammation	IL-6	p53	VC exacerbation	VSMCs	Activates the IL-6/sIL-6R/STAT3/p53/p21 pathway	[25, 239, 240]
	IL-1β	p53	VC exacerbation	VSMCs	Activates the NF-κB/p53/p21 pathway	[144]
	TNF-α	AP-1	VC exacerbation	VSMCs	Activates the TNF- α-AP-1/c-FOS signaling axis	[26]
MicroRNAs	miR-204	DNMT3a	VC alleviation	VSMCs	Affects the MiR-204/DNMT3a regulatory circuit	[192]

	miR-30B	SOX9	VC alleviation	VSMCs	Activates the MMP and autophagy involved in the mTOR signaling pathway	[191]
	miR-135A	KLF-4, STAT3	VC alleviation	VSMCs	Affects the KLF-4/STAT3 pathway	[241]
Enzymes/Small molecules	Phospholipase D	PKC	VC exacerbation	VSMCs	Affects PKC-independent manner activation	[242]
	CDC42	AKT	VC exacerbation	VSMCs	Activates the AKT signaling pathway	[243]
	OGT	Autophagy complex	VC exacerbation	VSMCs	Inhibits autophagy through YAP upregulation	[114]
	IMD1-53	Sirt1 and klotho	VC alleviation	VSMCs	Upregulates Sirt1 by activating the PI3K/Akt and cAMP/PKA signaling pathways and increases α-klotho via the CRLR/RAMP3 complex	[153, 154]
	LGR4	NF-κB	VC exacerbation	Kidneys, vessels, bones, and parathyroid gland	Activates the PTH/PKA signaling pathway	[23]
	MGP	Vitamin K	VC alleviation	Kidneys, vessels, and bones	Activated by vitamin K dependent γ-carboxylation	[45, 163, 244]
	Lamin A	RUNX2	VC exacerbation	VSMCs	Interacts with RUNX2 and facilitates their nuclear localization	[245]
Amino-acid metabolites	Homoarginine	NO	VC exacerbation	Kidney, vessels, and bones	Impairs NO production and triggers osteo-/chondrogenic signaling	[78]
	IS	Klotho, TRPM7	VC exacerbation	VSMCs	Mediates klotho gene expression or downregulates TRPM7, and induces cross-talking between OATP2B1 and Dll4-Notch axes	[79, 122, 123, 129]
	TMAO	NF-κB	VC exacerbation	VSMCs	Activates NLRP3 inflammation and NF-κB signaling	[77]

Dysregulated metabolites aggravate VC processes in patients with progressive CKD



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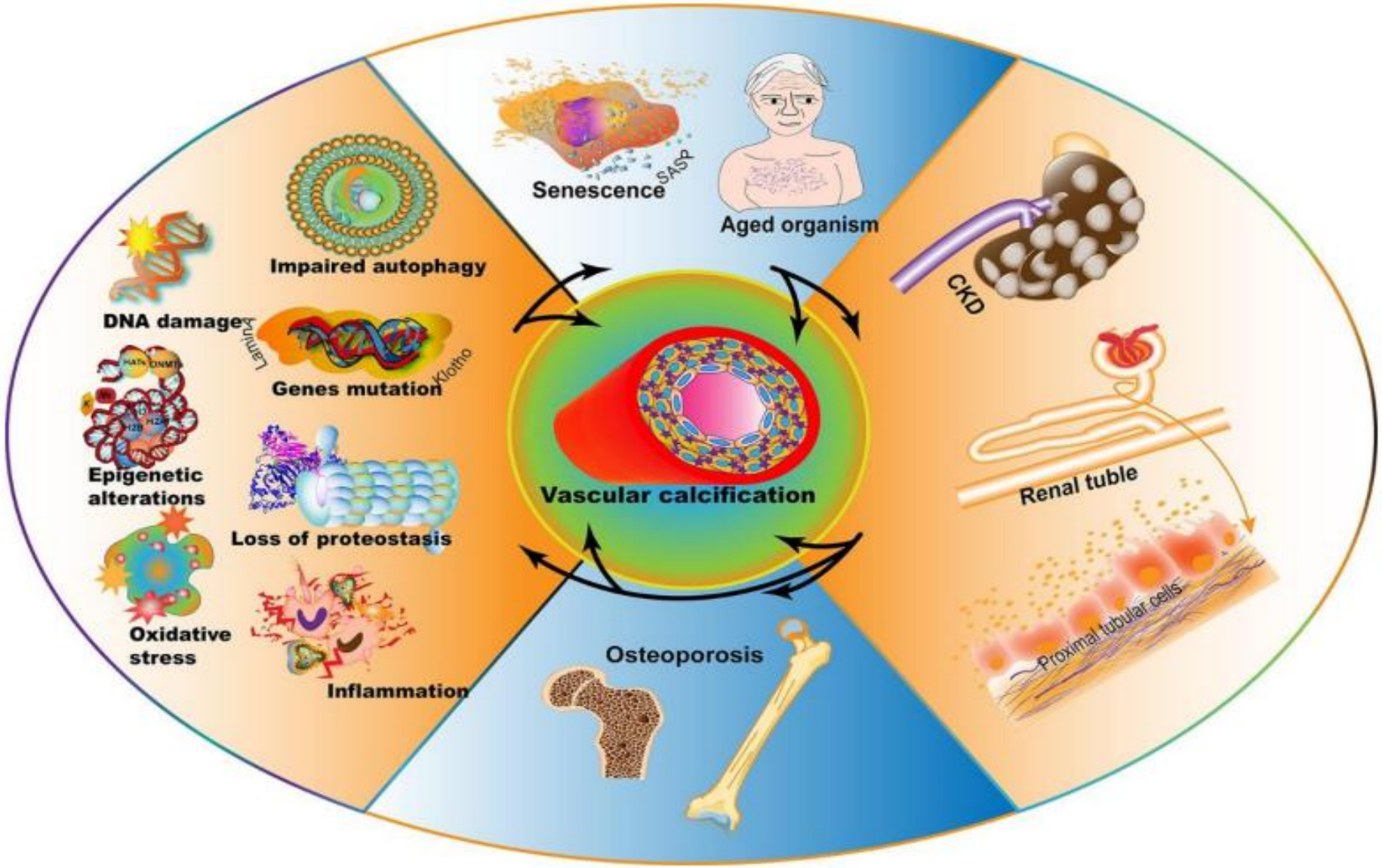
Aging as a vicious accelerator exacerbates VC progression in patients with CKD



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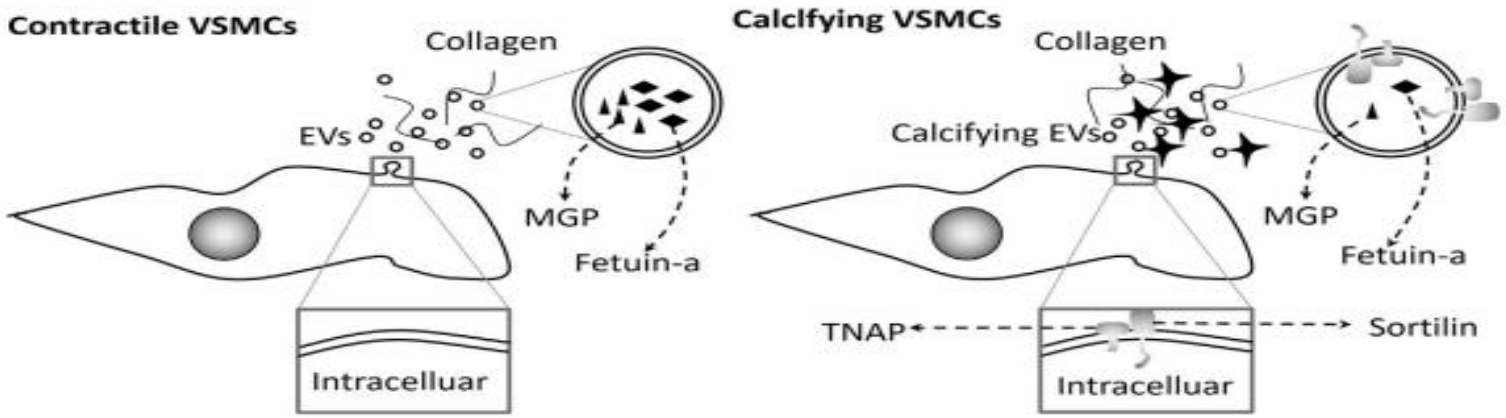
VC in CKD is associated with increased deposition of VSCM-associated extracellular

vesicles, which include matrix vesicles and apoptotic bodies [41–43]. Normally, contractileVSMCs release matrix vesicles to maintain homeostasis; however, in pathologic environments such as CKD (hyperphosphatemia, oxidative stress, inflammation), they can transform into a synthetic phenotype and increase secretion of matrix vesicles [44]. These transform target cells into calcified states, which then aggregate to form microcalcifications.They also decrease the expression of calcification inhibitors such as MGP and fetuin-A, like the osteogenic phenotypes. Biomedicines 2021, 9, 404



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Review

Extracellular vesicles in vascular calcification

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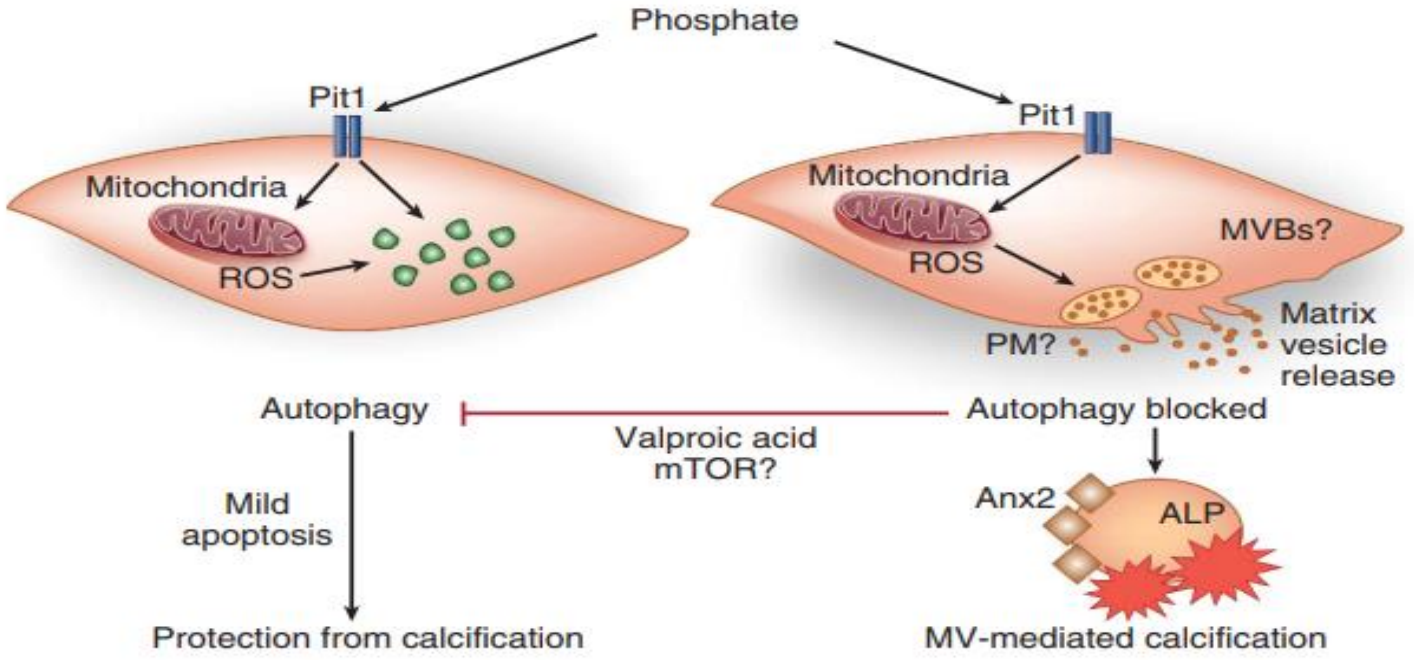
Along with phenotypic changes, VSMC apoptosis and autophagy play a significantrole in VC in CKD. Due to increased oxidative and uremic stress in CKD, there is a significant increase in VSMC apoptosis. Apoptotic bodies have significantly high calcium concentrations.

Upon apoptosis or necrosis of VSMCs, these vesicles release calcium and DNA, which ultimately deposit on the ECM of the vascular media leading to extensivecalcification. Extracellular DNA has been shown to precipitate calcium and phosphate,which may contribute to arterial calcification. This is especially prominent in CKD or ESRD patients undergoing hemodialysis, as it can lead to increased VSMC apoptosis/necrosis through direct membrane contact and complement activation

In normal physiologic conditions, low basal rates of autophagy are required for the removal of unwanted metabolites from the circulation .The increased mineral levels and stress in CKD upregulate these rates and degrade the proteins necessary to maintain the contractile phenotype. This leads to the differentiation of phenotype along with direct calcific deposition in the vasculature .

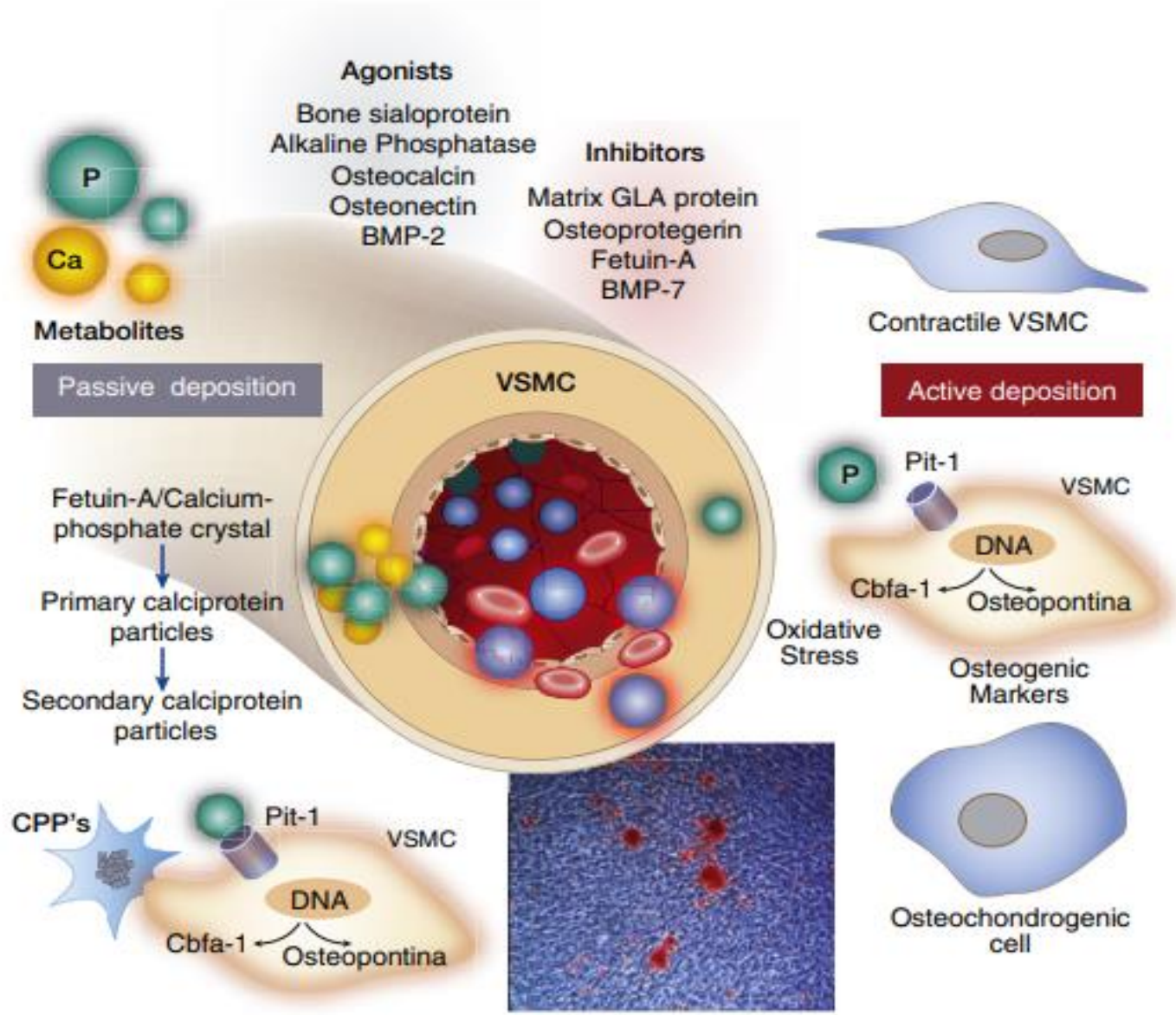
High phosphate–induced autophagy protects against vascular calafication



Autophagy and matrix vesicles: new partners in vascular calcification

Catherine M. Shanahan[1]

Kidney International (2013) 83, 984–986. doi:10.1038/ki.2013.75


Agonists
Bone sialoprotein
Alkaline Phosphatase
Osteocalcin
Osteonectin
BMP-2
Inhibitors
Matrix GLA protein
Osteoprotegerin
Fetuin-A
BMP-7
P
Ca
Metabolites
Contractile VSMC
Passive deposition
VSMC
Active deposition
Fetuin-A/Calcium-phosphate crystal
Primary calciprotein particles
Secondary calciprotein particles
P
Pit-1
VSMC
DNA
Cbfa-1
Osteopontina
Oxidative Stress
Osteogenic Markers
CPP's
Pit-1
VSMC
DNA
Cbfa-1
Osteopontina
Osteochondrogenic cell

Macrophages

Macrophages secrete many inflammatory substances such as TNF-a, IL-6, and IL-1b. These factors yield several processes that contribute to VC.

Firstly, the factors lead to the differentiation of vascular wall cells into chondrocytes and osteoblasts.

The two most common subsets of macrophages are the M1, or “classical activated macrophage”, and M2, or “alternative activated macrophage.”

In certain condition, and stimuli in various microenvironments, M1 and M2 macrophages display considerable plasticity and can transform between one phenotype and another.

M1 macrophages can directly release oncostatin M (OSM), which is a cytokine that belongs to the interleukin 6 cytokine group and stimulates vascular smooth muscle cells to take on an osteoblastic phenotype via the JAK3-STAT3 pathway .This subset of macrophages is also responsible for maintaining a persistent state of chronic inflammation that can interfere with the normal mechanism of VSMCs to differentiating into osteoblasts, leading to interspersed areas of fragmented calcification. This chronic state of inflammation maintained by the M1 macrophages is associated with high levels of TNF-α and IL-6, suggesting that a causal link between macrophage-mediated inflammation and cardiovascular calcification exists in the setting of CKD.

The formation of Ca/P nanocrystals in the vessels as a result of CKD stimulates macrophages to secrete pro-inflammatory cytokines, which in turn exacerbates VC .

In addition to the secretion of pro-inflammatory markers, high concentrations of Ca/P also trigger macrophages to release matrix vesicles (MVs). The MVs that are released have a proteomic profile similar to the MVs released by bone osteoblasts .In the early stages of the development of VC, macrophages release an abundance of calcifying matrix vesicles (MVs), which contain the phosphatidylserine-annexin V-S100A9 complex. Sophie et al. further studied this and confirmed that phosphatidylserine forms complexes with annexin V and S100A9 on the surface of macrophage-derived MV membranes. This complex then allows the entrance of calcium ions into the vesicles. The calcium and phosphate ions that enter the MVs via phosphate channels form calcium phosphorus complexes, which accumulate, forming the initial hydroxyapatite crystals. These hydroxyapatite crystals continue to grow, rupturing the membrane, and keep growing to form calcified nodules. Studies have shown that the pro-inflammatory mediators mentioned earlier, such as IL-6, TNF-a, IL-1b, and oncostatin M, are not only involved in the osteochondrogenic transition of vascular/valvular cells but also the release of calcifying MVs.

Other functional substances secreted by macrophages include osteogenic genes such as tissue nonspecific alkaline phosphatase (TNAP), osteoprotegerin (OPN), and runt-relatedtranscription factor 2 (Runx2), which further promote the osteogenic process.

Additionally, a recent study by Dube et al. showed that the M1 subtype of macrophages differentiated from mice bone marrow-derived macrophage (BMDM) exhibits osteogenic properties via the constitutive activation of BMP-2 signaling .

Dube and colleagues have also discovered that deleting transient potential classical receptor 3 (TRPC3), a nonselective calcium channel in macrophages, leads to a reduction in apoptosis of macrophages triggered by endoplasmic reticulum stress and downregulates the expression of Runx2 and BMP2, leading to a reduction in calcification in advanced atherosclerotic plaques.

The M2 phenotype is activated by Th2 cytokines, and these macrophages have an anti inflammatory effect. They are involved in parasitic infection resistance, lipid metabolism, allergic reactions, and tumor progression. Ricardo et al. studied how M2 macrophages are able to attenuate VSMCs from differentiating into osteogenic cells.

Ricardo et al. also demonstrated that the inhibitory effect of M2 is related to increased secretion of adenosine triphosphate (ATP) secretion and the synthesis of pyrophosphoric acid (PPi) via fatty acid β-oxidation .

Endothelial Cells

Studies show that endothelial cells secrete soluble factors that play a key role in the calcification of the VSMCs .The endothelial progenitor cells like macrophages are also known to be involved in the VC in CKD by expressing osteogenic factor osteocalcin. Endothelial cells also have the capacity to transform into mesenchymal stem cells to attain multipotency before they can differentiate into various cell types. This transformation is known as endothelial–mesenchymal transition (EndMT) .EndMT is a vital mechanism for endothelial cells to undergo osteo/chondrogenesis and secrete factors in VC.

Shear and mechanical stress are other factors that disrupt the endothelium and lead to worsening of VC. Vascular wall mechanical stress may contribute to endothelial and interstitial cell proliferation, altering the expression of calcification-related genes in cultured endothelial cells and fibroblasts .Mechanical stress triggers the differentiation of preosteoblasts into mature osteoblasts and can drive the progenitors down the osteogenic lineage .Mechanical stretch can upregulate the pro-osteogenic factors BMP-2 and Sprouty-1 ,and both of these factors modulate the basal expression of osteogenic factors in untreated vascular fibroblasts. Additionally, the application of steady tension to fibroblasts results in downregulation of anti-calcification factors periostin and osteopontin . Furthermore, mechanical stress leads to elevation of osteogenic genes thrombospondin and BMP-2 as well as other calcification-related genes.

Shear stress is a critical modulator of endothelial phenotypes, activating mechanosensors on the endothelial cytoskeleton,which triggers the phosphorylation and activation of genes leading to increased endothelial distress [94]. Furthermore, the stress-induced expression of factors that leads to proinflammatory, procoagulant, proliferative, and proapoptotic functions can contribute to worsening atherosclerosis and VC.

Hyperphosphatemia, another condition prevalent in CKD due to the high concentration of inorganic phosphate, suppresses the mammalian target of rapamycin (mTOR)signaling. This leads to an increase in the protective autophagic process for endothelial cells by counteracting the reactive-oxygen-species-induced VC.

Furthermore, a study by Bouabdallah, et al. shows that Pi and IS together fostered the secretion of interleukin-8 (IL-8) from the endothelial cells of human aortic smooth muscle cells, which induced calcification. It was proposed that IL-8 blocked the production of the potent calcification inhibitor, osteopontin.

Hypertension→ expression of the calcium promoting proteins, MMP-2, and MMP-9 levels in endothelial cells and vascular smooth muscle cell calcification leading to VC.

Uremic Toxin

The accumulation of uremic toxins in the circulation of CKD patients is the main driver of VC through the recruitment of monocytes and modulation of cells' inflammatory capabilities.

There are two notable uremic toxins: indoxyl sulfate (IS) and paracresyl sulfate (pCS). IS and pCS are correlated with the presence of inflammatory markers such as TNF-a, IL-6, and IL-1B in CKD patients.

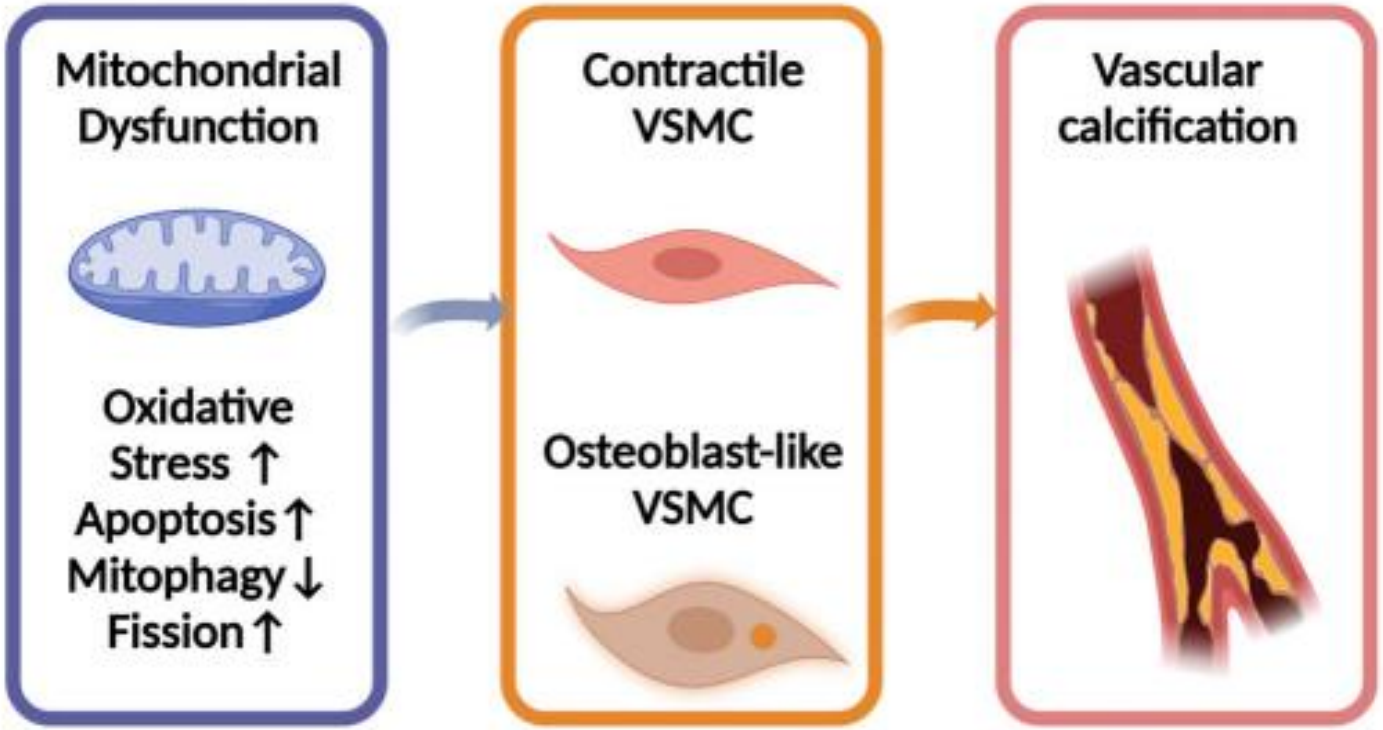
IS, inhibits the vascular klotho expression and downregulates TRPM7 levels, thus promoting VC processes.

IS, as an important pro-inflammatory molecule, may stimulate the secretion of interleukin (IL)-8 from the endothelium and impel calcium depositions by downregulating osteopontin in patients with CKD .Similar results have shown that IS releases inflammatory cytokines from activated macrophages in patients with CKD

Experiments by Six et al. determined a high expression of adhesion molecules such as VCAM-1 and ICAM-1 when CKD mice were fed a high-phosphate diet .This study essentially suggests when the expression of adhesion molecules by endothelial cells and monocytes is promoted, exposure to uremic toxins such as phosphate and IS leads to monocyte extravasation into cardiovascular tissues and thus inflammation-induced VC .Evidence from several experimental studies suggest phosphate (Pi)/IS-induced monocyte recruitment, inflammation, lipid accumulation, and fibrosis are the major drivers of atherosclerotic plaque development and calcific aortic valve disease in CKD patients.

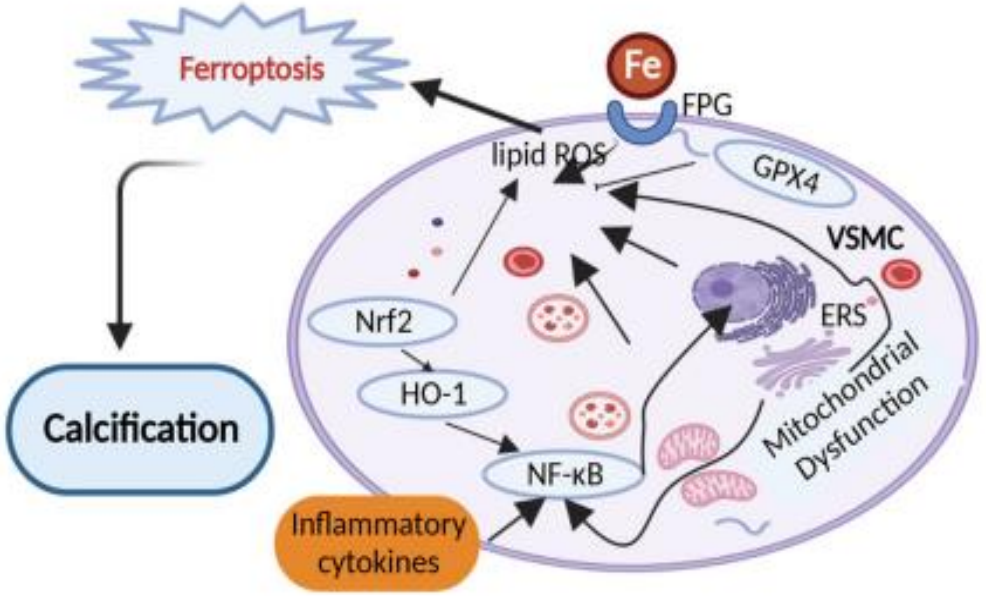
pCS is another uremic toxin that is produced by intestinal bacteria. Various studies suggest that there is an association between increased pCS levels and renal function deterioration, atherosclerosis, and inflammation. Experiments by Jing and colleagues demonstrate that when endothelial cells and macrophages are cultured with pCS in vitro, there is an increase in expression of inflammatory factors such as TNF-a and MCP-1, adhesion molecules .Their studies show that the high levels of pCS seen in CKD patients could potentially be responsible for medial and intimal calcification .

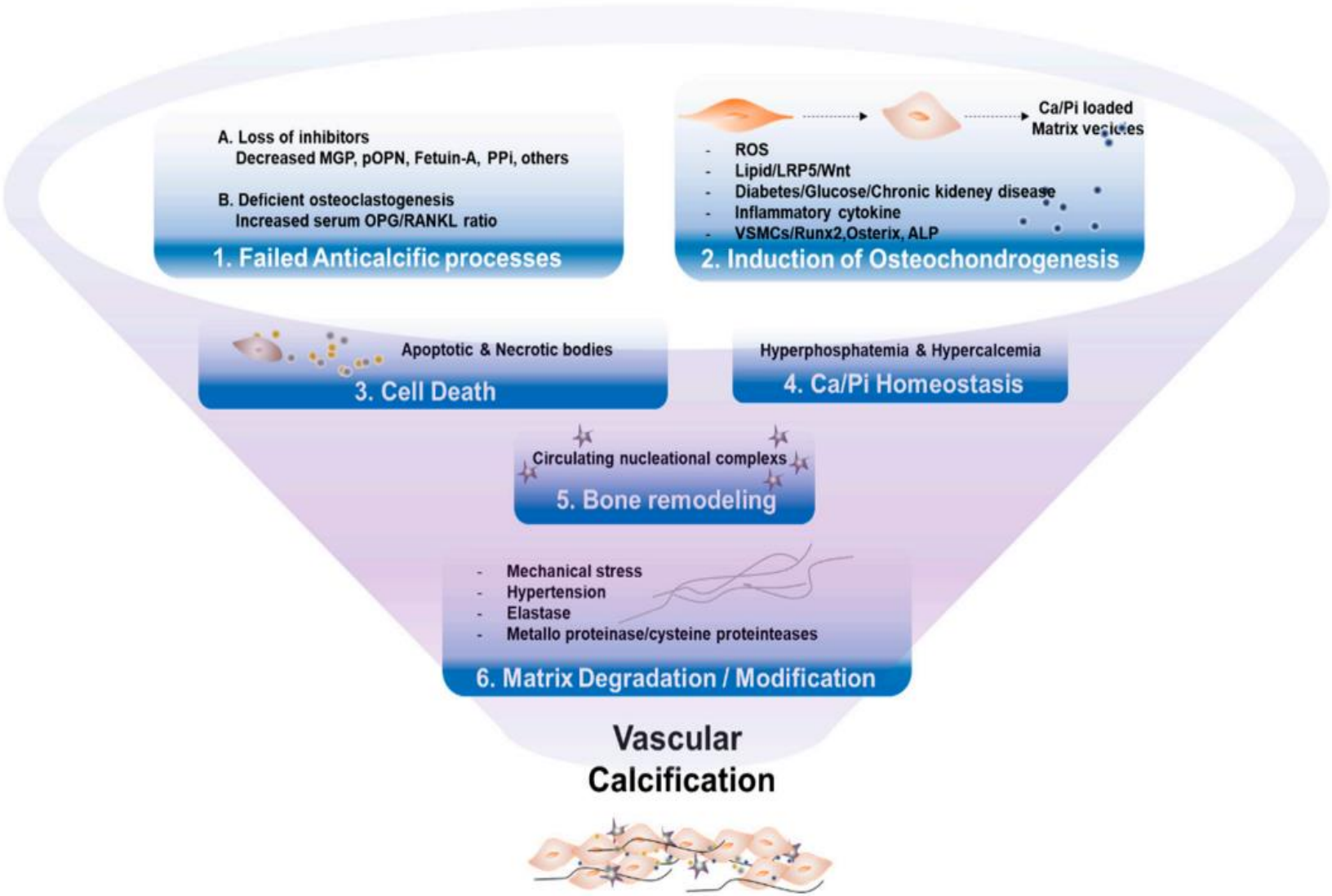
Mitochondrial dysfunction plays a key role in the progression of vascular calcification (VC)



MedComm. 2023;4:e200

- Recently, abundant studies have discovered that iron homeostasis can affect the process of inflammation, ERS, and mitochondria function to regulate VC.
- Macrophage iron canincrease the release of TNF-α, IL-6, and the potent monocyte–attracting chemokine monocyte chemoattractant protein-1, and so on.
- Iron overload impairs mitochondrial function.
- Iron influences ERS.
- Ferroptosis is a newly discovered type of PCD in 2012, is closely related with iron homeostasis. The process starts with the accumulation of excessive iron and lipid peroxidation in the body and ends up with the oxidative damage of the cells . If VC is regarded as the result of inflammation, ferroptosis can be considered the cause of inflammation.Current studies found that ferroptosis results in the initiation of inflammation in a lot of diseases.





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TYPES OF VASCULAR CALCIFICATION

- Intimal occurs almost exclusively in the context of atherosclerosis is associated with traditional atherogenic risk factors such as dyslipidemia, diabetes, hypertension, and cigarette smoking. CKD may promote, accelerate, or catalyze an already established, synchronous atherosclerotic calcification process rather than incite.
- Medial Unlike the often patchy distribution of intimal calcification, medial calcification tends to be more diffuse, forming sheets in topographic areas typically devoid of lipid or atherosclerotic change Although it is seen in vessels of all calibers, it is conspicuous for location in territories usually spared from atherosclerosis, such as the internal mammary, radial, and digital arteries. Medial cation is more specific to CKD, but also observed with diabetes mellitus and advanced age; these 3 entities potentially share linking pathophysiology of chronic inflammation and cellular senescence .

Compared with intimal calcification, medial calcification is rarely associated with local luminal compromise, and instead is linked to the systemic manifestations of increased arterial stiffness. A reduction in vascular compliance augments systolic blood pressure, which increases cardiac work and causes left ventricular hypertrophy .This is a finding observed in up to 75% of patients with higher than or equal to stage 3 CKD , providing a mechanistic basis to the increased rates of heart failure and atrial fibrillation observed in CKD.

- Calciphylaxis The exact cause of calciphylaxis is still unknown, but its pathology includes tunica medial calcification, necrosis

of tissue. It is common in ESRD patients, therefore it is likely that intimal hyperplasia and medialcalcification is entangled with etiology .

- Valvular

CT CORONARY ARTERY CALCIFICATION SCORE

There was a stepwise association between CAC severity (CAC score 0, 0 to 100, >100) and composite CV outcome. In multivariable modeling,the relative hazard ratios (HRs) associated with a 1 SDof log CAC were 1.40 (95% confidence interval [CI]:1.16 to 1.69; p < 0.001) for the composite CVD outcome(myocardial infarction, heart failure, and stroke), 1.44(95% CI: 1.02 to 2.02; p ¼ 0.04) for myocardial infarction, and 1.39 (95% CI: 1.10 to 1.76; p ¼ 0.006) for heart failure. CAC was not associated with all-cause mortality. The similar magnitude hazard ratios for atherosclerotic CVD and for HF suggest CAC scoring in the CKD population may be less specific for atherosclerotic burden and instead be an integrated marker of both medial and intimal calcification.

Reduction in radiation dose, application of semiautomated scoring mechanisms, ease of access, and validated age-standardization have resulted in the CT CAC score becoming the gold standard endpoint for trials that evaluated change in vascular calcification.

PLANE RADIOGRAPHY

The Kauppila score is a semiquantitative scoring method that attributes an ordinal value to calcification (0 to 3) at 8 sites along the abdominal aorta (total maximal score 24) as viewed on a lateral lumbar spine plane radiograph.

Another x-ray based scoring system that was described by Adragao involves semiquantitative scoring of linear calcification on pelvic and hand radiographs. **The deliberate focus on pattern of calcification and inclusion of hand vessels increases the specificity for medial calcification, which is a theory supported by its correlation with arterial stiffness.**

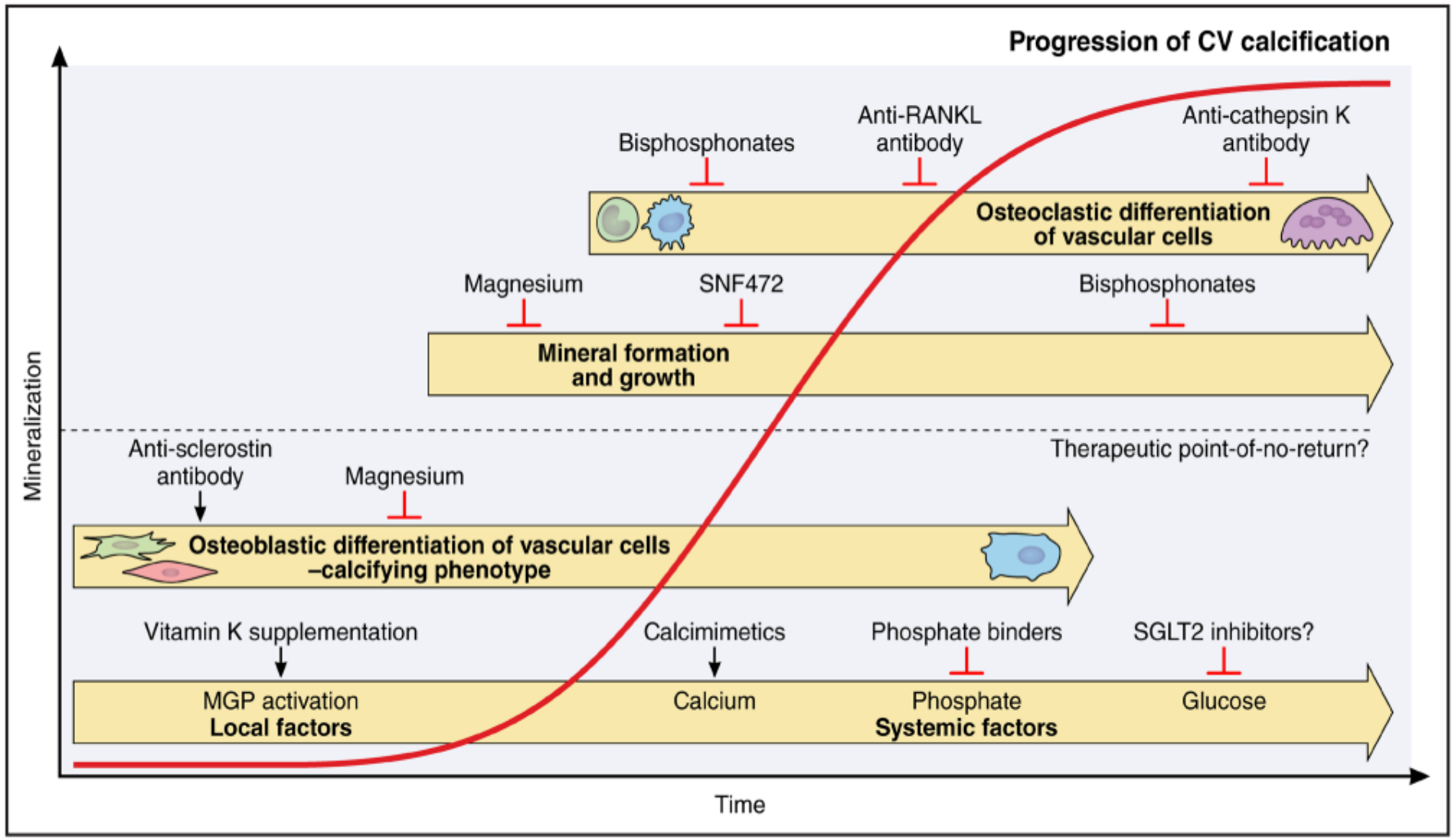
BREAST IMAGING

Breast arterial calcification is an attractive method for measuring exclusively medial artery calcification because atherosclerosis has not been shown to occur in these vessels. **This is a modality limited to the assessment of women, and at present, has only been retrospectively analyzed.**

SCREENING

- Have argued that all patients with CKD should be considered at the highest CV risk and, in the absence of specific vascular calcification therapies, screening for vascular calcification does not influence management.
- Routine vascular calcification screening using either lateral pelvic x-ray or CT imaging received a weak (level 2C) recommendation in the 2017 KDIGO guidelines, reflecting the paucity of outcomes-driven data.

Contributing cellular and noncellular factors to the progression of cardiovascular (CV) calcification and potential therapeutic options for interference



Circulation Research. 2023;132:993–1012

- Phosphate Binders The majority of RCTs revealed attenuated calcification progression of noncalcium-based phosphate binders when compared with calcium-based phosphate binders. Overall, however, clinical studies with various P binder therapies have been rather disappointing in terms of clinical outcomes and found only relatively small differences in the progression of vascular calcification. In end-stage renal disease, the avoidance or limited use of calcium-containing P binders is advocated in part based on a more rapid progression of CAC.

- Bisphosphonates Bisphosphates (BPs) are analogs of PPi compounds, which powerfully inhibit bone turnover, and are termed “osteoclast killers. They are distributed to two classes: non-nitrogen-containing BPs, including clodronate and etidronate; and a new generation of nitrogen-containing BPs comprising alendronate, ibandronate, zolendronate and pamidronate. Recent studies have discovered that alendronate effectively inhibits VC progression in patients who underwent kidney transplants. In elder subjects, NCBPs were observed to be related with a lower prevalence of cardio VC, whereas in younger subjects, NCBPs were related with a higher prevalence of cardio VC. BPs have a long half-life of approximately 10 years in the human body. Therefore, further research is warranted to clarify the therapeutic effects of bisphosphonates in valvular and vascular calcification, especially in the context of CKD and confirm the long-term side effects of BPs, including skeletal toxicity and osteonecrosis.

- Recent results from a randomized prospective clinical study demonstrated 56% lower thoracic aortic calcification and 68% lower CAC in hemodialysis patients treated with 5 mg vitamin K1 3× per week compared with patients only receiving standard care.
- supplementation of vitamin K2 in the form of MK-7 (menaquinone-7) in patients with CKD failed to show any beneficial cardiovascular effects ,explained by a disturbed lipoprotein-mediated MK-7 transport in patients with CKD.
- Magnesium A randomized, controlled clinical trial enrolled 59 subjects who underwent HD for endstage kidney disease (ESKD) for intervention. The result revealed that magnesium decreased calcification propensity in subjects undergoing maintenance HD.
- SNF472 A newly discovered medicine an (exogenous source of phytate) has been approved to enter into the final stage of clinical trial . Considered a leading potential compound for the treatment of VC in ESKD-stage patients, SNF472 exerts its function by targeting the hydroxyapatite deposited in the vascular wall directly.
- Calcimimetics In hemodialysis patients with secondary hyperparathyroidism, cinacalcet reduced the rate of clinical fractures and attenuated vascular and valvular calcification but did not affect all-cause mortality and cardiovascular events. However, a post hoc subgroup analysis revealed a decreased risk of death and major cardiovascular events in older, but not younger, patients. Analysis from a health care utilization general CKD cohort with secondary hyperparathyroidism in Sweden showed that cinacalcet reduced cardiovascular events.
- Anti-RANKL Antibody: Denosumab Smaller studies investigated the effect of denosumab in hemodialysis patients with low bone mass and showed reduced progression of CAC and aortic arch calcification203 after 6- and 30-month treatment and no effect on CAC after 12 months of treatment.