Archives of Medical Research 48 (2017) 12–26

REVIEW ARTICLE

Atherosclerosis and Cancer; A Resemblance with Far-reaching Implications

Juana Virginia Tapia-Vieyra, Blanca Delgado-Coello, and Jaime Mas-Oliva

Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Ciudad de México, México

Received for publication January 12, 2017; accepted February 2, 2017 (ARCMED-D-17-00048).

Atherosclerosis and cancer are chronic diseases considered two of the main causes of death all over the world. Taking into account that both diseases are multifactorial, they share not only several important molecular pathways but also many ethiological and mechanistical processes from the very early stages of development up to the advanced forms in both pathologies. Factors involved in their progression comprise genetic alterations, inflammatory processes, uncontrolled cell proliferation and oxidative stress, as the most important ones. The fact that external effectors such as an infective process or a chemical insult have been proposed to initiate the transformation of cells in the artery wall and the process of atherogenesis, emphasizes many similarities with the progression of the neoplastic process in cancer. Deregulation of cell proliferation and therefore cell cycle progression, changes in the synthesis of important transcription factors as well as adhesion molecules, an alteration in the control of angiogenesis and the molecular similarities that follow chronic inflammation, are just a few of the processes that become part of the phenomena that closely correlates atherosclerosis and cancer. The aim of the present study is therefore, to provide new evidence as well as to discuss new approaches that might promote the identification of closer molecular ties between these two pathologies that would permit the recognition of atherosclerosis as a pathological process with a very close resemblance to the way a neoplastic process develops, that might eventually lead to novel ways of treatment.

Key Words: Atherosclerosis, Cancer, Inflammation, Oxidative stress, Proliferation, Angiogenesis.

Introduction

Nowadays it is well established that although industrial development has represented a substantial progress for mankind, it has also promoted a notable increase in chronic pathologies including cardiovascular disease and cancer, both considered among the top causes of morbidity and mortality around the world (1–3). In this respect, atherosclerosis and cancer considered diseases that arise from multiple factors are consolidated along different stages in their development where different factors might be related to their origin, including; genetic, nutritional, psychosocial and environmental conditions (Figure 1). Cardiovascular diseases are primarily a result of complications promoted by atherosclerosis, defined as a chronic and progressive inflammatory state caused by and immune response correlated to an uncontrolled proliferation of vascular smooth muscle cells, endothelial cells and *in situ* macrophages (4,5). As an outcome, the progression along the different stages of the disease commonly ends in a thrombotic process that might lead to myocardial infarction or stroke (6–12). Interestingly, the development of cancer as a multifactorial disease also takes place through an alteration of molecular events catalyzed by the same factors previously mentioned for atherosclerosis and where their initiation and evolution could take years to develop (13). Therefore, although these two pathologies have been in the past considered to be unrelated, by performing a thorough analysis of the molecular manifestations in both diseases, important similarities have become clear showing evidence of a tight relationship (14,15). This analysis is particularly relevant when the identification of potential targets for therapeutic use comes into play.

Address reprint requests to: Jaime Mas-Oliva, Departamento de Bioquímica y Biología Estructural, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Apartado Postal 70-243, Ciudad de México 04510, México; Phone: (+52) (55) 5622-5584; FAX: (+52) (55) 5622-5611; E-mail: jmas@ifc.unam.mx.

http://dx.doi.org/10.1016/j.arcmed.2017.03.005

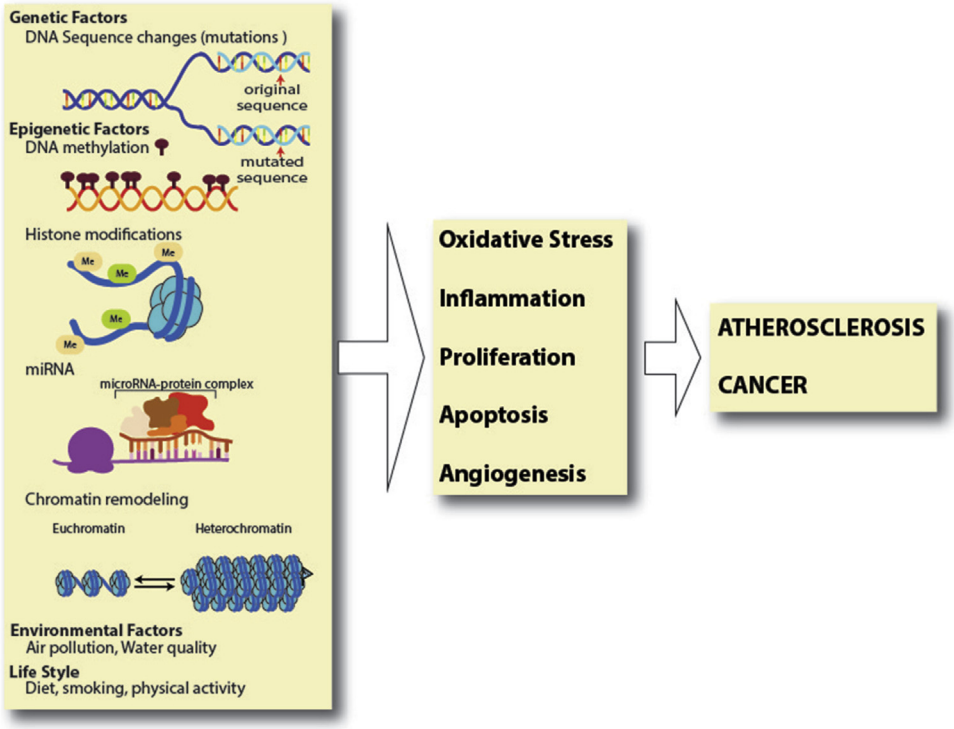

Figure 1. Factors involved in the early stages and development of atherosclerosis and cancer. Among the important similarities found in both multifactorial diseases, the identification of changes in the DNA sequence in close correlation to epigenetic modifications, can be transmitted across generations in relationship with key environmental factors. These external factors can by themselves start or potentiate anomalous processes evidenced in the long-term as oxidative stress, inflammation, aberrant apoptosis, uncontrolled cell proliferation and angiogenesis.

One of the most important characteristics in both diseases is uncontrolled cell proliferation favoring the establishment and severity of lesions in the later stages of both diseases (16,17). Deregulation of cell proliferation in many cases promoted by an oxidative stress condition, allows the development of the atherosclerotic plaque and also the establishment of different types of cancer (14,17,18). Other alterations that contribute to the development of both diseases are related to changes in cell adhesion molecules, an altered expression of proteases linked not only to the formation of plaque but also to tumor invasion, metastasis initiation (15) and the modulation of angiogenesis, an important process in both pathologies directly related to the expansion of the atherosclerotic plaque and tumor formation (17).

Inflammation

The process of inflammation is recognized as the initial response by cells to harmful stimuli and induced by the migration of leukocytes from the blood to a damaged tissue. The stimulus triggers a cascade of biochemical events that are propagated and enforce the inflammation response involving the local microvascular system, including the immune system, the connective tissue and parenchymal cells within the microenvironment of a damaged tissue (19–21). The inflammatory process during atherogenesis is mediated by monocyte migration to the vessel wall, a key event in the growth of an atherosclerotic lesion. Through differentiation, monocytes establish themselves as macrophages and eventually as lipid-rich foam cells (22,23). Macrophages derived from monocytes recognize and internalize oxidized lipoproteins via scavenger receptors where lipid-rich foam cells contribute to the development of the necrotic nucleus, a key element of the vulnerable atherosclerotic plaque. At a molecular level, the presence of cholesterol crystals also activates the inflammasome releasing IL-1β cytokines considered important mediators of inflammation (24–27) (Table 1) (Figure 2). On the other hand, monocyte-derived macrophages often found as host cells in tumors, operate as components of an inflammatory response that builds a supporting stroma (49) that takes part in tumor growth (27,50,51). These processes carried out by activated neutrophils, monocytes, endothelial cells and macrophages provide the pro-inflammatory response of damaged tissues (20,27,52).

In cancer, inflammation is manifested by tissue infiltration of inflammatory cells that include macrophages, B and T lymphocytes, natural killer cells, neutrophils, and

Table 1. Agents and inflammatory factors involved in atherosclerosis and/or cancer progression

Agents	Effects	Disease	Reference
Statins	Endothelial cells: decrease expression of VCAM-1, arrest and uptake of circulant monocytes. Inhibition of growth of macrophages and their metalloproteinase activity	Atherosclerosis	(28–31)
Antioxidants	Decrease of lipoproteins oxidation	Atherosclerosis	(32–34)
Phospholipase A2	Modifies phospholipids of oxLDLs. Increase of oxLDLs and production of non-esterified or oxidized fatty acids and lisophosphatidylcholine	Atherosclerosis	(35–37)
Leukotrienes pathway	Synthesis of eicosanoids with inflammatory effects	Atherosclerosis	(32,38,39)
Ciclooxigenase	Expression of COX1 (all tissues) and COX2 (induced in sites of inflammation) in atherosclerotic lesions	Atherosclerosis	(40–42)
Cytokines produced by inflammatory immune cells	Increase of transcriptional activity of NF-Kβ, STAT 3, and AP1	Cancer	(43–45)
TNF-α	Promotes DNA damage through oxidative stress. Induces the secretion of VEGF by human fibroblasts, promoting angiogenesis	Cancer/atherosclerosis	(46–48)
IL-6	Promotes proliferation and apoptosis, induces oxidative stress	Cancer/atherosclerosis	(46)
TGF-β	Promotes tumoral growth	Cancer	(46)

VCAM-1, molecule 1 of vascular cellular adhesion; VEGF, vascular endothelial growth factor.

granulocytes (53). Macrophages and T cells are the predominant inflammatory cells since they are responsible for the secretion into the microenvironment of large amounts of inflammatory cytokines, proangiogenic factors and reactive oxygen species (ROS) (20).

Moreover, oncogenic changes initiated through the induction of several inflammatory pathways mediated by cytokines and prostaglandins have been found (54,55). Tissue infiltration of monocytes has been reported not only to promote tumorigenesis by inhibiting specific protective immune responses, but in several cases also activating the exactly opposite effect, meaning activating an antitumor response (56). In accordance to this phenomenon, parallel events take place when a cascade of biochemical events, on the one hand consolidate the inflammatory response, and on the other, trigger what can be considered a series of recovery mechanisms (57). For instance, the proangiogenic vascular endothelial growth factor (VEGF) is overexpressed with the concomitant development of new blood vessels that tend to improve an adequate supply of oxygen and nutrients, necessary for tissue repair and regeneration (20). The release of several other growth factors warranty an optimal cell cycle function and therefore the development of cell proliferation (27).

When the beneficial effects of an initial inflammatory response are not terminated on time, becomes a chronic process with deleterious effects both in atherosclerosis and cancer. For instance, a downregulation of pro-inflammatory molecules such as leukotrienes appears in parallel to an upregulation of anti-inflammatory molecules such as tumor necrosis factor (TNF) and interleukin 1 receptor antagonist (58). Also it has been observed that during this transition, a release of transforming growth factor beta (TGFβ) from macrophages takes place (59). Although several pro-resolving mediators such as the ones mentioned before share several activation mechanisms in both diseases, the full understanding of the final mechanisms that prevent the establishment of a chronic situation and therefore tissue damage still requires thorough investigation (57).

Oxidative Stress

Oxidative stress that occurs as a result of an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in association with a failure of the antioxidant systems responsible for their neutralization, promotes the development of inflammatory processes in different tissues and therefore relevant in the development of both atherosclerosis and cancer (60). Antioxidant molecules such as vitamins, coenzyme Q10, glutathione or phenols all take part in these defense systems along with antioxidant enzymatic systems such as glutathione peroxidase, catalase and mitochondrial superoxide dismutase (SOD) among others. While a high plasma ROS concentration has been observed in late-stage cancer patients, the levels of antioxidant systems such as glutathione peroxidase and SOD are diminished (61,62). Nevertheless, given that oxidative damage is accumulated over the life cycle of cells, it has been associated to the origin of both diseases (63,64).

ROS are oxygen-derived metabolites of endogenous and/or exogenous origin, characterized for being partially reduced and considered electron acceptors, characteristic that interferes with the structure and/or function of macromolecules (65,66). The main endogenous source of ROS is

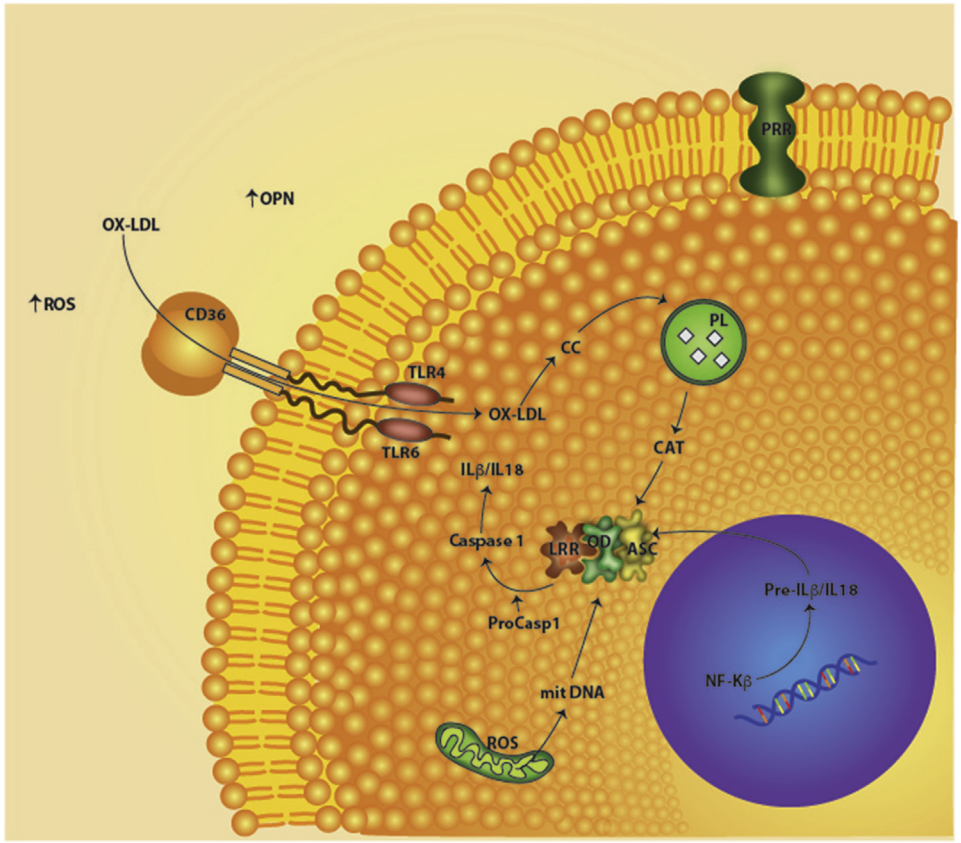

Figure 2. Mechanisms involved in the activation of the inflammasome in atherosclerosis and cancer. In the case of atherome formation, a tissue environment associated to high oxidative stress conditions rich in reactive oxygen species (ROS), osteopontin (OPN), circulating oxLDLs and high cholesterol levels, promote further oxidization of LDLs and accumulation of cholesterol crystals (CC) for instance in vascular endothelial cells. This environment also contributes to the activation of the inflammasome when receptors such as the B-type scavenger receptor CD36 associated to oxLDL results in the formation of the signaling complex CD36-TLR4-TLR6. CD36 also allows the internalization of oxLDL and prompts the accumulation of CC inside cells. These crystals are uptaken by phagolysosomes (PL) that in turn induce the synthesis of cathepsins (CAT) and the activation of the multimeric protein complex LRR/OD/ASC (inflammasome NLRP3). When the mechanisms that control autophagy fail, the accumulation of ROS in the mitochondria allows the release of DNA to the cytoplasm contributing also to the activation of inflammasome NLRP3. Pro-caspase-1 is recruited by a specific domain in the inflammasome (caspase recruitment domain, CARD) in the ASC component, to express the active enzyme that in turn promotes the activation of interleukines such as IL/β IL-18. Inside the nucleus, basal levels of NF-κβ increase, controlling the expression of pre-IL-β and several genes associated to processes involved in proliferation and therefore with the progress of diseases such as atherosclerosis and cancer. Other signals like an increase in the levels of intracellular calcium can also be involved in the activation of the inflammasome. This type of mechanism can also be sensed and triggered by a group of receptors generically known as pattern-recognizing-receptors or PRR that recognize molecular patterns associated to immunological responses to pathogens (PAMPs) or damage associated molecular patterns (DAMPS). NBD/LRR/ASC: nucleotide-binding domain/Leu-rich-repeat/apoptosis-associated speck-like protein containing caspase recruitment domain (CARD) and N-terminal pyrin-domain (PYD).

the mitochondrial respiratory chain, associated with enzymatic reactions catalyzed by the NADH/NADPH oxidase, xanthine oxidase and nitric oxide synthase (67,68). When leukocyte chemotaxis takes place during the early formation of an atherosclerotic lesion, xanthine oxidase and nitric oxide synthase also contribute to the damage of smooth muscle and endothelial cells in the vascular wall (63,69).

ROS production has been also linked to other cardiovascular risk factors such as hyperlipidemia, hypertension and smoking (70). Oxidative stress associated to endothelial dysfunction, local inflammation, tissue remodeling, plaque formation and smooth muscle growth (71), has also been related to the production of mitogens and growth factors that may stimulate cell proliferation in early atheromatous lesion sites (72−74). In this context, from the transcriptomic point of view, our group has shown that human vascular smooth muscle cells (hVSMC) exposed for a short incubation time with chemically oxidized LDLs (oxLDL) present a very much similar molecular response as cells exposed to normal non-treated LDL particles for long periods of incubation (75). In the long-term, the exposure of these cells to oxLDL promotes among other proteins, the overexpression of osteopontin, a versatile protein related not only to oxidative stress, but also to vascular calcification (76). Since osteopontin corresponds to a glycoprotein secreted by activated macrophages at sites of inflammation interacting

with a series of cell surface receptors, such as several integrins and CD44 stimulating cell adhesion and migration, its participation in cancer and the process of metastasis has been also found.

On the other hand, oxidative stress in cancer has been tightly related to DNA instability and hyper-methylation as well as DNA mutation repair genes, loss of heterozygosity and point mutations of DNA microsatellites (18,64,77). It is tightly associated with the deregulation and shortening of the cell cycle and reduces the opportunity for cells to repair DNA mutations before the transition from phase G1 to S takes place. Consequently, oxidative stress considered an effector of several genetic mutations that antagonizes the correction to a normal status of affected cells, is recognized as a contributing factor in the development of atherosclerosis and cancer.

Uncontrolled Proliferation

Cell division and programmed cell death are two of the predominant physiological processes regulating tissue homeostasis, where deregulation of one of them provokes the development of several diseases including cancer and atherosclerosis. The cell cycle as the main process that controls cell proliferation (78) involves numerous endogenous factors that interfere positively or negatively with its progression directed and coordinated in time by the synthesis, activation, inhibition and degradation of several regulatory proteins such as cyclins and cyclin-dependent kinases (CDKs) (79,80).

On the other hand, clonal proliferation of endothelial, smooth muscle cells and macrophages, promote the development of the atherosclerotic plaque and in several tissues stimulate the development of several types of cancer (81,82). Concurrently, the cell cycle studied in different types of cancer cells has shown deregulation in several control points as the G1-S transition, one of the main causes of accelerated cell growth and accumulated mutations. Since clonal expansion within the malignant cell population is fundamental for primary tumor growth and the subsequent cell invasion of other tissues, several authors have also considered DNA instability and cell cycle deregulation related to clonal expansion to be also important in the development of atherosclerosis.

Angiogenesis

The process of angiogenesis has been described as a group of biochemical events involved in the development of new vessels in a determined tissue where many genes and their products related to both pro and antiangiogenic effects coexist in a very fine equilibrium. Since the formation of micro-vessels in an atherosclerotic lesion contributes to the development of plaque, the formation of micro-vessels stimulated by hypoxia, the hypoxia-inducible factor (HIF) and the presence of ROS have been thoroughly investigated in atherogenesis (83). It has been reported that these intra-plaque micro-vessels represent an entry point for molecules and cell components such as erythrocytes, inflammatory cells and lipoproteins (84). These micro-vessels named *vasa vasorum* considered important in the tunica adventitia, supply oxygen and nutrients at the same time of draining waste products from the vessel wall (83).

The process of angiogenesis presents both beneficial and detrimental effects in atherosclerosis. For instance, an increased angiogenesis can be a favorable sign in the recovery of an ischemic tissue in events like myocardial infarction or lower limb necrosis (85). Considering that the progression of the primary atherosclerotic lesion requires angiogenesis, it is known that the expansion of plaque and its risk complications such as rupture or vascular thrombosis depends on this mechanism (86,87). On the other hand, tumor vascular development is also important for proliferation in processes such as metastatic expansion since cancer cells depend on an adequate supply of oxygen and nutrients for this phenomenon to occur, where new blood and lymphatic vessels are formed through angiogenesis and lymphangiogenesis (88). Angiogenesis is regulated by a variety of activating and inhibiting regulatory molecules (Table 2) where, for example, the presence of an angiogenic factor might reflect the aggressiveness of tumor cells (92) and normally considered as a variable for a negative prediction, such as in the case of breast and prostate cancer (93).

MicroRNAs in Atherosclerosis and Cancer

MicroRNAs (miRNAs) are a class of highly conserved, non-coding small RNAs that regulate gene expression on the post-transcriptional level by inhibiting the translation of proteins or by promoting the degradation of mRNA (94). Following a process of gene repression, miRNAs bind to complementary sequences in the non-translated 3' region (3′UTRs) of target mRNAs avoiding translation (95). MiRNAs have been detected in human plasma where they are protected from endogenous RNase activity due to their location in microvesicles and their association with plasma components such as protein/lipoprotein miRNA complexes (96). They play an important role in gene regulation by acting as repressors or activators, since a single miRNA may have various genes as targets and several miRNAs may share the same target (97). Another regulating pathway in the expression of miRNAs, corresponds to the level present for several processing components, such as ribonuclease III (RNase III), DROSHA, and DICER 1 (98). In this sense, low levels of these components have been found in several types of cancer, including those associated to the lung, ovary and brain (98). In atherosclerosis and cancer, the presence and regulation of several miRNAs has been also associated to the control of cell proliferation, differentiation and genomic stability among other functions

Table 2. Regulators of angiogenesis

Activators	Inhibitors	Reference
Growth factors: VEGF, FGF, angiogenine, angiostatin, TGF, TNFα, PDGF, HGF, EFG, PGF, GCSF		(89)
Cytokines: IL-1, IL-6, IL-8	IL-10, IL-12	(90)
Proteases and inhibitors of proteases: cathepsine, gelatinases A and B, stromelysin, uPA	Metalloprotease inhibitor, plasminogen activator inhibitor-1	(91)
Copper	Zinc	(90)
Oncogenes: c-myc, ras, c-src, v-raf, c-jun	p53, Rb	(90)
Modulators: integrins α5 and β3, angiopoietin-1	Angiopoietin, angiotensine	(89)
Angiostatine II (receptor ATI)	Angiostatine II (receptor ATII)	(89)
Endothelin	Caveolins 1 and 2	(89)
Erythropoietin	Endostatin	(89)
Hypoxia	Interferon α	(89)
Nitric oxide synthase	Isoflavones	(89)
Factor 4 of platelets activation		(89)
Prostaglandin E		(89)
Prolactin (16 kD fragment)		(89)

EFG, epidermal growth factor; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; GCSF, stimulation factor of granulocytes; PDGF, platelet-derived growth factor; PGF, placental growth factor; TGF, transformant growth factor; TNFα, tumor necrosis factor α; uPA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor.

(Table 3). Since miRNAs have been found to regulate the development of atherosclerosis and cancer, it becomes of importance to investigate if similar therapeutic strategies involving miRNAs could apply to both diseases.

Apoptosis

Apoptosis, first described by Kerr et al. in 1972, is characterized by morphological and molecular changes in cells including cell shrinking, membrane vesicle formation and loss of adhesion to neighboring cells (114,115). Biochemical changes include fragmentation of chromosomal DNA into internucleosomal fragments, externalization of phosphatidylserine and associated high proteolytic activity promoted through two induction pathways: a death receptor extrinsic pathway and a mitochondrial pathway (116). The extrinsic or death receptor pathway is triggered by binding of Fas plasma membrane death receptor and other similar receptors such as the tumor necrosis factor receptor 1 (TNFR1), to its extracellular ligand Fas-L. When the death stimulus appears, Fas-L is combined with Fas to form a death complex Fas/Fas-L which in turn recruits the protein FADD containing a death domain and procaspase-8 (114). On the other hand, the intrinsic pathway promotes apoptosis through the modulation of mitochondrial proenzymes. In this case, the mitochondria become permeable to cytochrome c, which is released into the cytosol. In turn, cytochrome c recruits Apaf-1 and procaspase-9 to compose the apoptosome, which activates the caspase-9/caspase-3 signaling pathway culminating in apoptosis (117). It has been reported that an alteration of the mechanisms that control apoptosis, plays an important role in the development of atherosclerosis and cancer (118).

The process of apoptosis considered a self-regulating event in the life of a cell (119), has been identified as a determining factor in the regression or progression of atherosclerosis (2). This is mainly due to the fact that apoptosis intervenes in the stability of the plaque, controlling the regression of the disease in the early stages of progression (120). On the other hand, apoptosis has been

Table 3. MicroRNAs as regulators of atherosclerosis and/or cancer

microRNAs	Function	Associated disease	Reference
Let7-f, miR-27b and miR-130a	Proangiogenic	Cancer and atherosclerosis	(99−101)
miR-221, miR-222	Inhibition of cellular migration, endothelial proliferation, and angiogenesis	Cancer and atherosclerosis	(94,102,103)
miR-17-92 cluster (miR-17, miR-18a, miR-19a, miR-20a, miR-19b); miR-92a, miR-378	Tumoral angiogenesis	Cancer	(104−108)
miR-155, miR-21, miR-126	Vascular inflammation	Cancer	(94,109,110)
miR-21	Interaction in transductional pathways	Several types of cancer, CVD, e.g. atherosclerosis	(111−113)

CVD, cardiovascular disease.

recognized as an important player in cancer development, since it functions as a molecular tool that cells employ to avoid proliferation of damaged cells. When the process is altered, cells tend to proliferate promoting tumor growth and the subsequent mechanisms that cause a malignant phenotype (121).

Research performed on apoptosis employing macrophages during the early and late stages of atherosclerosis has been carried out using various models with genetically manipulated mice (2). Bone marrow reconstitution in mice lacking pro-apoptotic proteins reduced macrophage apoptosis and increased the size of aortic lesions (122). Another study investigating LDLR-knockout mice has shown the inactivation of an apoptosis inhibitor expressed by macrophages (Spα/Api6), increasing macrophage apoptosis and therefore inhibiting atherosclerosis (123). Moreover, an investigation studying rabbits with proven hypercholesterolemia, the nitric oxide precursor L-arginine when administered in the intima layer of a vessel, macrophage apoptosis was induced causing the reversion of pre-established atherosclerotic lesions (124). Several studies have also revealed that an excessive accumulation of modified LDLs in cells is capable of provoking endoplasmic reticulum stress and macrophage apoptosis, deregulating Ca^{2+} homeostasis and activating the mitochondrial apoptotic pathway (125). At this stage, it is interesting to mention that palmitic acid upregulates oxidized-LDL receptor 1 and enhances its uptake in macrophages (Figure 2) (125). Recent studies have also demonstrated that serum amyloid A (SAA) may participate in the pathogenesis of atherosclerosis, initiating apoptosis and inflammation through the activation of NF-kβ (120). In addition, it is worth mentioning that oxysterols as cholesterol metabolites that promote inflammatory and apoptotic mechanisms, are also considered contributing factors in the development of atherosclerosis (126).

Several reports describe alternative splicing mechanisms as possible tools to regulate apoptotic events in both atherosclerosis and cancer (127,128). These processes can be regulated by competition between spliceosomes, splicing sites and splicing factors (127,129,130). Numerous apoptotic factor genes including NF-kβ and Bcl-2 suffer alternative splicing mechanisms, originating the production of several protein isoforms that in some cases present antagonistic functions; for example, they can function as pro-apoptotic or anti-apoptotic molecules (127). Another example is represented by caspases that correspond to apoptosis effectors present in the cell as inactive procaspases, that under specific apoptotic stimuli become activated. Caspase-encoding RNAs may suffer alternative splicing and produce different isoforms, including the three isoforms of procaspase-2 (131). In this sense, our group isolated the cDNA encoding the protein named apoptosis regulating protein 2 (ARP2) from androgen-independent prostate cancer cells (LNCaP) (132). We demonstrated that the channel forming protein ARP2 promotes apoptosis in LNCaP cells as well as in epithelial cells of the Chinese hamster ovary (CHO), provoking a sustained increased flux of Ca^{2+} across the membrane (132,133). Since by the time we suggested that ARP2 might be potentially forming part of splicing factor Prp8 which has been recently related with the androgen receptor (134), it is possible that ARP2 developing apoptosis could modulate the function of this receptor during cancer development. In support of this possibility, it is known that several splicing factors such as factor SNW1 that make up the spliceosome have been linked to the development of breast cancer (135). Therefore, deregulation of the apoptotic phenomena has been proposed to be an important point to take into consideration in both atherosclerosis and several types of cancer (136). Nowadays, our group is actively studying the possibility that ARP2 might be also participating in the development of apoptosis in cells that form part of the blood vessel, and therefore taking part in the process of atherogenesis.

Calcium Homeostasis

Calcium signals are determined by the coordinated activities of calcium channels, exchangers, pumps and binding proteins that all together are capable of guiding the destination of calcium in the cell and therefore control calcium homeostasis not only in normal cells but also during a pathological process such as cancer or atherosclerosis. The most frequent type of alteration in the homeostasis of calcium is generally evidenced as an increase in the intracellular concentration of this cation, where the epigenetic regulation of gene expression has been associated to Ca^{2+} fluctuations that participate in carcinogenesis as well as atherosclerosis development (137,138). Also, the process of shear stress has been shown to be important during the formation of an atheroma when molecules embedded in the plasma membrane of cells such as the transient receptor potential channels (TRP) sense a change (139). These channels allow calcium entry in the cell and activate multiple receptors and signaling cascades that communicate with the cytoskeleton responsible for maintaining cell structure. Several TRP channels also take part in phagocytic activities (139) relevant to various types of cancer; including prostate, breast, and lung cancer (140,141).

Another regulatory system important in the control of the intracellular Ca^{2+} concentration is the calcium pump supported by a Ca^{2+}-ATPase activity found in the sarco/endoplasmic reticulum (SERCA) and the plasma membrane of cells (PMCA). These systems present the differential expression of several isoforms depending on the type of cancer (142–144) and in the case of SERCA, different isoforms have been shown to play an important role in the control of cytosolic calcium in atherogenesis (145).

Additionally, the calcium-sensing receptor (CaSR), whose activity is linked to G proteins, has been found to

participate in disease processes, including cancer and atherosclerosis (146). In some types of hypercalcemic cancers (prostate and breast), CaSR activation promotes the progress of the disease through the action of the parathyroid hormone-related peptide (PTH-rP), which in turn, induces osteolysis and the subsequent release of bone growth-promoting factors (147). In atherosclerosis, under-expression or complete loss of CaSR associated to vascular smooth muscle cells (VSMC) has been reported in response to vascular calcification (148).

A relevant clinical correlation reported recently establishes that a multiethnic population in remission of several types of cancer (breast, lymphoma, and testicle) shows a higher risk of suffering from events related to coronary atherosclerosis (myocardial infarction, coronary diseases, and angina) (149). Nevertheless, since this correlation was established while tracking coronary artery calcium concentration (CAC) considered a subclinical marker for atherosclerosis, this type of associations has been difficult to be established.

Epigenetics

Epigenetic changes are DNA modifications that affect gene expression and their function without altering the sequence for DNA (150). Epigenetic modifications have been associated to DNA methylation, acetylation and phosphorylation, as well as chromatin remodeling and gene expression mechanisms controlled by small non-encoding miRNAs and long chain RNAs (151−153). Since chromatin remodeling is an important process in the regulation of embryonic cell development, cell differentiation and organogenesis (154,155), the modification patterns for DNA methylation have been associated to inflammation, autoimmune disease, cardiovascular disease and cancer (156−158).

Although the main epigenetic change in mammals is considered to be DNA methylation and specifically the modification of histones (159), mechanisms that involve miRNAs and long chain RNAs in the regulation of gene expression have been also included within the epigenetic changes that could influence the development of disease (160). DNA methylation involves the addition of a methyl group at the site of C5 cytosine residues within the CpG di-nucleotide, where only a fraction of cytosines are physiologically methylated in the mammal genome (161,162). S-adenosylmethionine (SAM) acts as a methyl donor in the methylation reaction, which is catalyzed by the DNA methyltransferase (DNMT). This DNA methylation reaction is catalyzed by at least 3 DNMT's that add methyl groups into the C5 cytosine ring to form 5-methylcytosine (151). During the S phase, DNMT's found in the replication fork, copy the methylation pattern of the parent strand on the daughter strand and creates heritable patterns that can be copied over many cycles of cell division (151).

Cytosine methylation changes the structure of the major groove of DNA and interrupts the adhesion of DNA binding proteins and transcription factors. In general, methylated genes at specific sites (for example, upstream of the promoter region) are not transcribed to mRNA or are transcribed at a smaller scale, consequently, translation is also decreased (163).

There are two levels of methylation present in tumors: hypo and hyper-methylation. In hypo-methylation, DNA of malignant and benign tumors show decreased levels of methylation when compared to adjacent normal tissues. This mechanism that is associated with an increased transcription and proto-oncogene expression, stimulates malignant cell growth, and in addition, can precede mutation and deletion events. Hyper-methylation is associated with gene silencing and in the case of cytosine, occurs in the promoter region of tumor suppressor genes, such as DNA repair genes or genes that negatively control cell proliferation. It has been reported that hyper-methylation events are already evident in several inflammatory lesions that might predispose precancerous stages as well as being present in benign tumors (164).

Epigenetic processes such as DNA methylation have been also described in atherosclerosis, where hypo-methylation has been detected in early stages of the disease (165). In human atherosclerosis, hypo-methylation of genes that code for the estrogen α and β receptors (ESR1 and ESR2) in smooth vascular cells is considered an atheroprotective event (166,167). In cultured aorta and coronary artery segments with different degrees of atherosclerosis, it has been shown that methylation of the gene that codes for the monocarboxylic transporter (MCT3) suppresses transcription and allows smooth muscle cell proliferation (168).

It has been also shown in the human, that prenatal exposure to tobacco alters the methylation patterns of specific genes associated to premature cardiovascular disease (160). Methylation of the Alu-Yb8 repetitive element has been shown to be associated to the exposure of tobacco during prenatal stages of development, closely related to the effect observed upon methylation of LINE1 that depends on the absence of the glutathione S-transferase P (GSTP1) detoxifying enzyme (169). Variations in the level of these detoxifying genes may modulate the effects of exposure *in utero* through epigenetic mechanisms (160). DNA methylation that occurs in the endothelial cell plays a critical role in directing the expression patterns of numerous genes, such as the one that codes for the nitric oxide synthase 3 (NOS3) (170).

Newman et al. (1999) suggested that abnormal DNA methylation of the vascular cell may contribute to atherogenesis (171), where an increased level of homocysteine inhibits the synthesis of SAM promoting global vasculature hypo-methylation (172). Other results have shown that the homozygous knockout for the methylen-tetrahydrofolate

reductase (MTHFR), a gene that codes for an essential enzyme required for SAM generation, may result in hypo-methylation of aorta cells (173).

Cardiac hypertrophy (CH), which has been associated with histone acetylation, involves histone acetyl transferases (HATs) and histone deacetylases (HDACs). Since HAT activity appears to have a positive effect on CH, therefore the overexpression of transcriptional coactivators of HAT such as the CREB-binding protein (CBP) and p300 produce hypertrophy in cardiomyocytes. On the other hand, the overexpression of a mutated CBP and HAT lacking p300 does not produce this hypertrophy (174). While in neonate cardiomyocytes HDAC activity has been reported in pro and anti-hypertrophic pathways, the overexpression of miR-23a, miR-23b, miR-24, miR-195, and miR-214 induce CH, whereas overexpression of miR-133 inhibits the phenotype (175,176).

Therapeutic Considerations

Nowadays, atherosclerosis is considered a chronic inflammatory disease related to an abnormal stimulus to the endothelium mostly given by conditions such as dyslipidemia, hypertension, diabetes, and obesity. These conditions have also been considered as predisposing risk factors for cancer development. Therefore, the elevated presence of pro-inflammatory-systemic molecules, such as interleukins (e.g., IL-6), C reactive protein (CRP) and TNF-α (177−180) have been associated with both, cardiovascular disease and the presence of several malignancies, especially of the epithelial type (e.g., prostate, colon, ovary, lung) (181,182).

In general, there seems to be an inverse association between atherosclerosis and cancer closely related to the type of cancer and the type of chemotherapy employed. For instance, tumors treated with oxazaphosphorines and pyrimidine antagonists have been associated with a lower incidence and presence of atherosclerotic lesions (183).

As in atherosclerosis, the presence of pro-inflammatory agents affects the behavior of different components of a tumor cell and the interactions that might occur between them. In fact, many of the active signaling cascades present in the endothelial tissue affected by atherosclerosis are present in an exacerbated way in cancer. Such cascades allow the counteraction of molecules that normally induce apoptosis and suppress the ability to inhibit the recognition by the immune system; therefore, leading to the acquisition of resistance, uncontrolled proliferation and metabolic adaptation (184). For years now, although there is evidence linking inflammation and chronic infection with the process of atherogenesis (185,186) both experimental and epidemiological evidence closely correlate these processes to the genesis of several epithelial cancers with associated risk factors such as smoking and dyslipidemia (178).

Changes in the concentration of free cholesterol in the plasma membrane of cells affecting the formation of lipid rafts and caveolae can be directly correlated to the function of key receptors, such as the epidermal growth factor receptor (EGFR), members of the TNF receptor family and also the TRAIL receptor that correlates well in both atherogenesis and cancer development (187). In many cases, depletion of membrane cholesterol induced by the action of statins inhibiting the HMG-CoA reductase would disturb the formation of microdomains, such as membrane lipid rafts and caveolae, affecting the functionality and localization of receptors (188). This situation has been correlated to the therapeutic response as well as prognosis of several types of cancer (189−191).

In this respect, many studies supporting the effect of statins upon atherosclerosis are based on the effect they exert on the synthesis pathway of cholesterol and specifically on the activity of the enzyme HMG-CoA reductase (188,192,193). Related to this finding, there is evidence suggesting that in certain types of cancer, statins may affect the metastatic capability and invasiveness of tumors (194−196). At this stage it is interesting to mention that combined immunotherapies employing gefitinib or trastuzumab or chemotherapies employing cisplatin or doxorubicin, when combined with the use of statins, can yield a greater therapeutic response in gastrointestinal and lung cancers (197−199). The synergistic induction of cytotoxicity employing immune- or chemo-therapy in conjunction with statins has shown an improved survival rate in patients with ovarian cancer receiving only statins as a way to prevent a negative cardiovascular event (188,200).

It seems that the sensitization outcome of the combined treatment in the presence of statins might have changed the correlation structure/function of receptors located in the plasma membrane of the tumor cell, affecting ion transport and the binding and movement of drugs in and out the cell. On the other hand, although there seems to be no conclusive experimental evidence to support an increased risk of developing cancer among patients being treated with statins (201), epidemiological data shows that a prolonged use of statins may increase the incidence of specific types of cancer, such as hepatocellular carcinoma and thyroid cancer. Moreover, novel therapeutic approaches of statins, independent of the clear effect they exert upon the HMG-CoA reductase, they influence heme oxygenase 1 (HO-1) and HO-1-related signaling pathways, i.e., activator protein (AP)-1, protein kinase G (PKG), extracellular matrix-regulated kinase (ERK), p38 MAPK, and NFκβ in vascular epithelia (202).

In this respect, our laboratory has reported that changes in the concentration of cholesterol in the plasma membrane of different cell types can be directly correlated to the activity of ion channels and transporters, most probably by changing the equilibrium found in the amount of cholesterol bound to membrane proteins and, therefore, promoting

subtle changes in protein structure that affect their function (203,204). More specifically, for the first time 30 years ago, we proposed the thesis that cell calcium extrusion systems such as the calcium pump and associated (Ca^{2+}, Mg^{2+})-ATPase activity from cardiac muscle sarcolemma while being surrounded in the plasma membrane by free cholesterol, effectively modulates its activity. It was shown that the association of the enzyme with high levels of cholesterol decreases its activity and the intracellular calcium concentration starts to increase giving rise to a pathological molecular condition that, in turn, predisposes cells to die or to acquire a neoplastic phenotype (205). In this sense, two members of the so-called calcium antagonist family, felodipine and nefedipine, which interfere with the entrance of calcium to the cell, have been reported to reduce atherosclerosis (206,207).

An interesting work investigating the development of atherosclerosis in high-cholesterol-diet experiments, ApoE knockout mice showed that felodipine as a calcium-channel blocker retards atherogenesis showing a marked increase in the expression of NADPH oxidase subunits (p47phox and Rac-1), nuclear factor-κβ (NFκβ), phospho-inhibitors of κβ (p-Iκβ), tumor necrosis-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and vascular cell-adhesion molecule-1 (VCAM-1) (208).

Another interesting correlation has been described between the concentration of pro-inflammatory molecules and high levels of leptin in obese patients. In this case, the presence of increased concentrations of leptin would favor an amplification of the signal given by transmembrane receptors such as OBR receptors and several members of the AGFR family. This correlation has been observed in the most aggressive forms of epithelial cancers such as prostate cancer (209). Leptin, a peptide hormone secreted by adipocytes that presents a ubiquitous distribution (209) potentiates the secretion of IL-2 and IL-6, TNF-α, stimulates the expression of monocyte chemoattractant protein-1 and promotes the accumulation of reactive oxygen species (210,211). Leptin induces mitochondrial superoxide production and monocyte chemoattractant protein-1 expression in aortic endothelial cells by increasing fatty acids oxidation via protein kinase A (212). Moreover, leptin has been observed to contribute to the process of atherogenesis and used as a predictive value for the development of cardiovascular events independent of the classical and well-known risk factors for atherosclerosis (212). Although the molecular mechanisms that correlate obesity with cancer development and atherogenesis are not clearly elucidated yet, it has been reported that weight loss results in a lower rate of appearance of both atherosclerosis and cancer (213). On the other hand, since adipose tissue macrophages and the way they are activated is very much related to the activation of macrophages in a tumor, much in a similar fashion to what occurs in an atherosclerotic plaque, targeting macrophages might constitute an efficacious way to regulate common anomalous signaling cascades and the key pro-inflammatory state (214). It has been also interesting to recognize that several therapies potentially useful to treat both atherosclerosis and cancer have been focused on platelet function inhibition given their multifactorial character (multitarget antiplatelet therapies) (215). New approaches for the treatment of inflammation in atherosclerosis and cancer have involved the use of nanomaterials as vehicles to carry different molecules (for example, siRNAs or miRNAs) employing different cell types as targets, where miRNA-155 has proven to be relevant from a clinical point of view in both diseases (216).

As recently tested in the treatment of several types of cancer, the development of vaccines employing a series of protein and peptide targets has proven to be a promising possibility to attack the disease and control its progression (217). In this respect, our group has developed a vaccine of nasal application against the development of atherosclerosis that involves the use of micelle nanoparticles containing the carboxy-end segment of the cholesterol-ester transfer protein (CETP), proven to be effective in preclinical studies to control the disease and now entering its clinical stages (218,219).

Since cells become malignant when a myriad of signals are triggered to prevent the immune system to function properly, one of the goals of immune therapies in cancer treatment has been to find a way capable of blocking these signals facilitating an adequate immune response and therefore the consequent prevention of malignancy development. A CD47-monoclonal antibody has been used in animal models, apparently not only effective against the development of cancer, but also to treat atherosclerosis (220). Apparently, when cells approach their death, the CD47 protein gradually begins to disappear from their surfaces. At this time, cells of the immune system responsible for their phagocytosis become activated. It appears tumor cells have developed a way to maintain or overexpress CD47, avoiding the attack by cells of the immune system. Therefore, the effect found upon the development of atherosclerosis could be also related to the maintenance or overexpression of CD47 in the plasma membrane of macrophages (220).

This type of potential therapeutic strategies shared by both atherosclerosis and cancer, although still difficult nowadays to support a general common pathway for treatment, recent advances in the understanding at the molecular level of both diseases, undoubtedly leads to the fact that in the near future atherogenesis and cancer development will be cataloged as related diseases.

Acknowledgments

Studies by J.M.-O. research group described in this review were supported by CONACyT (Grants 180726 and 255778) and DGAPA-UNAM (Grant IN-205814-3). The authors thank Jorge Bravo-Martínez for helpful discussions and graphic art support.

References

1. Li JJ, Gao RL. Should atherosclerosis be considered a cancer of the vascular wall? Med Hypotheses 2005;64:694–698.
2. Andrés V, Pello OM, Silvestre-Roig C. Macrophage proliferation and apoptosis in atherosclerosis. Curr Opin Lipidol 2012;23:429–438.
3. Ramos KS, Partdrige CR. Atherosclerosis and cancer flip sides of the neoplastic response in mammalian cells? Cardiovasc Toxicol 2005;5: 245–255.
4. Cuéllar RA, Nuche ML. Aterosclerosis y lesión endotelial: ¿proceso irreversible? Med Int Mex 2010;26:590–596.
5. Ouimet M. Autophagy in obesity and atherosclerosis: Interrelationships between cholesterol homeostasis, lipoprotein metabolism and autophagy in macrophages and other systems. Biochim Biophys Acta 2013;1831:1124–1133.
6. Sarrazy V, Sore S, Viaud M, et al. Maintenance of macrophage redox status by ChREBP limits inflammation and apoptosis and protects against advanced atherosclerotic lesion formation. Cell Rep 2015; 13:132–144.
7. Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. Cell 2011;145:341–355.
8. Zernecke A, Weber C. Chemokines in atherosclerosis: proceedings resumed. Arterioscler Thromb Vasc Biol 2014;34:742–750.
9. Randolph GJ. Mechanisms that regulate macrophage burden in atherosclerosis. Circ Res 2014;114:1757–1771.
10. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nat Immunol Rev 2015;15:104–116.
11. Hasty AH, Yvan-Charvet L. Liver X receptor a-dependent iron handling in M2 macrophages: The missing link between cholesterol and intraplaque hemorrhage? Circ Res 2013;113:1182–1185.
12. Kolodgie FD, Virmani R, Burke AP, et al. Pathologic assessment of the vulnerable human coronary plaque. Heart 2004;90: 1385–1391.
13. Wingo PA, Ries LA, Rosenberg HM. Cancer incidence and mortality, 1973–1995: a report card for the US. Cancer 1998;82:1197–1207.
14. Ross JS, Stagliano NE, Donovan MJ. Atherosclerosis and cancer: common molecular pathway of disease development and progression. Ann N Y Acad Sci 2001;947:271–292.
15. Ross JS, Stagliano NE, Donovan MJ. Atherosclerosis: a cancer of blood vessels. Am J Clin Pathol 2001;116:S97–S107.
16. De Nigris F, Sica V, Herrmann J. c-Myconcoprotein: cell cycle-related events and new therapeutic challenges in cancer and cardiovascular disease. Cell Cycle 2003;2:325–328.
17. Li JJ, Fang CH, Chen MZ, et al. Activation of nuclear factor-kB and correlation with elevated C-reactive protein in patients with unstable angina. Heart Lung Circ 2004;13:173–178.
18. Bartsch H. Studies on biomarkers in cancer etiology and prevention: a summary and challenge of 20 years of interdisciplinary research. Mutat Res 2000;462:V255–V279.
19. Schaftenaar F, Frodermann V, Kuiper J, et al. Atherosclerosis: the interplay between lipids and immune cells. Curr Opin Lipidol 2016;27:209–215.
20. Vidal-Vanaclocha F. Inflammation in the molecular pathogenesis of cancer and atherosclerosis. Reumatol Clin 2009;5:40–43.
21. Stoll G, Bendszus M. Inflammation and atherosclerosis, novel insights into plaque formation and destabilization. Stroke 2006;37: 1923–1932.
22. Swirski FK, Weissleder R, Pittet MJ. Heterogeneous in vivo behavior of monocyte subsets in atherosclerosis. Arterioscler ThrombVasc Biol 2009;29:1424–1432.
23. Weber C, Zemecke A, Libby P. The multifaceted contributions of leukocyte subsets to atherosclerosis: lessons from mouse models. Nat Rev Immunol 2008;8:802–815.
24. Duewell P, Kono O, Rayner KJ, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010;464:1357–1361.
25. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. Nature Med 2015;21:677–687.
26. Fleet JC, Clinton SK, Salomon RN, et al. Atherogenic diets enhance endotoxin-stimulated interleukin-1 and tumor necrosis factor gene expression in rabbit aortae. J Nutr 1992;122:294–305.
27. Pittet MJ, Swirski FK. Monocytes link atherosclerosis and cancer. Eur J Immunol 2011;41:2470–2525.
28. Zapolska-Downar D, Sieniccka A, Kazckmarckzick M, et al. Simvastatin modulates TNF alpha induced adhesion molecules expression in human endothelial cells. Life Sci 2004;75:1287–1302.
29. Ferriéres J. Effects on choronary atherosclerosis by targeting low-density lipoprotein cholesterol with statins. Am J Cardiovasc Drugs 2009;9:109–115.
30. Chen MJ, Tsan YT, Chen PC. Author's reply to: Statins and the risk of pancreatic cancer in type 2 diabetic patients: Immortal time bias in survival analysis? Int J Cancer 2016;139:1182–1183.
31. Hu YW. Statins and the risk of pancreatic cancer in Type 2 diabetic patients: Immortal time bias in survival analysis? Int J Cancer 2016; 139:232.
32. Charo IF, Taub R. Anti-inflammatory therapeutics for the treatment of atherosclerosis. Nat Rev Drug Discov 2011;10:365–376.
33. Goya L, Martin MA, Sarriá B, et al. Effect of cocoa and its flavonoids on biomarkers of inflammation: Studies of cell culture, animals and humans. Nutrients 2016;8:212.
34. Salvayre R, Negre-Salvayre A, Camaré C. Oxidative theory of atherosclerosis and antioxidants. Biochimie 2015;125:281–296.
35. Garg PK, Arnold AM, Hinckley Stukovsky KD, et al. Lipoprotein-associated phospholipase A2 and incident peripheral arterial disease in older adults: the cardiovascular health study. Arterioscler Thromb Vasc Biol 2016;36:750–756.
36. Maiolino G, Bisogni V, Rossitto G, et al. Lipoprotein-associated phospholipase A2 prognostic role in atherosclerotic complications. World J Cardiol 2015;7:609–620.
37. Bonnefont-Rousselot D. Lp-PLA2, a biomarker of vascular inflammation and vulnerability of atherosclerosis plaques. Ann Pharm Fr 2016;74:190–197.
38. Bäck M, Weber C, Lutgens E. Regulation of atherosclerotic plaque inflammation. J Intern Med 2015;278:462–482.
39. Tuttolomondo A, Di Raimondo D, Pecoraro R, et al. Atherosclerosis as an inflammatory disease. Curr Pharm Des 2012;18: 4266–4288.
40. Paoletti R, Gotto AM Jr, Hajjar DP. Inflammation in atherosclerosis and implications for therapy. Circulation 2004;109:III20–III26.
41. Li S, Liu B, Luo W, et al. Role of cyclooxygenase-1 and -2 in endothelium-dependent contraction of atherosclerotic mouse abdominal aortas. Clin Exp Pharmacol Physiol 2016;43:67–74.
42. Liu B, Zhang Y, Zhu N, et al. A vasoconstrictor role for cyclooxygenase-1-mediated prostacyclin synthesis in mouse renal arteries. Am J Physiol Renal Physiol 2013;305:F1315–F1322.
43. Grivennikob SI, Karin M. Dangerous liaisons: STAT3 and NF-kappaB collaboration and crosstalk in cancer. Cytokine Growth Factor Rev 2010;21:1199.
44. Zarour HM. Reversing T-cell dysfunction and exhaustion in cancer. Clin Cancer Res 2016;22:1856–1864.
45. Hegde PS, Karanikas V, Evers S. The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition. Clin Cancer Res 2016;22:1865–1874.
46. Landskron G, De la Fuente M, Thuwajit P, et al. Chronic inflammation and cytokines in the tumour microenvironment. J Immunol Res 2014;2014:1–19.
47. Tousoulis D, Oikonomou E, Economou EK, et al. Inflammatory cytokines in atherosclerosis: current therapeutic approaches. Eur Heart J 2016;37:1723–1732.
48. Bergh N, Larsson P, Ulfhammer E, et al. Effect of shear stress, statins and TNF-alpha on hemostatic genes in human endothelial cells. Biochem Biophys Res Commun 2012;420:166–171.

49. Grivennikob SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883−899.
50. Maeda S, Omata M. Inflammation and cancer: role of nuclear factor-kappa beta activation. Cancer Sci 2008;99:836−842.
51. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell 2010;141:39−51.
52. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation 2004;109:III27−III32.
53. Munn LL. Cancer and inflammation. Wiley Interdiscip Rev Syst Biol Med 2017;9.
54. Mantovani A, Allavena P, Sica A, et al. Cancer related inflammation. Nature 2008;454:433−444.
55. Crusz SM, Balkwill FR. Inflammation and cancer: advances and new agents. Nat Rev Clin Oncol 2015;12:584−596.
56. Grivennikob SI, Karin M. Inflammation and oncogenesis: a vicious connection. Curr Opin Genet Dev 2010;20:65−71.
57. Headland SE, Norling LV. The resolution of inflammation: Principles and challenges. Semin Immunol 2015;27:149−160.
58. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nat Immunol 2005;6:1191−1197.
59. Werner F, Feinberg MW, Sibinga NE, et al. Transforming growth factor-β1 inhibition of macrophage activation is mediated via Smad3. J Biol Chem 2000;275:36653−36658.
60. García-Uribe LP, Marquéz-Lázaro JP, Viola-Rhenals M. Estrés oxidativo, daño al ADN y cáncer. Revista Ciencias Biomédicas 2015; 6:107−117.
61. Sharma A, Tripathi M, Satyam A, et al. Study of antioxidant levels in patients with multiple myeloma. Leuk Lymphoma 2009;50: 809−815.
62. Stachowicz-Stencel T, Synakiewicz A, Bien E, et al. Multiple primary cranio-spinal tumours in a 13-year-old female with neurofibromatosis type 2 management strategy. Childs Nerv Syst 2011;27: 175−178.
63. Cathcart MK, Folcik VA. Lipoxygenases and atherosclerosis: protection versus pathogenesis. Free Radic Biol Med 2000;28: 1726−1734.
64. Shackelford RE, Kaufmann WK, Paules RS. Oxidative stress and cell cycle checkpoint function. Free Radic Biol Med 2000;28: 1387−1404.
65. Dixon S, Stockwell BR. The role of iron and reactive oxygen species in cell death. Nat Chem Biol 2014;10:9−17.
66. Ziech D, Franco R, Pappa A, et al. The role of reactive oxygen species and oxidative stress in environmental carcinogenesis and biomarker development. Chem Biol Interact 2010;188:334−339.
67. Battisti V, Maders L, Bagatini M, et al. Oxidative stress and antioxidant status in prostate cancer patients: relation to Gleason score, treatment and bone metastasis. Biomed Pharmacother 2011;65: 516−524.
68. Sosa V, Moliné T, Somoza R, et al. Oxidative stress and cancer: A Overview. Ageing Res Rev 2013;12:376−390.
69. Aviram M. Review of human studies on oxidative damage and antioxidant protection related to cardiovascular diseases. Free Radic Res 2000;33:S85−S97.
70. Zalba G, Beaumont J, San Jose G. Vascular oxidant stress: molecular mechanisms and pathophysiological implications. J Physiol Biochem 2000;56:57−64.
71. Cai H, Harrison DJ. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87:840−844.
72. Irani K. Oxidant signaling in vascular cell growth, death, and survival: a review of the roles of reactive oxygen species in smooth muscle and endothelial cell mitogenic and apoptotic signaling. Circ Res 2000;87:179−183.
73. Jeremy JY, Rowe D, Emsley AM, et al. Nitric oxide and the proliferation of vascular smooth muscle cells. Cardiovasc Res 1999;43: 580−594.
74. Zettler ME, Pierce YN. Growth-promoting effects of oxidized low-density lipoprotein. Can J Cardiol 2000;17:73−79.
75. Damián-Zamacona S, Toledo-Ibelles P, Ibarra-Abundis MZ, et al. Early transcriptomic response to LDL and oxLDL in human vascular smooth muscle cells. PLoS One 2016;11:e0163924.
76. Jiménez-Corona AE, Damián-Zamacona S, Pérez-Torres A, et al. Osteopontin upregulation in atherogenesis is associated with cellular oxidative stress triggered by the activation of scavenger receptors. Arch Med Res 2012;43:102−111.
77. Marnett LJ. Oxyradicals and DNA damage. Carcinogenesis 2000;21: 361−370.
78. Zhivotovsky B, Orrenius S. Cell cycle and cell death in disease: past present and future. J Intern Med 2010;268:395−409.
79. Sriram V, Patterson C. Cell cycle in vasculoproliferative diseases: potential interventions and routes of delivery. Circulation 2001;103: 2414−2419.
80. Wessely R. Atherosclerosis and cell cycle: put the brakes on! Critical role for cyclin dependent kinase inhibitors. J Am Coll Cardiol 2010; 55:2269−2271.
81. Schwartz SM, Murry CW. Proliferation and the monoclonal origins of atherosclerotic lesions. Annu Rev Med 1998;49:437−460.
82. Chang BD, Watanabe K, Broude EV, et al. Effects of p21Waf1/Cip1/Sdi1on cellular gene expression: implications for carcinogenesis, senescence, and age related diseases. Proc Natl Acad Sci USA 2000;97:4291−4296.
83. Sluimer JC, Daemen MJ. Novel concepts in atherogenesis: angiogenesis and hypoxia in atherosclerosis. J Pathol 2009;218: 7−29.
84. Virmani R, Kolodgie FE, Burke AP, et al. Atherosclerotic plaque progression and vulnerability to rupture angiogenesis as a source of intraplaque hemorrhage. Arterioscler Thromb Vasc Biol 2005;25: 2054−2061.
85. Isner JM, Losordo DW. Therapeutic angiogenesis for heart failure. Nat Med 1999;5:491−492.
86. Kahlon R, Shapero J, Gotlieb AI. Angiogenesis in atherosclerosis. Can J Cardiol 1992;8:60−64.
87. Isner JM. Cancer and atherosclerosis: the broad mandate of angiogenesis. Circulation 1999;99:1653−1655.
88. Folkman J. Tumor angiogenesis therapeutic implications. N Engl J Med 1971;285:1182−1186.
89. Yadav L, Puri N, Rastogi V, et al. Tumour angiogenesis and angiogenic inhibitors: a review. J Clin Diagn Res 2015;9: XE01−XE05.
90. Gupta MK, Qin RY. Mechanism and its regulation of tumour induced angiogenesis. World J Gastroenterol 2003;9:1144−1155.
91. Norden AD, Drappatz J, Wen PY. Novel anti-angiogenic therapies for malignant gliomas. Lancet Neurol 2008;7:1152−1160.
92. Nishida N, Yano H, Komai K. Vascular endothelial growth factor C and vascular endothelial growth factor receptor 2 are related closely to the prognosis of ovarian carcinoma. Cancer 2004;101:1364−1374.
93. Cavallaro U, Christofori G. Molecular mechanisms of tumor angiogenesis and tumor progression. J Neurooncol 2000;50:63−70.
94. Urbich C, Kuehbacher A, Dimmeler S. Role of microRNAs in vascular diseases, inflammation and angiogenesis. Cardiovasc Res 2008;79:581−588.
95. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009;136:215−233.
96. Thum T, Galuppo P, Wolf C. MicroRNAs in the human heart: a clue to fetal gene reprogramming in hearth failure. Circulation 2007;116: 258−267.
97. Olivieri F, Rippo MR, Procopio AD, et al. Circulating inflammamiRs in aging and age-related diseases. Front Genet 2013;4:121.
98. Lin R. microRNA signature and expression of Drisher and Drosha can predict prognosis and delineate risks groups in neuroblastoma. Cancer Res 2010;70:7841−7850.

99. Suarez Y, Fernandez-Hernando C, Pober JS, et al. Dicerdependent microRNAs regulate gene expression and functions in human endothelial cells. Circ Res 2007;100:1164–1173.
100. Kuehbacher A, Urbich C, Zeiher AM, et al. Role of Dicer and Drosha for endothelial microRNA expression and angiogenesis. Circ Res 2007;101:59–68.
101. Roush S, Slack FJ. The let-7 family of microRNAs. Trends Cell Biol 2008;18:505–516.
102. Durso M, Gaglione M, Piras L, et al. Chemical modifications in the seed region of miRNAs 221/222 increase the silencing performances in gastrointestinal stromal tumor cells. Eur J Med Chem 2016;23: 15–25.
103. Ihle MA, Trautmann M, Kuenstlinger H, et al. miRNA-221 and miRNA-222 induce apoptosis via the KIT/AKT signalling pathway in gastrointestinal stromal tumours. Mol Oncol 2015; 9:1421–1433.
104. Venturini L, Battmer K, Castoldi M, et al. Expression of the miR-17-92 polycistron in chronic myeloid leukemia (CML) CD34+ cells. Blood 2007;109:4399–4405.
105. Ma H, Pan JS, Jin LX, et al. MicroRNA-17~92 inhibits colorectal cancer progression by targeting angiogenesis. Cancer Lett 2016; 3835:30242–30247.
106. Robaina MC, Faccion RS, Mazzoccoli L, et al. miR-17-92 cluster components analysis in Burkitt lymphoma: overexpression of miR-17 is associated with poor prognosis. Ann Hematol 2016;95: 881–891.
107. Zhou P, Ma L, Zhou J, et al. miR-17-92 plays an oncogenic role and conveys chemo-resistance to cisplatin in human prostate cancer cells. Int J Oncol 2016;48:1737–1748.
108. Bahari F, Emadi-Baygi M, Nikpour P. miR-17-92 host gene, underexpressed in gastric cancer and its expression was negatively correlated with the metastasis. Indian J Cancer 2015;52:22–25.
109. Huang Y, Chen J, Zhou Y, et al. Circulating miR155 expression level is positive with blood pressure parameters: Potential markers of target-organ damage. Clin Exp Hypertens 2016;38: 331–336.
110. Zhang L, Wang W, Li X, et al. MicroRNA-155 promotes tumor growth of human hepatocellular carcinoma by targeting ARID2. Int J Oncol 2016;48:2425–2434.
111. Jazbutyte V, Thum T. MicroRNA-21: from cancer to cardiovascular disease. Curr Drug Targets 2010;11:926–935.
112. Kan X, Sun Y, Lu J, et al. Co-inhibition of miRNA-21 and miRNA-221 induces apoptosis by enhancing the p53-mediated expression of pro-apoptotic miRNAs in laryngeal squamous cell carcinoma. Mol Med Rep 2016;13:4315–4320.
113. Cao J, Liu J, Xu R, et al. MicroRNA-21 stimulates epithelial-to-mesenchymal transition and tumorigenesis in clear cell renal cells. Mol Med Rep 2016;13:75–82.
114. Kerr JFR, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 1972;26:239–257.
115. Nishida K, Yamaguchi O, Otsu K. Crosstalk between autophagy and apoptosis in heart disease. Circ Res 2008;103:343–351.
116. Eum KH, Lee M. Crosstalk between autophagy and apoptosis in the regulation of paclitaxel-induced cell death in v-Ha-ras transformed fibroblasts. Mol Cell Biochem 2011;348:61–68.
117. Ghobrial IM, Witzig TE, Adjei AA. Targeting apoptosis pathways in cancer therapy. Cancer J Clin 2005;55:178–194.
118. Giovannini C, Scazzocchio B, Varì R, et al. Apoptosis in cancer and atherosclerosis: polyphenol activities. Ann Ist Super Sanita 2007;43: 406–416.
119. Fogarty CE, Bergmann A. The sound of silence: signaling by apoptotic cells. Curr Top Dev Biol 2015;114:241–265.
120. Tan SZ, Ooi DSQ, Shen HM, et al. The atherogenic effects of serum amyloid A are potentially mediated via inflammation and apoptosis. J Atheroscler Thromb 2014;21:854–867.
121. Green DR, Llambi F. Cell Death Signaling. Cold Spring Harb Perspect Biol 2015;7:1–24.
122. Liu J, Thewke DP, Su YR, et al. Reduced macrophage apoptosis is associated with accelerated atherosclerosis in low-density lipoprotein receptor-null mice. Arterioscler Thromb Vasc Biol 2005;25: 174–179.
123. Arai S, Shelton JM, Chen M, et al. A role for the apoptosis inhibitory factor AIM/Spalpha/Api6 in atherosclerosis development. Cell Metab 2005;1:201–213.
124. Wang BY, Ho HK, Lin PS, et al. Regression of atherosclerosis: role of nitric oxide and apoptosis. Circulation 1999;99:1236–1241.
125. Ishiyama J, Taguchi R, Akasaka Y, et al. Unsaturated FAs prevent palmitate induced LOX-1 induction via inhibition of ER stress in macrophages. J Lipid Res 2011;52:299–307.
126. Sato R. Functions of cholesterol metabolites. J Nutr Sci Vitaminol 2015;61:S151–S153.
127. Dlamini Z, Tshidino SC, Hull R. Abnormalities in alternative splicing of apoptotic genes and cardiovascular diseases. Int J Mol Sci 2015;16:27171–27190.
128. Venables JP, Klinck R, Koh C, et al. Cancer-associated regulation of alternative splicing. Nat Struct Mol Biol 2009;16:670–676.
129. Bauman J, Jearawiriyapaisarn N, Kole R. Therapeutic potential of splice-switching oligonucleotides. Oligonucleotides 2009;19: 1–13.
130. Miura K, Fujibuchi W, Unno M. Splice variants in apoptotic pathway. Exp Oncol 2012;34:212–217.
131. Droin N, Beauchemin M, Solary E, et al. Identification of a caspase-2 isoform that behaves as an endogenous inhibitor of the caspase cascade. Cancer Res 2000;60:7039–7047.
132. Tapia-Vieyra JV, Arellano RO, Mas-Oliva J. ARP2 a novel protein involved in apoptosis of LNCaP cells shares a high degree homology with splicing factor Prp8. Mol Cell Biochem 2005;269: 189–201.
133. Mas-Oliva J, Navarro-Vidal E, Tapia-Vieyra JV. ARP2, a novel pro-apoptotic protein expressed in epithelial prostate cancer LNCaP cells and epithelial ovary CHO transformed cells. PLoS One 2014;9: e86089.
134. Wang D, Nguyen MN, Masoodi KZ, et al. Splicing factor Prp8 interacts with NES(AR) and regulates androgen receptor in prostate cancer cells. Mol Endocrinol 2015;29:1731–1742.
135. Sato N, Maeda M, Sugiyama M, et al. Inhibition of SNW1 association with spliceosomal proteins promotes apoptosis in breast cancer cells. Cancer Med 2015;4:268–277.
136. Brown JM, Attardi LD. The role of apoptosis in cancer development and treatment response. Nat Rev Cancer 2005;5:231–237.
137. Jaffe L. Cell polarity: don't forget calcium's role. BioEssays 2005; 27:671.
138. Dolmetsch R. Excitation-transcription coupling: signaling by ion channels to the nucleus. Sci STKE 2003;2003:PE4.
139. Tano JYK, Lee RH, Vazquez G. Macrophage function in atherosclerosis. Potential roles of TRP channels. Channels 2012;6:3.
140. Tapia-Vieyra JV, Mas-Oliva J. Apoptosis and cell death channels in prostate cancer. Arch Med Res 2001;3:175–185.
141. Jiang HN, Zeng B, Zhang Y, et al. Involvement of TRPC channels in lung cancer cell differentiation and the correlation analysis in human non-small cell lung cancer. PLos One 2013;8:e67637.
142. Delgado-Coello B, Santiago-García J, Zarain-Herzberg A, et al. Plasma membrane Ca^{2+}-ATPase mRNA expression in murine hepatocarcinoma and regenerating liver cells. Mol Cell Biochem 2003; 247:177–184.
143. Parkash J, Asotra K. Calcium wave signaling in cancer cells. Life Sci 2010;87:587–595.
144. Dang D, Rao R. Calcium-ATPases: gene disorders and dysregulation in cancer. Biochim Biophys Acta 2016;1836:1344–1350.
145. Lipskaia L, Keuylian Z, Lirando K, et al. Expression of sarco (endo) plasmic reticulum calcium ATPase (SERCA) system in normal

mouse cardiovascular tissues, heat failure and atherosclerosis. Biochim Biophys Acta 2014;1843:2705−2718.
146. Diez-Fraile A, Lammens T, Benoit Y, D'Herde KGMA. Calcium sensing receptor as a regulator of cellular fate in normal and pathological conditions. Curr Mol Med 2013;13:282−295.
147. Sanders JL, Chattopadhyay N, Kifor O, et al. Ca(2+)-sensing receptor expression and PTHrP secretion in PC-3 human prostate cancer cells. Am J Physiol Endrocrinol Metab 2001;281: E1267−E1274.
148. Alam MU, Kirton JP, Wilkinson FL, et al. Calcification is associated with loss functional calcium-sensing receptor in vascular smooth muscle cells. Cardiovasc Res 2009;81:260−268.
149. Whitlock MC, Yeboah J, Burke GL, et al. Cancer and its association with the development of coronary artery calcification: an assessment from the multi-ethnic study of atherosclerosis. J Am Heart Assoc 2015;4:e002533.
150. Duthie SJ. Epigenetic modifications and human pathologies: cancer and CVD. Proc Nutr Soc 2011;70:47−56.
151. Gal-Yam EN, Saito Y, Egger G, et al. Cancer epigenetics: modifications, screening, and therapy. Annu Rev Med 2008;59: 267−280.
152. Wilson A. Epigenetic regulation of gene expression in the inflammatory response and relevance to common diseases. J Periodontol 2008; 79:1514−1519.
153. Abi Khalil C. The emerging role of epigenetics in cardiovascular disease. Ther Adv Chronic Dis 2014;5:178−187.
154. Jones PA, Baylin SB. The epigenomics of cancer. Cell 2007;128: 683−692.
155. Turunen MP, Aavik E, Yla-Herttula S. Epigenetics and atherosclerosis. Biochim Biophys Acta 2009;1790:886−891.
156. Bierne H, Hamon M, Cossart P. Epigenetics and bacterial infections. Cold Spring Harbor Perspect Med 2012;2:a010272.
157. Dang M, Buzzetti R, Pozzilli P. Epigenetics in autoimmune diseases with focus on type 1 diabetes. Diabetes Metab Res Rev 2013;29: 8−18.
158. Esteller M. Epigenetics in cancer. N Engl J Med 2008;358: 1148−1159.
159. Matouk CC, Marsden PA. 2008 Epigenetic regulation of vascular endothelial gene expression. Circ Res 2008;102:873−887.
160. Lorenzen JM, Martino F, Thum T. Epigenetic modifications in cardiovascular disease. Basic Res Cardiol 2012;107:245.
161. Gama-Sosa MA, Midgett RM, Slagel VA, et al. Tissue-specific differences in DNA methylation in various mammals. Biochim Biophys Acta 1983;740:212−219.
162. Mund C, Brueckner B, Lyko F. Reactivation of epigenetically silenced genes by DNA methyltransferase inhibitors: basic concepts and clinical applications. Epigenetics 2006;1:7−13.
163. Costello JF, Plass C. 2001 Methylation matters. J Med Genet 2001; 38:285−303.
164. Gaudet F, Hodgson JG, Eden A, et al. Induction of tumors in mice by genomic hypomethylation. Science 2003;300:489−492.
165. Lund G, Andersson L, Lauria M, et al. DNA methylation polymorphisms precede any histological sign of atherosclerosis in mice lacking apolipoprotein E. J Biol Chem 2004;279:29147−29154.
166. Kim GH. MicroRNA regulation of cardiac conduction and arrhythmias. Transl Res 2013;161:381−392.
167. Post W, Goldschmidt-Clermont P, Wilhide C, et al. Methylation of the estrogen receptor gene is associated with aging and atherosclerosis in the cardiovascular system. Cardiovasc Res 1999;43: 985−991.
168. Zhu S, Goldschmidt-Clermont P, Dong C. Inactivation of monocarboxylate transporter MCT3 by DNA methylation in atherosclerosis. Circulation 2005;112:1353−1361.
169. Breton CV, Byun HM, Wenten M, et al. Prenatal tobacco smoke exposure affects global and gene specific DNA methylation. Am J Respir Crit Care Med 2009;180:462−467.
170. Shirodkar AV, St Bernard R, Gavryushova A, et al. A mechanistic role for DNA methylation in endothelial cell (EC)-enriched gene expression: relationship with DNA replication timing. Blood 2013; 121:3531−3540.
171. Newman PE. Can reduced folic acid and vitamin B12 levels cause deficient DNA methylation producing mutations which initiate atherosclerosis? Med Hypotheses 1999;53:421−424.
172. Chen Z, Karaplis AC, Ackerman SL, et al. Mice deficient in methylenetetrahydrofolate reductase exhibit hyperhomocysteinemia and decreased methylation capacity, with neuropathology and aortic lipid deposition. Hum Mol Genet 2001;10:433−443.
173. Man HS, Yan MS, Lee JJ, et al. Epigenetic determinants of cardiovascular gene expression: vascular endothelium. Epigenomics 2016;8:959−979.
174. Gusterson R, Jazrawi E, Adcock I, et al. The transcriptional coactivators CREB binding protein (CBP) and p300 play a critical role in cardiac hypertrophy that is dependent on their histone acetyltransferase activity. J Biol Chem 2003;278:6838−6847.
175. Carè A, Catalucci D, Felicetti F, et al. MicroRNA-133 controls cardiac hypertrophy. Nat Med 2007;13:613−618.
176. Latronico M, Condorelli G. MicroRNAs and cardiac pathology. Nat Rev Cardiol 2009;6:419−429.
177. Balanescu S, Calmac L, Constantinescu D, et al. Systemic inflammation and early atheroma formation: are they related? Maedica (Buchar) 2010;5:292−301.
178. Aggarwal BB, Shishodia S, Sandur SK, et al. Inflammation and cancer: how hot is the link? Biochem Pharmacol 2006;72:1605−1621.
179. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420: 860−867.
180. Dobrzycka B, Terlikowski SJ, Kowalczuk O, et al. Circulating levels of TNF-alpha and its soluble receptors in the plasma of patients with epithelial ovarian cancer. Eur Cytokine Netw 2009;20:131−134.
181. Pine SR, Mechanic LE, Enewold L, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. J Natl Cancer Inst 2011;103:1112−1122.
182. Kemik O, Sumer A, Kemik AS, et al. The relationship among acute-phase response proteins, cytokines and hormones in cachectic patients with colon cancer. World J Surg Oncol 2010;8:85.
183. Budczies J, von Winterfeld M, Klauschen F, et al. Comprehensive analysis of clinico-pathological data reveals heterogeneous relations between atherosclerosis and cancer. J Clin Pathol 2014;67: 482−490.
184. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646−674.
185. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature 2011;473:317−325.
186. Lusis AJ. Atherosclerosis. Nature 2000;407:233−241.
187. Staubach S, Hanisch FG. Lipid rafts: signaling and sorting platforms of cells and their roles in cancer. Expert Rev Proteomics 2011;8: 263−277.
188. Kato S, Smalley S, Sadarangani A, et al. Lipophilic but not hydrophilic statins selectively induce cell death in gynaecological cancers expressing high levels of HMGCoA reductase. J Cell Mol Med 2010; 14:1180−1193.
189. Brennan DJ, Laursen H, O'Connor DP, et al. Tumor-specific HMG-CoA reductase expression in primary premenopausal breast cancer predicts response to tamoxifen. Breast Cancer Res 2011;13:R12.
190. Brennan DJ, Brandstedt J, Rexhepaj E, et al. Tumour-specific HMG-CoAR is an independent predictor of recurrence free survival in epithelial ovarian cancer. BMC Cancer 2010;10:125.
191. Clendening JW, Pandyra A, Boutros PC, et al. Dysregulation of the mevalonate pathway promotes transformation. Proc Natl Acad Sci USA 2010;107:15051−15056.
192. Papadopoulos G, Delakas D, Nakopoulou L, et al. Statins and prostate cancer: molecular and clinical aspects. Eur J Cancer 2011;47: 819−830.

193. Bardou M, Barkun A, Martel M. Effect of statin therapy on colorectal cancer. Gut 2010;59:1572−1585.
194. Gonyeau MJ, Yuen DW. A clinical review of statins and cancer: helpful or harmful? Pharmacotherapy 2010;30:177−194.
195. Boudreau DM, Yu O, Johnson J. Statin use and cancer risk: a comprehensive review. Expert Opin Drug Saf 2010;9:603−621.
196. Gauthaman K, Fong CY, Bongso A. Statins, stem cells, and cancer. J Cell Biochem 2009;106:975−983.
197. Budman DR, Tai J, Calabro A. Fluvastatin enhancement of trastuzumab and classical cytotoxic agents in defined breast cancer cell lines in vitro. Breast Cancer Res Treat 2007;104:93−101.
198. Mantha AJ, Hanson JE, Goss G, et al. Targeting the mevalonate pathway inhibits the function of the epidermal growth factor receptor. Clin Cancer Res 2005;11:2398−2407.
199. Feleszko W, Mlynarczuk I, Balkowiec-Iskra EZ, et al. Lovastatin potentiates antitumor activity and attenuates cardiotoxicity of doxorubicin in three tumor models in mice. Clin Cancer Res 2000;6:2044−2052.
200. Elmore RG, Ioffe Y, Scoles DR, et al. Impact of statin therapy on survival in epithelial ovarian cancer. Gynecol Oncol 2008;111:102−105.
201. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to statins and risk of common cancers: a series of nested case-control studies. BMC Cancer 2011;11:409.
202. Piechota-Polanczyk A, Jozkowicz A. The role of statins in heme oxygenase-1 activation in cardiovascular diseases. Curr Drug Targets 2017;18.
203. Mas-Oliva J, Santiago-García J. Cholesterol effect on thermostability of the (Ca2+,Mg2+) ATPase from cardiac muscle sarcolemma. Biochem Int 1990;21:233−241.
204. Mas-Oliva J, Pérez-Montfort R, Cárdenas-García M, et al. Altered coupling states between calcium transport and (Ca2+,Mg2+) ATPase in the AS-30D ascites hepatocarcinoma plasma membrane. Mol Cell Biochem 1991;100:39−50.
205. Ortega A, Mas-Oliva J. Direct regulatory effect of cholesterol on the calmodulin stimulated calcium pump of cardiac sarcolemma. Biochem Biophys Res Commun 1986;139:868−874.
206. Pettersson K, Björk H, Nordlander M. Anti-atherosclerotic effect of the calcium-antagonist felodipine in cholesterol-fed Russian rabbits. 9th International Symposium on Atherosclerosis; 1991 Oct 6-11; Rosemont Illinois, USA.
207. Lichtlen PR, Hugenholtz PG, Rafflenbeul W, et al. Retardation of angiographic progression of coronary artery disease by nifedipine. Results of the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT). INTACT Group Investigators. Lancet 1990;335:1109−1113.
208. Yao R, Cheng X, Liao YH, et al. Molecular mechanisms of felodipine suppressing atherosclerosis in high-cholesterol-diet apolipoprotein E-knockout mice. J Cardiovasc Pharmacol 2008;51:188−195.
209. Lago R, Gómez R, Lago F, et al. Leptin beyond body weight regulation−current concepts concerning its role in immune function and inflammation. Cell Immunol 2008;252:139−145.
210. Loffreda S, Yang SQ, Lin HZ, et al. Leptin regulates proinflammatory immune responses. FASEB J 1998;12:57−65.
211. Yamagishi SI, Edelstein D, Du XL, et al. Leptin induces mitochondrial superoxide production and monocyte chemoattractant protein-1 expression in aortic endothelial cells by increasing fatty acid oxidation via protein kinase A. J Biol Chem 2001;276:25096−25100.
212. Wallace AM, McMahon AD, Packard CJ, et al. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation 2001;104:3052−3056.
213. Adams TD, Hunt SC. Cancer and obesity: effect of bariatric surgery. World J Surg 2009;33:2028−2033.
214. Bäck M, Hansson GK. Anti-inflammatory therapies for atherosclerosis. Nat Rev Cardiol 2015;12:199−211.
215. Landré V, Amelio I, Barlev NA, et al. Perspective on multi-target antiplatelet therapies: high content phenotypic screening as an unbiased source of novel polypharmacological strategies. Mini Rev Med Chem 2015;15:622−629.
216. Allen S, Liu YG, Scott E. Engineering nanomaterials to address cell-mediated inflammation in atherosclerosis. Regen Eng Transl Med 2016;2:37−50.
217. Kumai T, Kobayashi H, Harabuchi Y, et al. Peptide vaccines in cancer-old concept revisited. Curr Opin Immunol 2016;45:1−7.
218. Mas-Oliva J, Delgado-Coello BA, Gonzalez-Garcia VG, et al. Nasal vaccine against the development of atherosclerosis and fatty liver. US Patent 9,539,312. 2017 Jan 10.
219. García-González V, Delgado-Coello B, Pérez-Torres A, et al. Reality of a vaccine in the prevention and treatment of atherosclerosis. Arch Med Res 2015;46:427−437.
220. Kojima Y, Volkmer JP, McKenna K, et al. CD47-blocking antibodies restore phagocytosis and prevent atherosclerosis. Nature 2016;536:86−90.