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Invited Editorial

Jay and Jeanie Schottenstein Prize in Cardiovascular Science: Predicting Cardiovascular Illnesses for the 21st Century, and the Unpredictable . . .

Pascal J. Goldschmidt-Clermont

Abstract

Changes in our society such as the increasing cost of retirement and age redistribution toward a larger elderly population will require humans to remain highly functional until an advanced age. As a consequence, chronic illnesses that are primarily responsible for reducing functionality and life expectancy will require improved prevention and therapeutic strategies. In a global way, cardiovascular disease and cancer represent the most challenging disorders to maintaining the functional integrity of our fellow humans. A new theory has been derived from recent progress in our understanding of atherosclerosis as a key mechanism for cardiovascular disease and of cancer. Instructively, this theory provides a bridge at the stem cell level, linking most chronic disorders. *Antioxid. Redox Signal*. 11, 401–406.

Atherosclerosis and Exhaustion of Efficient Arterial Repair

Atherosclerosis has been described as an inflammatory process triggered by risk factors that have been carefully characterized by studies like the Framingham Heart Study. Hence, cigarette smoking, diabetes mellitus, elevated low-density lipoprotein cholesterol, reduced high-density lipoprotein cholesterol, hypertension, or excessive inflammation all can contribute to injuring the arterial wall. However, a couple of years ago, we showed for the first time that atherosclerosis is not simply the result of direct injury to the arterial wall, but instead the consequence of such injury in a context in which the intrinsic repair process for the arterial wall is no longer fully functional (6, 7). Our laboratory (11) and other groups of investigators (5) have shown that arterial repair is triggered by arterial injury, which, in turn, provokes a local inflammatory reaction (7) (Fig. 1). This inflammatory reaction, if sufficiently pronounced, can lead to a generalized signaling process that helps recruit progenitor cells and, in particular, endothelial progenitor cells that originate from the bone marrow, the spleen, and other adult stem cell reservoirs and circulate with other blood cells to specific areas of arteries that are prone to develop lesions of atherosclerosis (5, 17). Endothelial progenitor cells (EPCs) are capable of forming a bond with the extracellular matrix and cells of the damaged arterial wall, and of integrating within the surface layer of the arterial wall (Fig. 2). There, they may contribute to regenerating a functional endothelium through cell growth, differentiation, and many other activities that include paracrine functions (3). We have shown that mice that are exposed to proatherosclerotic factors, such as a high lipid content of the blood, lose over time their capacity to mount a functional repair activity (11, 17) (Fig. 3). We have also shown that the loss of functional arterial repair in sick mice is associated with the exhaustion or the disappearance of a specific marrow population that can otherwise differentiate, within appropriate conditions, into mature and functional endothelial cells (26).

By using gene-expression analysis, we have reconstituted the natural history of atherosclerosis by analyzing changes in gene expression that are associated with successive stages of the atherosclerotic process (11) (Fig. 3). With an apolipoprotein E (ApoE) knockout model on a high-fat diet

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FIG. 1. Award ceremony for the Jay and Jeanie Schottenstein Prize in Cardiovascular Science. (*Left to right*): The Ohio State University President Gordon Gee; Pascal J. Goldschmidt, Laureate, first recipient of the Jay and Jeanie Schottenstein Prize in Cardiovascular Science; Jeanie and Jay Schottenstein; and Steve Gabbe, Senior Vice President for Health Sciences at The Ohio State University.

in which mice rapidly develop lesions rather typical of human atherosclerosis (total cholesterol usually exceeds 1,000 mg/dl), we have characterized the molecular signature for various stages of the progression of atherosclerosis. Through the identification of genes whose expression is pathognomonic for each stage of the disease, we reconstituted the molecular puzzle of atherosclerosis progression (11) (Fig. 3). Early on, genes that characterize the arterial wall have to do with altered metabolism. At that stage, lesions of atherosclerosis are undetectable (before 6 weeks of age). Next, lesions (fatty streaks) become barely detectable (up to 12 weeks); genes that characterize this stage through their expression all have to do with inflammation. Later on, and as lesions become more organized and involve thicker atheroma (12-plus weeks), the genes whose expression is specific to this stage have to do with tissue remodeling.

We also were able to define a molecular signature that corresponds to efficient repair of the arterial wall (11). Genes that constitute this pool often have to do with cellular functions that are important for stem cells. We used this "repair signature" to survey arterial walls at various stages of the atherosclerosis disease process for the presence of successful arterial repair. Although this signature was detectable early in the disease process (before the presence of detectable atherosclerotic lesions), the molecular signature for efficient repair became blurred and no longer significantly detectable as early lesions of atherosclerosis started to appear (11). At later stages of the atherosclerotic process, no signs of active and efficient arterial repair could be detected. These studies contributed to the conclusion that atherosclerosis is not simply the response of the arterial wall to an injury, but instead represents the altered response of the arterial wall in which injury continues to apply, once an effective repair response can no longer be recruited to the arterial wall (7) (Fig. 4).

Today, the molecular mechanism(s) responsible for the loss in ability to produce functional endothelial progenitor cells capable of maintaining an effective repair response are not fully identified. Early evidence suggests that such mechanisms may involve changes in chromatin conformation

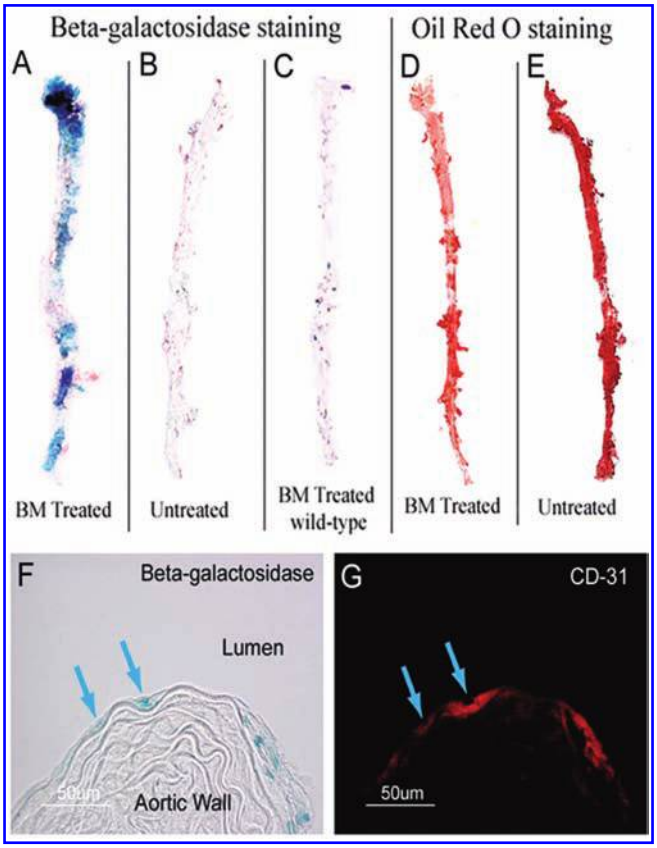

FIG. 2. Repair of artery by endothelial progenitor cells. Cultured bone marrow cells from ROSA26 mice (expressing β-galactosidase in their nucleus) were injected intravenously into apolipoprotein E (ApoE)-deficient (knockout) C57 black 6 mice, fed a high-fat diet. Shown are the aortae of recipient animals, after staining for β-galactosidase (blue coloration of positive cells). (*Upper panels, left to right*): (**A**) Blue cells have anchored in areas of the recipient aorta that otherwise would develop atherosclerosis. (**B**) ApoE-knockout mice that did not receive ROSA26 cells (medium alone). In this case, no blue cells could be detected in the recipient aorta. (**C**) Wild-type C57 black 6 mice who received cultured bone marrow cells from ROSA26 mice do not display blue cells, indicating that attachment and homing of progenitor cells require an injury to the aorta (for ApoE-knockout animals, injury corresponds to high circulating lipid levels). (**D**) Oil Red O staining of ApoE-knockout mice. Aorta from a mouse that received repeated injections of cultured bone marrow cells showing reduced atherosclerosis (Oil Red O-positive lesions) of treated animals. (**E**) Same staining as in (**D**), for a mock-treated ApoE knockout mouse. (**F, G**) Fate of injected cultured bone marrow cells (blue cells) in recipient aorta. A majority of the cells with a blue nucleus (**F**) stain positive for markers of endothelial cells, such as PECAM (CD 31), indicating that most blue cells become endothelial cells that are incorporated within the surface area of the artery (**G**).

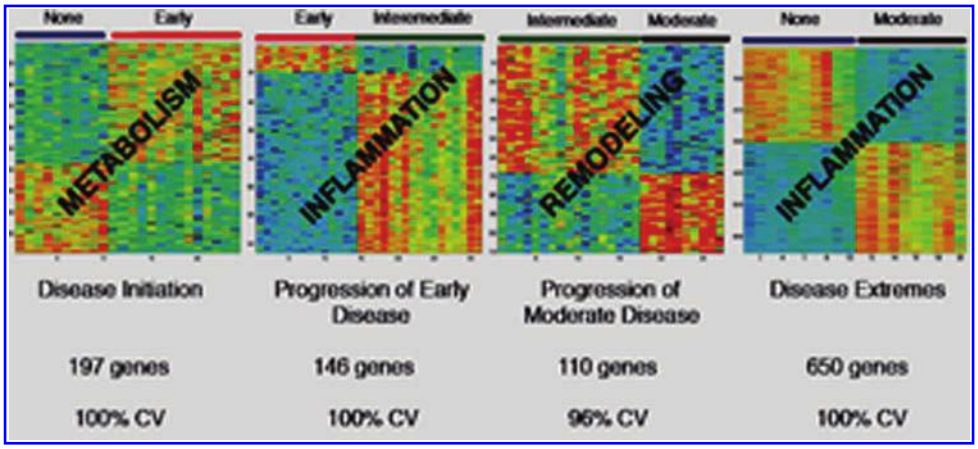

FIG. 3. Natural history of atherosclerosis according to gene-expressions profiling. We have analyzed arteries by using Affymetrix chips to survey gene expression of the aorta tissue at various stages in ApoE-knockout mice on a high-fat diet (11). In the early stage, <12 weeks typically, genes that differentiate aortae from ApoE-knockout mice from the aortae of wild-type mice have to do with metabolism. At this stage, the aortae did not display lesions of atherosclerosis. The next stage, 12-plus weeks (when compared with the 6-week group), is characterized by the expression of genes that have to do with inflammation; at this stage, early lesions of atherosclerosis become detectable. The next stage, 18 weeks (when compared with the 12-week group), is characterized by more-mature lesions. At this stage, gene expression is typical of a process of arterial remodeling. When aortae of wild-type mice are compared with those of 18-week mice, genes whose expression differentiates those extreme states have to do with inflammation. With gene-expression analysis to characterize aortae from older (6 months) ApoE-knockout mice that have received competent cultured bone marrow cells (the aorta repair "molecular signature"), we surveyed the various stages of the molecular disease process as defined by gene-expression analysis for the presence of a statistically significant repair molecular signature. Whereas the repair signature was clearly detectable in the pre-lesion stage of the disease process, this repair signature became blurred and disappeared once lesions of atherosclerosis became detectable (11). The data suggest that atherosclerosis develops not just once an injury is applied to the arterial wall, but instead, once such injury is applied when the repair potential of the organism for arterial tissue becomes exhausted (8). [Reported with permission by Karra et al. (11). Copyright 2005 National Academy of Sciences, U.S.A.]

(through epigenetic alterations) for precursor cells within the bone marrow and other reservoirs for progenitor cells (4). It is also highly likely that micro-RNAs (miRNAs) are implicated in the obsolescence of bone-marrow–derived endothelial progenitor cells.

These studies are supported by a body of research performed in human conditions that result from atherosclerosis, such as coronary artery disease, myocardial infarction, and stroke. It has been shown that the level of circulating endothelial progenitor cells is lower in the blood of patients who experience risk factors for coronary artery disease (9) or advanced arterial lesions (12, 16, 22). Furthermore, Werner and colleagues (22) showed that patients with low levels of circulating EPCs are at high risk for coronary events. Moreover, they showed that the level of EPCs that circulate in the blood is inversely proportional to the mortality of patients with coronary artery disease (22). Such associations support the concept that maintaining a functional repair system that involves competent EPCs is critical for a life sheltered from coronary artery disease and, for patients at risk, from deadly events. The replacement of dysfunctional EPCs in patients with atherosclerosis and advanced coronary artery disease remains elusive. Even in animal models, the specific progenitor cells capable of repairing arteries have not been fully identified (26). What is known is that after a lifetime of atherosclerosis, it is highly likely that these cells cannot simply be extracted from the bone marrow of patients or animal models (17). It is tempting to speculate that with adequate treatment of marrow progenitor cells *in vitro* before injection into patients, functional repair capacity may be restored (2, 20).

The Importance of Chronic Tissue Repair in the Development of Cancer

Instructively, it appears that for most cancers that affect humans, a specific triggering factor can be identified. Cigarette smoking for lung cancer, asbestos for mesothelioma, *Helicobacter pylori* for gastric cancer, Epstein–Barr virus for Burkitt lymphoma, and ultraviolet rays (UV) of sunlight for melanoma represent well-known examples. These injuries, when applied over the long term to a specific target organ, can promote the development of a cancer illness in susceptible patients. Some cancers have not yet been associated with a specific noxious stimulus, but it is increasingly clear that an association exists between such injuries and the disease process. Recent progress in cancer research indicates that the biology of stem cells may be implicated in tumor formation (18). Metastases often limit the life expectancy of patients who have cancer. The development of metastases was believed to be at a late stage in cancer progression, but new evidence suggests that cancer cells metastasize early on and lodge in homing tissues early with the onset of cancer (15). In their new location, mutations and selection lead to oncogene activation and disruption of suppressor genes, allowing the heightened growth of metastases.

It is highly likely that risk factors that contribute to the de-

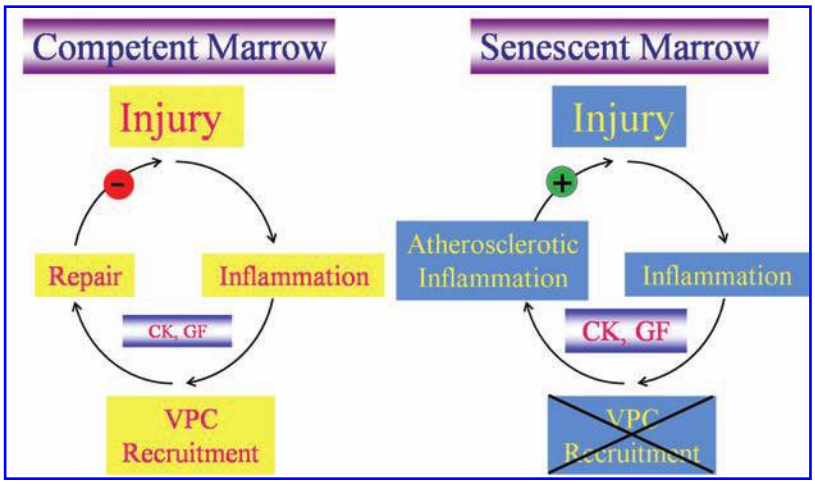

FIG. 4. Effect of endothelial progenitor cell exhaustion in response to arterial injury. When animals or individuals are young, bone marrow and other reservoirs for endothelial progenitor cells are still intact, and as a consequence, an arterial injury triggers a limited inflammatory response, which serves as a signal for the recruitment of endothelial progenitor cells to the area of damaged arteries (6, 7). Consequently, the artery is successfully repaired, and the inflammation ceases (negative-feedback loop). In contrast (*right*), once the bone marrow and other reservoirs for endothelial progenitor cells are depleted, injury to the arterial wall triggers an inflammatory reaction that does not result in successful repair, and consequently, in the absence of a negative-feedback loop, inflammation continues to expand. Such unchecked inflammatory reaction at the level of the arterial walls contributes to the worsening of atherosclerosis inflammation, larger atheromas, and unstable lesions. In this case, we have a positive-feedback loop as opposed to a situation in which the reservoir of endothelial progenitor cells is functional. C-reactive protein (CRP) has been shown to be a reliable marker for risk in patients with CAD or even in individuals who are unaware of having CAD (25). It was shown recently (1) (Jupiter Study) that the risk for individuals with elevated CRP is much improved with the administration of a statin, even if their initial cholesterol level is within normal ranges. Perhaps the known beneficial effect of these drugs on endothelial progenitor cells (2) may explain the benefit of statins in a situation in which arterial inflammation goes unchecked. Furthermore, polymorphisms in the CRP gene that are associated with genetically elevated levels of CRP do not result in heightened risks of CAD events (25). The latter finding suggests that CRP is a marker for, and not an actor in, the process of atherosclerosis.

velopment of organ-specific cancers trigger a chronic repair process that is, for a while, responsible for the maintenance of affected tissues in a rather functional state (Fig. 5). It is possible that the maintenance of a noxious stimulus for a long period for a patient with a predisposition to a given type of cancer will eventually lead to transformation of the tissue-specific repair stem cell(s), thus leading to tumor formation. It is also likely that aging of the immune system leads to reduced surveillance capacity for the elimination of cells that have undergone malignant transformation. Hence, disruption of repair mechanisms can lead to two very different types of chronic illnesses: (a) exhaustion of repair cells for atherosclerosis with its thromboembolic complications of acute myocardial infarction, sudden cardiac death, symptomatic coronary artery disease, stroke, and other symptomatic cerebral vascular disease; and (b) transformation of repair cells for cancer illnesses. A deficient repair process is probably sustaining most chronic illnesses based on available information at this point (8).

Rac1 as a Molecular Connection between Atherosclerosis and Cancers

Kaposi sarcoma is triggered by the human herpesvirus 8 (HHV8). The likelihood for Kaposi sarcoma to develop in HHV8-infected patients is particularly high in patients infected with the human immunodeficiency virus (patients with AIDS). A key gene for the development of Kaposi sarcoma is coded for by the HHV8 genome, vGPCR. vGPCR, when expressed on the surface of endothelial cells, is required for their transformation in Kaposi sarcoma cells and for the generation of Kaposi sarcoma in nude mice (13). We have discovered that the small GTP-binding protein Rac1, when constitutively activated and expressed in cells that also express smooth muscle cell α-actin, can induce Kaposi sarcoma lesions that are identical to lesions found in human patients (unpublished observation). Among the various targets of Rac1, which functions as a biologic timer for specific cellular activities, the most relevant is NADPH-oxidase and, in particular, the isoforms that bind Rac1 for activity (14).

We have shown that Rac1 is an important regulator of mitogenic activity induced by oncogenic Ras in transformed fibroblasts. The mitogenic and transforming effect of activated Rac1 requires activation of NADPH-oxidase and production of superoxide and derived reactive oxygen species (14). The fact that activated Rac1, when expressed in cells that also express smooth muscle actin, can induce Kaposi sarcoma came as a surprise and was not anticipated. The mouse Kaposi sarcoma (KS) induced by constitutively activated Rac1 (Rac CA) is indistinguishable from the human KS. Interestingly, mouse KS lesions occurred primarily in homozygous animals, mainly in males (as human KS), and are located in hairless regions such as the tail, nose, and ears of mice overexpressing Rac CA. Spindle cells and immature vascular structures are typical of human KS in Rac CA lesions. We demonstrated that the activation of NADPH-oxidase and production of reactive oxygen species are necessary for Rac-induced mitogenesis and oncogenic transformation. By suppressing reactive oxygen species, resulting from the activation of NADPH-oxidase by Rac1, we were able to prevent mitogenic response to activated Rac1, transformation of cells, and formation of KS in mice expressing Rac CA (unpublished observation).

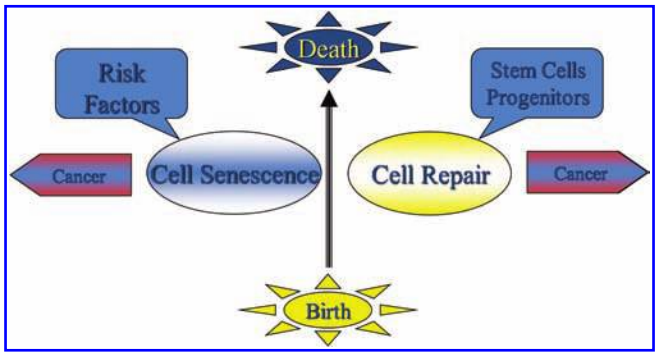

FIG. 5. The life cycle of chronic illnesses. The maintenance of a trillion cells that constitute the human body in functional state, and away from cancer transformation, is a daunting task. Evolution has addressed this challenge by establishing "senescence" as a rather stable condition for most cells of the adult organism. A senescent state for a cell does not mean dysfunction. Actually, a mild degree of senescence is readily compatible with maintenance of functionality for most cells in various tissues. However, senescence also means that the propensity for cells to enter mitosis and proliferate is lesser. Hence, such a state probably helps prevent the otherwise too frequent malignant transformation of cells and tissues. Senescent cells regularly undergo apoptosis and replacement without creating an inflammatory process, by progenitor cells that rise from various reservoirs of the human body for adult stem cells. Such a process of "autonomic repairing" is critical to the maintenance of homeostasis for functional tissues. However, because of risk factors and other noxious stimuli, the senescence of cells can be accelerated and may overwhelm the capacity for the repair process of the organism for the specific injured tissue. As a consequence, repair of tissue may fail and lead to tissue dysfunction. Such conditions often lead to chronic illnesses. Hence, a rather careful homeostasis between senescence and risk factors *versus* tissue repair and progenitor cells must be maintained for the sustainability of tissue integrity. Those organisms that have the best repair capacity and the least exposure to risk factors last the longest; those exposed to risk factors and with a genetically limited repair capacity last the shortest time. Aging corresponds to the loss of homeostasis between senescence and repair in which the equilibrium tilts toward less repair and more senescence. Furthermore, excessive and prolonged repair activity for a tissue may lead to malignant transformation, a process that may itself be enhanced by the age-related deterioration of the immune system due to senescence and exhaustion of immune cells required for competent immune surveillance of the organism.

While we were attempting to identify genes that could contribute to susceptibility to atherosclerosis and cardiovascular complications in a framework that was unrelated to work described in prior sections of this review, three genes that belong to the Rac1 pathways were found to be critical for definition of risk for CAD. In a genome-wide scan study called GENECARD for early-onset CAD, we reported on the association of segments of the genome with the development of premature CAD and cardiac events such as myocardial infarction. A region strongly associated with such events was located on chromosome 3q13. On combing the 3q13 region (21), we identified single-nucleotide polymorphisms associated with CAD within genes that belong to the Rac1 pathway. Genes coding for the proteins kalirin, CDGAP, and MYLK are all implicated in the susceptibility for premature CAD. The protein kalirin functions to accelerate the exchange of the GTP nucleotide bound to Rac1 and other Rho-family proteins. The protein CDGAP accelerates the hydrolysis of the GTP nucleotide bound to Rac1. Finally, the protein MYLK is a kinase that functions downstream from Rac1. Hence, in a nonbiased way, three proteins and their single-nucleotide polymorphisms (SNPs) that belong to the Rac1 pathway were implicated in susceptibility for developing premature coronary artery disease. It remains to be defined whether SNPs that are associated with susceptibility for CAD directly affect protein level or structure in a way that would modify the activity of the pathway. Because Rac1 contributes to pathways that involve oncogenes such as Ras, as well as critical pathways involved in stem cell biology, such as the canonic Wnt pathway (23), it is tempting to speculate that polymorphisms of proteins of the Rac1 pathway may affect repair processes and the repair stem cells that are important for prevention of both CAD and cancers.

The connection between cancer and atherosclerosis through Rac1 is puzzling, but highly interesting. It could be that the connection has to do with chronic injury and tissue repair, in which Rac1 is likely to play a pivotal role. Chronic repair reactions ongoing in arterial vessels or in areas of the skin (for Kaposi sarcoma) may constitute the defective processes that involve Rac1. In the case of atherosclerosis, the disease process may occur once the repair process becomes insufficient to maintain the homeostasis of arteries (due to progenitor cell exhaustion). Polymorphisms in genes that code for proteins of the Rac1 pathway may increase the susceptibility for a deficient repair process or exhaustion of progenitor cells capable of arterial repair or both. In the case of cancer, the constitutive activation of Rac1 may lead to deterioration of the cells involved in repairing damaged skin, which eventually leads to the oncogenic differentiation (KS). In both cases, production of reactive oxygen species through activation of NADPH-oxidase may represent an important contributor. Our studies illustrate the importance of furthering our understanding of cellular repair activities involving stem cells and other progenitor cells to unveil new mechanisms for chronic illnesses that affect cohorts of humans. Such studies will create new opportunities for therapeutic interventions to predict, prevent, and reverse chronic disease processes, opportunities that may represent the greatest advance in medicine for the 21st century.

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