ATHEROSCLEROSIS: RECENT ADVANCES

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Abstract

Atherosclerosis is heart and blood vein diseases (STDs) and stroke main reason was large arteries inflammation disease. Here we are talking about an individual path and system point of view from the point of view atherosclerosis molecular, cellular, genetic and to the environment impact about current the concept seeing We are the last ones. to changes attention, we looked at them some unexpected biological laws brought released, atherosclerotic in lesions inflammation and smooth muscle of cells previously unknown heterogeneity, old age and clonal in hematopoiesis roles and intestine microflora with dependency these from the sentence.

INTRODUCTION

Atherosclerosis or coronary artery cardiovascular disease (CVD) vein most common diseases (STDs) wide widespread shape is , its main component lipids accumulation and large arteries inflammation eventually his/her clinical complications , myocardial myocardial infarction (MI) and to stroke take arrival possible . Slowly developing disease as clinical in terms of significant atherosclerosis mainly old in people occurs and some in countries illness decreasing to the one who is going despite , all world along of death main reason become Atherosclerotic lesions of the veins internal the wall covering one multi-storey endothelial cells (EH) under intimate in the void lipids , inflammation cells , smooth muscle cells and necrotic cell remains life height accumulation and change with Usually , the lesion is growth blood vein internal through the gap blood Reduces flow by >50% possible and especially this physical exercises or during stress in ischemia take arrival Lesions , especially those with oily skin , may and inflammatory to the content has if they are relatively unstable became , and later rupture possible . If this coronary in the arteries happened if so, this blood flow complete block takes it to MI arrival possible was local grave appeared to be taken arrival possible. With this one in a row, thrombus from the heart out, into the brain going if, there to stroke take arrival possible.

Latest at times atherosclerosis in development molecular and cellular mutual effects in understanding big to achievements achieved. These one via cellular RNA sequencing (scRNA - seq) determined atherosclerotic in lesions previously unknown was cellular heterogeneity Aging during to the surface coming processes , such as aging and clonal hematopoiesis important role It is also recognized that he plays Also , the intestine microflora and atherosclerosis between connections increasingly clear become Atherosclerosis is progressing . genetic and ecological danger factors mutual the impact and his/her cardiometabolic features with connection systematic in understanding noticeable to achievements is being achieved.

ORIGIN AND DEVELOPMENT OF ATHEROSCLEROTIC LESION

Vein internal wall blood flow from the limiting EH monolayer consists of. Based on this mainly glycosaminoglycans and from collagen consists of the so-called "intimacy" that is cellular layer lies. Then smooth muscle cells from the layers the so-called "media" consists of middle floor and finally, external fibrous " adventitia " layer. Atherosclerosis mainly plasma known lipoproteins, including low- density lipoproteins lipoproteins (LDL) and triglyceride- rich lipoprotein residues in the vascular intima accumulation with This process begins. still complete misunderstood mechanism through, possibly, inflammation instigator oxidized lipids harvest to be with related without, above endothelial activates the cells (EH). Then, the blood monocytes endothelial adhesive to molecules joins, intimately enters and to macrophages These macrophages lipoproteins absorb cholesterol rich in esters " foam" " cells" harvest does (Figure 1) . This in the department lesions at the beginning participation provider cell types and molecular mutual effects discussion will be done.
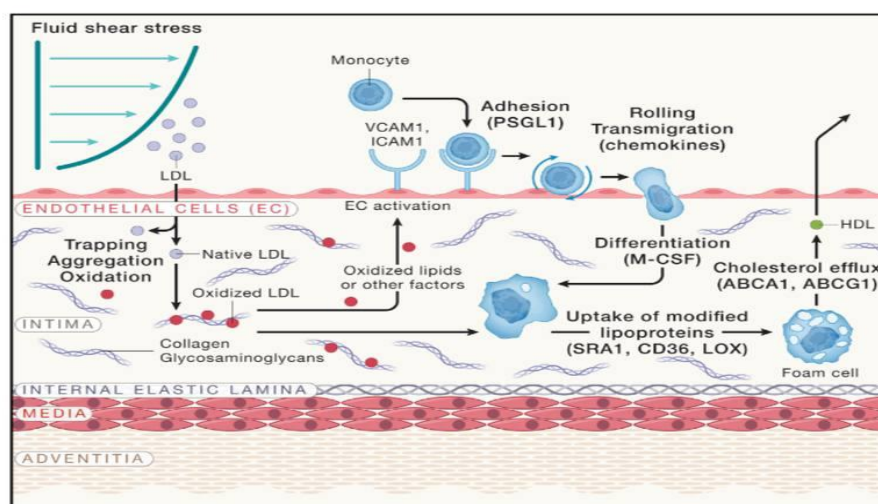

Figure 1. Lesions oily traces development

Lipoproteins intimate damaged from places intimate Then lipoproteins accumulate, oxidizes and other to changes occurs, as a result above endothelial cells (EH) monocytes for adhesive and chemical guide molecules to express activates monocytes intimate enter macrophages turns and changed lipoproteins absorb, foam cells harvest the intima layer in the picture enlarged without illustrated.

ENDOTHELIAL CELLS (EC)

As shown in Figure 1 , endothelial cells (EH) blood and vein the wall separate standing dense from associations consists of one layered cell layer harvest does . Blood of the flow broken in conditions of EH and their dense The connections are " permeable " it remains , this and LDL in plasma and trans -endothelial transport of triglyceride- rich lipoproteins or intercellular in the gaps diffusion through the passage strengthens *(Zhang and et al ., 2018).* Later, the EHs activation of lipoprotein lipids oxidation and other inflammation factors in response to the surface resulting in the formation of P- selectin , E- selectin , VACM1 and ICAM1 molecules These molecules are monocytes , other leukocytes and CCR2 and CCR5 chemical guide of factors adhesion encourages *(Gimbrone and García-Cardena, 2016).* Broken blood flow Of the dysfunction brought releasing alternative mechanism – erosion also trigger the process This is

possible through TLR2. controlled EC apoptosis and IL-8 secretion as a result to the surface comes , as a result neurophiles accumulation , activation and neurophiles extracellular nets release This is observed . process EC layer damage strengthens and blood clot harvest to be take arrival possible *(Luo and et al ., 2021).*

BLOOD FLOW AND LIPID ACCUMULATION

Atherosclerosis usually arteries branching in places , laminar flow relatively turbulent blood flow observable in the regions develops . Turbulent flow endothelial cells (EC) cell structure changes and their large to molecules conductivity increases . This of the answer based on lying down one how many roads identified , including BMP-TGFβ, WNT and Notch pathways *(Soulhall and et al ., 2020).* Conductivity increase as a result , known lipoproteins in the intima accumulates , partly intimal glycosaminoglycans with mutual impact through *(Boren and Williams , 2016).* This in a way from the catch then , LDL and triglyceride- rich residue lipoproteins aggregation and chemical to changes meeting possible **(Figure 1).**

LIPID OXIDATION and INFLAMMATION

Many evidence this shows that the vein on the wall caught remaining in lipoproteins lipids oxidation inflammation instigator of substances harvest to be take comes and this leukocytes accumulation and inflammation brought For example , oxidized phospholipids or with oxidized LDL processing to give endothelial in cells adhesive molecules and chemical guide factors expression brought releases (Figure **1).** However , this hypothesis straight away proof difficult became . Antioxidant medicine of tools atherosclerosis reduces not getting some such as aggregated LDL alternative mechanisms inflammation cause to the fact that conclusion to do take arrived *(Libby, 2021).* However , oxidized to phospholipids against natural antibody transgender expression in mice lesions suppression shown studies lipid oxidation hypothesis supports *(Which and et al ., 2018).* Also , lipoproteins macrophages in lysosomes oxidation It is possible that this lipid oxidation of products separated to the exit take This oxidation occurs antioxidant cysteamine using Suppression of LDL receptors no was in mice lesion development blocked and even return sent *(Ahmad and et al ., 2021).* Recent lipid oxidation product was octanol vein in macrophages olfactory with receptor 2 binds to and activates the NLRP3 inflammasome activation and interleukin 1b incitement This is defined . receptor to the target to take atherosclerosis reduced octanol level increase and him/her strengthened *(Orecchioni and et al ., 2022).* Research also in the intestine lipids oxidation systematic inflammation and atherosclerosis contribution add possible showed *(Mukherjee and et al ., 2022).*

MONOCYTES, MACROPHAGS, AND FOAM CELLS

Monocytes vein to the wall endothelial by cells (EC) working issued adhesive molecules and chemical guide proteins under the influence attraction Intimate area When they entered , they local working released M-CSF and other cytokines under the influence to macrophages turns **(Figure 1).** Mice on held research this shows that early in lesions macrophages abundance mainly their attraction to be done related , but developed in lesions this many in terms of macrophages increase as a result to the surface comes *(Robbins and et al ., 2013).* Macrophages lesions to

develop very big contribution Addictive , because M-CSF deficient , hypercholesterolemic background mice almost lesion from the development Protected . Normal LDL macrophages by not be assimilated , but rather it is first oxidation or from aggregation to pass needed . Lesion macrophages such " modified " intimal lipoproteins scavenger receptors through or aggregated lipoproteins phagocytosis to do through acceptance so , cholesterol with full macrophages or " foam" "cells" harvest Foam cells cholesterol transporters ABCA1 and ABCG1 through release possible although they often apoptosis or to necrosis This is cholesterol esters , cholesterol crystals and cell from the remains consists of " necrotic" to the growth of the nucleus take it comes , this lesion crack probability Macrophages atherosclerosis various in stages metabolic to changes occurs and this their to the functions impact to do possible *(Smile and Bornfeldt , 2020).*

ADVANCED ATHEROSCLEROTIC LESIONS

Elementary from the stage then , lipids and foam cells in the gathering continue will , other leukocytes , especially T cells to the lesion macrophages enter with mutual impact does . Time to pass with foam cells perish is a cell remains and from cholesterol consists of necrotic core harvest It also makes smooth muscle cells (SMH) contractile from the situation reproduction to the state passing through EC (endothelial cells) under to the area move , lesion from cracking protection " fibrosis " " cover " crop SMH also makes foam . cells and calcium phosphate minerals collecting bony cells harvest to do macrophage similar to cells rotation possible . Lesions blood flow block put at the level enlargement possible although , clinical in terms of the most important event — lesion rupture or endothelial erosion because of blood clot harvest to be as a result myocardium development of myocardial infarction (MI) **(Figures 2 and 3)** . This in the department SMH and lymphocytes lesion in development role , as well as inflammation , calcification and lesion to stability impact doer processes discussion Finally , the lesions cell diversity study single cell for from the sequence use about word is maintained .

SMOOTH MUSCLE CELLS (SMC)

Lesions growth During , SMHs are in the medial layer contractile from the situation multiplying to the situation passing by , into intimacy moves . Time to pass with , from intimal SMH collagen consists of was and from cracking protection doer fibrosis cover harvest doer from the cell outside matrix separates **(Figure 2).** Intimacy entrance ability has was SMHs number relatively less although they clonal from expansion after , then again contractile To SMHs rotation possible . Generation observation research this shows that this cells macrophage similar and osteochondrogenic for generations transition to the possibility has *(Alencar and et al ., 2020; Pan et al. et al ., 2020).* To the macrophage similar SMHs lipids absorb , foam cells harvest to do possible . This foam cells to apoptosis meeting and efferocytosis suppression through secondary necrosis and to inflammation take arrival SMHs have also recently illustrated from the membrane taken particles way through close surrounding macrophage foam from cells cholesterol to receive possible *(Yes and et al ., 2018).* Animal in models From SMH harvest was foam cells in lesions all foam up to 50% of cells part organization to be able possibility guess will be done (Basatemur and et al ., 2019) . SMCs also macrophages colony stimulation doer factor (M-CSF) releases, this and in lesions macrophages increase stimulates osteochondrocytes

and calcification granules harvest to do and they later calcium to the nodes merger possible (Basatemur and et al ., 2019).
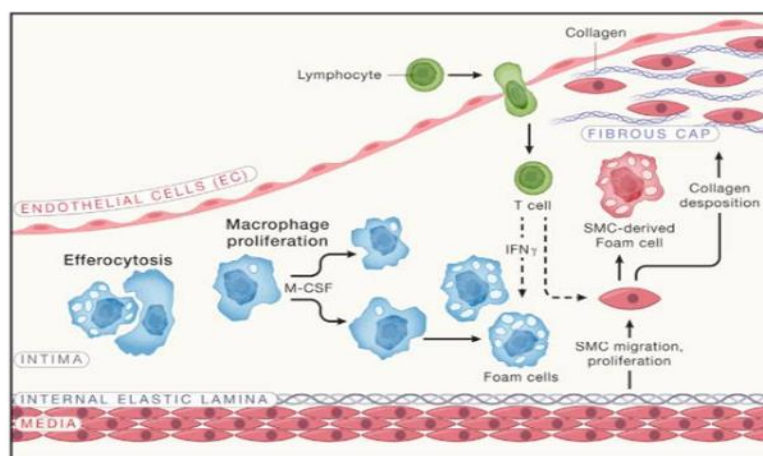

Figure 2. Atherosclerotic lesions development
Macrophages M-CSF (macrophages colony stimulation doer factor) under the influence increases, and foam cells macrophages by is swallowed, this the process is called "efferocytosis." Smooth muscle proliferative stem cells (SMC) to the situation passing, endothelial industry side moves and collagen separate, " fibrosis" " cover " crop SMHs also produce lipid - rich foam. cells harvest to do for macrophage similar to cells rotation Both T and B cells can be involved in the lesion. enter, another cell types with mutual impact so that the lesions development acceleration or slow down possible.

T lymphocytes
Atherosclerosis chronic inflammation adaptive and congenital immunity controls , and T cells one how many classes disease to develop impact shows *(Roy and et al ., 2022*). T cells atherosclerosis all in stages there is is , their to the lesion entrance chemokine receptors (CCR5 and CXCR6) and by ligands (CCL5 and CXCL16) T cells are controlled . immune both induce and suppress activation possible , also to B cells antibodies working in the release help gives . In lesions the most many occurring TH1 cells secrete interferon-gamma are cells , they plaque growth and instability Treg cells to inflammation against cytokines (IL-10 and TGFβ) represents , macrophage efferocytosis encourages and atherosclerosis with negative correlation TH2 cells secrete IL-5 and IL-13 . represents, both are protective to the effect T cells , as well as B cells in lesions there is was antigens by is activated , and atherosclerosis antigens received dendrite cells lesion abandonment to , another in places the answers encouragement possible *(Proto and et al ., 2018; Roy et al. et al ., 2022).*

B lymphocytes
B cells atherosclerosis chronic to inflammation contribution adding local and systematic immune in the answer's participation will *(Sage and et al., 2019).* They are bone bone from cells harvest will be and in the divorce Each B cell matures known one antigen recognize him /her antibody working issuer plasma to cells rotating rare B cell receptor working Antiatherosclerotic and proatherosclerotic B cell types existence identified. Some B cells oxidized in lipoproteins and

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necrotic in the remains there is was oxidized to epitopes " natural " antibodies that bind working releases and thus inflammation inhibition LDL, oxidized LDL, apolipoprotein B (LDL) main protein) and cytomegalovirus such as to pathogens against antibodies atherosclerosis with related. Recently held research this shows that macrophages inflammation instigator IgE immunoglobulins high level atherosclerosis increases with noticeable at the level related. B cells autoimmunity also contributes to atherosclerosis contribution add possible; for example, some to lupus related mouse in models' atherosclerosis increased observed *(Sage and et al., 2019).*

GEMOPOEZ

Strong evidence this shows that blood cells update process was hemopoiesis increase atherosclerosis Smoking, stress and unhealthy food hemopoiesis and turnover leukocytes increases, physical exercises and high dense lipoproteins (HDL) levels increase and them reduces . Recently held research mice and in people hemopoiesis amplification, clonal hemopoiesis and atherosclerosis between causal dependency supported *(Heyde and et al., 2021).* Hyperlipidemia hemopoiesis partially cholesterol out to leave to their paths impact through encourages and this process ABCA1, ABCG1 and HDL functions by suppressed (Schloss and et al ., 2020). SREBP2 and Notch signaling both regulate hematopoiesis order in the field participation enough factors as being watched (Gu and et al ., 2019).

EFFERCYTOSIS and INFLAMMATION ELIMINATION

Efferocytosis is apoptotic cells no to do process is , this secondary necrosis and inflammation prevent This process mainly macrophages by done increased , they perish happening cells wins and necrotic of the nuclei growth in reduction important role plays **(Figure 2)** *(Doran and et al ., 2020)* . Inflammation eliminates to do is inflammation in the process of tissues integrity and function to restore aimed at active process. This is a projectile. from macrophages to inflammation against to macrophages transition with related is , this process resolvins and called lipoxins special lipids , proteins and nitrogen oxide through managed *(Beck and et al ., 2019).* Recently held research this shows that efferocytosis to inflammation take unreachable macrophages increase encouragement and of tissues to recovery contribution add possible *(Gerlach and et al ., 2021).*

CALCIFICATION

Coronary calcification developed lesions with together to the surface comes and him/her various to describe methods using assessment Calcification is possible in the intima and media layers. happened to be possible and plaque stability increase with related to be There is a possibility. This process apoptotic SMC (smooth muscle cells) and from macrophages come outgoing very small matrix vesicles with These vesicles time to pass with usually together necrotic core near large to the masses turns and eventually calcium layers harvest does **(Figure 3). In** such areas , BMP-1, BMP-4 and matrix GLA protein such as bone with related proteins often is expressed *(Basatemur and et al ., 2019; Mori et al. et al ., 2018).*

FIBROSIS CAP

Developed in lesions endothelial to the cell (EC) layer close located fibrosis binder tissue layer there is is , it is fibrosis It is called a lid . It is made of collagen, elastin and smooth muscle from collections of stem cells (SMCs) , as well as macrophages and from lymphocytes organization Previously , on the cover from the cell outside matrix working issuer of cells almost all From SMC come thought to have come out was . However, the last research this shows that this of cells noticeable part from endothelial mesenchymal transition or from macrophage mesenchymal transition process from the head forgiven EC or from macrophages come comes out *(Newman and et al ., 2021).*

LOSS STABILITY

Myocardium myocardial infarction (MI) usually lesion rupture as a result blood bottom harvest when happened will be **(Figure 3).** "Unprotected plaques" more their composition with related is the size of with not. Bold fibrosis cover with covered fibrosis lesions oily and to inflammation inclined to lesions relatively more stable to be The lesion is to stability impact doer one row factors defined, including smooth muscle cells (SMC) and endothelial aging of cells (EC) . Macrophages plaque instability inflammation strengthens and fibrosis cover to the target recipient proteases working release through MI also increases endothelial erosion also occurred as a result to be possible **(Figure 3).** Neutrophils in lesions less Although they meet neurophiles net and matrix metalloproteinases separate release through endothelial erosion strengthen possible *(Libby, 2021).* Recently held research this showed that oxidized lipids neurophiles extracellular of the net's formation encourages and mice in the model carotid artery thrombosis accelerates *(Dow and et al., 2021).*
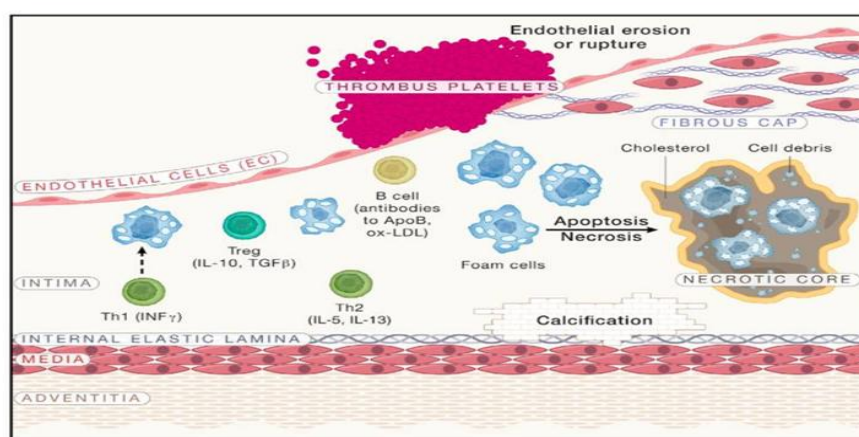

Figure 3. Developed atherosclerotic lesions. Foam cells and other cells perish cholesterol rich necrotic with nuclei harvest Calcification often in the intima or media layers to the surface comes. Lesions rupture or endothelial cells erosion blood clot harvest to be take arrival it is possible , this and myocardium myocardial infarction (MI) or to stroke take arrival There is a possibility

CELL DIVERSITY AND PLASTICITY

Atherosclerosis researchers for main from problems one this in process participation arterial wall of cells diversity become arrived . Recently held one cellular RNA-seq studies this cell

phenotypes high to plastic has that and atherosclerosis development during changing to go For example , the arterial wall is smooth muscle (SMH) muscle cells) cells phenotypic plastic noticeable at the level manifestation it happened , they late step by step atherosclerotic plaque harvest in being bone to the cells similar to cells rotation observed (Alencar and et al ., 2020). Also , SMH cells proatherogenic macrophage similar and fibrochondrocyte similar to cells many edged differentiation opportunity with intermediate cell to the state to pass and atherosclerosis against protection to the original SMH phenotype as return shown . Retinoic acid signals symptomatic atherosclerosis with related in humans intermediate SMH status order puts (Pan and et al ., 2020) . Human coronary arteries according to held again one in research genome along association by GWAS studies identified CAD risk gene TCF21 SMC plastic CAD protection over role done increased was determined (Wirka and et al ., 2019). From SMH except , recently immune cells and atherosclerosis endothelial of cells one cellular The landscape is also in people (Fernandez and (et al ., 2019) and in mice (Winkels and (et al ., 2018) studied . Previously mice 13 types in the aorta myeloid cell population determined is , their some healthy and atherosclerotic in the aortas there is was resident macrophages Monocytes , from monocyte come came out dendrite cells and TREM2 expressing inflammation macrophages two population and mainly only atherosclerotic in the aortas observed (Cochain and et al ., 2018). These results human carotid also confirmed on plaques and additional accordingly endothelial-mesenchymal transition and CD4+ and CD8+ cells cytotoxicity decrease shown (Depuydt and et al ., 2020). From this a little different symptomatically of patients carotid on their plaques activated and of differentiated CD4+ T cells separately population existence determined (Fernandez and et al ., 2019). Recently human atherosclerotic in lesions one nuclear chromatin permeability profiling (using snATAC -seq) cell to the types typical cis - ordered eater elements This method has been studied . via CAD risk by GWAS on determined genetic of options endothelial and To SMH typical open in chromatin noticeable at the level enriched determined (Ord and et al ., 2021). With this together , a CAD GWAS candidate called ATF3 gene recent SMC transitions suppressor as determined blood vein inflammation strengthen determined (Wang and et al ., 2021).

OLD AGE AND ATHEROSCLEROSIS
Atherosclerosis mainly old aged in people occurring disease myocardium myocardial infarction (MI) or stroke most are over 55 increased in people is observed (Tyrrell and Goldstein, 2021). However , some early beginning forms , for example , family hypercholesterolemia (FH) or very less Hutchinson-Gilford progeria, which occurs such as There are also diseases . This in the department we are old with related to atherosclerosis contribution adding relatively recently determined three the process discussion we will do .

OLD AGE
Endothelial cells (EC), smooth muscle cells (SMC) and macrophages cell senescence of lesions growth , inflammation and in stability participation will (Grootaert and et al ., 2021; Kotla et al. et al ., 2019). Old age oxidative stress, DNA damage and recurring fatigue through to the surface arrival possible . This process useful and harmful to the effects has : he has cancer from illness

protection does and tissues to restore supports , but is outdated in the tissues cell aging degeneration and dysfunction reason will be . Aged cells surrounding to cells various inflammation cytokines , immune modulators and proteases separate release through impact shows . This substances together aging with related secretary called phenotype (SASP) (Figure 4). Aged cells pharmacological in a way , for example , of the BCL-2 family members to the target " senolytic " drugs such as ABT263 using no to do possible . In atherosclerosis old cells plaque of rupture prevent in receiving important was fibrosis of the lid degeneration contribution addictive , but senolytic cleaning SMC number and cover thickness to restore help gives (Childs and et al ., 2021). SIRT6, a class III member of the sirtuin family histone deacetylase member , SMC cells telomere damage in lesions suppression through from aging protection does (Grootaert and et al ., 2021).

INFLAMMATION AGING (INFLAMMAGING)

Without infection in a state of development young with chronic , low- grade inflammation develops and atherosclerosis such as to age related to pathologies contribution This inflammation is lipid and glucose exchange such as systematic to functions noticeable impact to show possible . Old age from the characteristics one macrophages increase and their in polarization are changes . The latest research this shows that it is old from cells except for M1 type similar macrophages such as IL-1beta, IL-6 and TNF inflammation instigator cytokines main source to be It is also possible that NLRP3 activation in aging increase is observed (Covarrubias and et al ., 2021). NAD+ levels in old age decreases and last research this showed that NAD+ levels restorative additions in old age metabolic and heart and blood vein dysfunctions protection NAD + levels to decrease take incoming from mechanisms one projector CD38 enzyme in macrophages expression CD38 MI type macrophages by will be issued and NAD+ hydrolysis does (Abdellatif and etc. , 2021) (Figure 4).
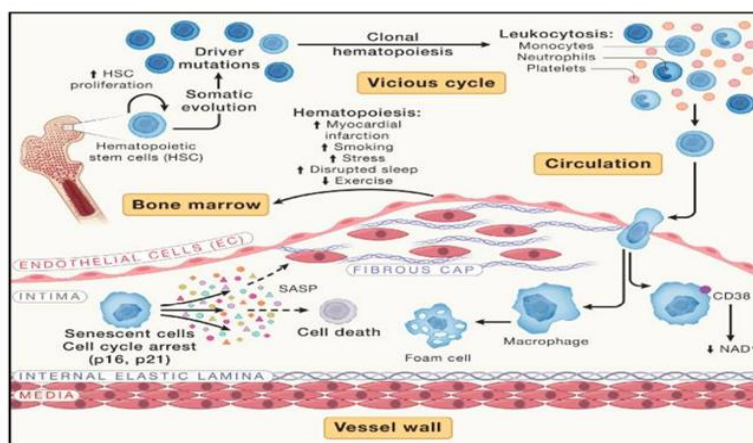

Figure 4. Old age and atherosclerosis

Picture old age with related was and atherosclerosis instigator three main the event describes: clonal hemopoiesis , cell aging (senescence) and immunosenescence . Clonal hemopoiesis old age and atherosclerosis danger factors under the influence hemopoiesis encouragement as a result somatic mutations probability increase with related was harmful cycle as This is considered. mutations reproduction to the advantage has was root cell clones harvest does . Increased hemopoiesis to leukocytosis take comes, and to the surface arrived clones to inflammation inclined features manifestation to do , that's it through lesions growth strengthen possible . Cell senescent evidence

in mice atherosclerotic in lesions one row cell types for observed. This old cells inflammation instigator or close surrounding cells perish doer various kind cytokines and immune modulators (aging with related secretary proteins, SASP) . Immunoaging old age with together coming chronic inflammation to become inflamed inclined cytokines M1 macrophages expressing with This is related to NAD+ in the process The enzyme that breaks down CD38 is also involved will reach.

GENETICS OF ATHEROSCLEROSIS

It is said that genetics to biology mathematics to physics how if so , then so impact shows , and genetic research atherosclerosis in understanding important role Atherosclerosis big part , about 40%, genetic to changes Rare Mendelian disorders , such as familial hypercholesterolemia (FH) and recently discovered PCSK9 mutations , new mechanisms open gave or important therapeutic to achievements take arrived . Last exam sequence according to research big in quantity in people atherosclerosis and to him/her related to the features big impact indicating additional less occurring options determination opportunity gives (Backman and et al ., 2021). However , the inheritance main part many genes joint from the influence consists of is , their every one general to sensitivity small share addictive (Figure 5). Such options separately to danger small impact shown although they biological on the networks connected many bottom genes order in the field together noticeable impact shows . This In the section we will discuss atherosclerosis wide widespread to the forms contribution adding general genetic changes , including sexual the differences we also study molecular and clinical features unifying systematic genetics approaches discussion we will do .

WIDESPREAD GENETIC VARIATIONS

GWAS studies on CAD of the disease wide widespread , complex to the forms contribution adding genes located loci in determining important role played . Current more than 200 at the time loci for CAD determined , in which mainly Europe from the lineage was very big cohorts and meta- analyses , including CARDIOGRAM and UK BIOBANK, as well as a large Japanese cohort (Erdmann and et al ., 2018; Koyama et al. (et al ., 2020) (5 pictures). However , this loci of the disease inheritance become passing part of doesn't even explain the half of it , this and many additional genes still not defined shows . Some big impact to the measurements has variants (ODD ratios around 2) identified although , most loci very less impact shows and danger assessment for separately useful Not . Atherosclerosis impact provider the most important wide widespread genetic variant, called ANRIL long of non-coding RNA expression Now atherosclerosis related to processes impact to do many long non-coding RNA and microRNAs have been identified (Pierce and Feinberg, 2020). CVD risk with related in loci candidate genes big part currently approved , mainly mice models through , and this disease about new concepts presented Many genes , but all not of the disease mechanistic the basics indicator one how many canonical to the roads correct comes (5 pictures). Atherosclerosis contribution adding properties , for example , plasma lipids , hypertension and diabetes for hundreds of genetic loci determined (Cabrera and et al ., 2019; Graham et al. et al ., 2021; Mahajan et al. et al ., 2018). Such loci most CAD loci with mutual not connected , because CAD 's impact measurements even very big also identified in research very small become remains . Atherosclerosis and other complicated in the

characteristics many mutual effects add in the style of It will be , but man in research negative mutual effects determination difficult
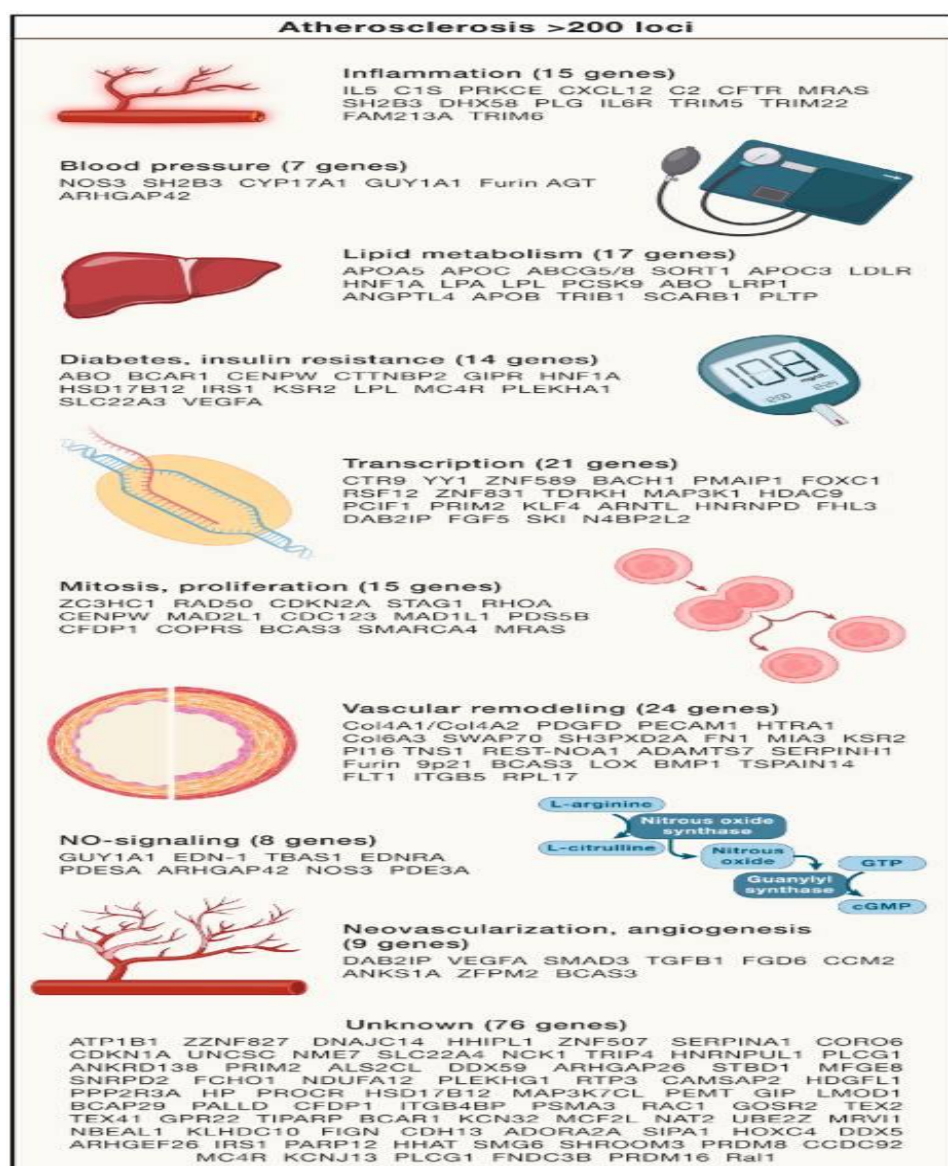

Figure 5. Atherosclerosis to the tendency contribution additive genetic factors

Heart- blood vein GWAS studies on cardiovascular diseases (CVD) one how many danger categories suitable coming candidate genes own inside received about 200 loci However , very many numerical genes still known was any to the category suitable Plasma lipid levels (Graham and et al ., 2021), hypertension (Cabrera et et al ., 2019) and diabetes (Mahajan et al. CVD risk (e.g. , 2018) factors GWAS loci on mainly to each other suitable unreachable , hundreds additional loci The picture is Erdmann and by al . (2018) customized.

WAY TO THE FUTURE

The last 5 or 10 years inside atherosclerosis understanding according to separated standing achievements event Clinical also important in the field achievements is , is a how many new treatment methods current To great achievements despite , in the future forward shift for many problems available . Many knowledge from the gaps some The following are : Lipids subendothelial in space accumulation how as inflammation increases ? Through GWAS

determined , none how causal category inside inaccessible dozens genes role What is a cell ? aging human in diseases how much Important ? Diabetes , hypertension and kidney diseases atherosclerosis how Physical activity protection doer effects how mechanisms organization How ? factors to women atherosclerosis initial from the forms protection Does it ? Answer these questions answer in finding main factor — disease related gene activity in tissues to measure opportunity giving increasingly becoming complicated going technologies it will be , this atherosclerotic in lesions one in cells open chromatin to the state until to be possible . Also , " from above " " downwards " (i.e. , systems) and " from below " " up " (i.e. , paths) approaches combine atherosclerosis one how many aspects goal did treatment methods working on the way out important will be and this methods clear medicine promises within every one the patient's to the needs customized to be Such treatment is possible . strategies to the success achieve probability , possibility , risk under was individuals early to determine related will be and invasive not been diagnostics , of course , future of research central topic will be .

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