



# Mechanical stress as the common denominator between chronic inflammation, cancer, and Alzheimer's disease

Marcel Levy Nogueira<sup>1,2,3</sup>, Jorgelindo da Veiga Moreira<sup>3</sup>, Gian Franco Baronzio<sup>4</sup>, Bruno Dubois<sup>1,2,5</sup>, Jean-Marc Steyaert<sup>3</sup> and Laurent Schwartz<sup>3\*</sup>

<sup>1</sup> Département de Neurologie, Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A), Hôpital de la Pitié-Salpêtrière, AP-HP, Paris, France, <sup>2</sup> Institut des Neurosciences Translationnelles de Paris (IHU-A-ICM), Institut du Cerveau et de la Moelle Epinière (ICM), Paris, France, <sup>3</sup> UMR 7161, Laboratoire d'informatique (LIX), Ecole Polytechnique, Université Paris-Saclay, Palaiseau, France, <sup>4</sup> Integrative Oncology, Kines Medical Center, Milan, Italy, <sup>5</sup> UMR-S975, CNRS, INSERM, Institut du Cerveau et de la Moelle Epinière (ICM), Paris, France

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### \*Correspondence:

Laurent Schwartz,  
Laboratoire d'Informatique (LIX),  
École Polytechnique, 91128  
Palaiseau Cedex, France  
laurent.schwartz@polytechnique.edu

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The pathogenesis of common diseases, such as Alzheimer's disease (AD) and cancer, are currently poorly understood. Inflammation is a common risk factor for cancer and AD. Recent data, provided by our group and from others, demonstrate that increased pressure and inflammation are synonymous. There is a continuous increase in pressure from inflammation to fibrosis and then cancer. This is in line with the numerous papers reporting high interstitial pressure in cancer. But most authors focus on the role of pressure in the lack of delivery of chemotherapy in the center of the tumor. Pressure may also be a key factor in carcinogenesis. Increased pressure is responsible for oncogene activation and cytokine secretion. Accumulation of mechanical stress plays a key role in the development of diseases of old age, such as cardiomyopathy, atherosclerosis, and osteoarthritis. Growing evidence suggest also a possible link between mechanical stress in the pathogenesis of AD. The aim of this review is to describe environmental and endogenous mechanical factors possibly playing a pivotal role in the mechanism of chronic inflammation, AD, and cancer.

**Keywords:** cancer, inflammation, fibrosis, pressure, Alzheimer's disease, mechanical stress

## Introduction

Mechanical stress defines the distribution of forces exerted in a solid or fluid body being deformed as a result of external loads. Deformation changes the relative locations of molecules within a body which gives rise to internal forces balancing external loads. We already have an intuitive understanding of distribution of forces when we consider pressure. Mechanical stress is analogous to pressure when the forces are perpendicular to a surface (compressive or tensile stress). When the forces run parallel to a surface there is a shear stress. The influence of mechanical stress of living organisms is omnipresent. It depends not only on environmental and endogenous loads (pressure exerted by cavities and blood) but also on intrinsic mechanical factors of organs, such as shape, architecture, and mechanical properties of tissues (1, 2).

Mechanical stress could be the cause, the consequence, and/or might also simultaneously interact with biological processes. Cells are continuously subjected to mechanical forces that influence cell

division, gene expression, cell migration, morphogenesis, cell adhesion, fluid homeostasis, ion channel gating, and vesicular transport (3–5). The seminal work of D'Arcy Thompson demonstrated that physical forces play a key role in plant and animal morphogenesis (6). Aging-associated diseases of different mechanisms, such as cardiomyopathy (7), degenerative valvular disease (8), atherosclerosis (9), and osteoarthritis (10), and cataract (11) present mechanical factors interacting with their pathogenesis. The aim of this review is to describe the potential role of mechanical stress as a pathway underlying the mechanism of chronic inflammation, cancer, and Alzheimer's disease (AD). Cancer and AD are obviously different diseases but they share multiple common epidemiological and biological features.

## Common Denominators Between Cancer and AD

In both cancer and AD, there are a small (<3%) but informative proportion of the patients who have inheritable genetically transmissible risk factors. More than 50 different genes are known to be involved in cancer. For example, BCRA1 and BCRA2 carriers are at a very risk not only for breast cancer but also for ovarian cancer and sarcoma. This risk is high enough (80%) as to warrant prophylactic surgery, such as mastectomies. To the difference with the much more common sporadic cancer, these tumors arise in young patients most commonly before the age of 50. Around 0.1% of the cases of AD are familial forms of autosomal-dominant inheritance, which usually have an onset before age 65 (12). Most of autosomal-dominant familial AD can be attributed to mutations in one of three genes: those encoding amyloid precursor protein (APP) and presenilin 1 and 2 (13). Most mutations in the APP and presenilin genes increase the production of a small protein called amyloid  $\beta$  ( $A\beta$ ), which is the main component of senile plaques (14). Most cases of AD do not exhibit autosomal-dominant inheritance, and thus are termed sporadic AD. These genetic features are rare and should not let us miss the main features.

Cancer and AD share two major risk factors: age and sex. Two-thirds of cancer and AD arise after age 70 (15). Two-thirds of the patients are over 70 when diagnosed either with cancer or AD. The second risk factor is sex. Men are at a given age at a higher risk for cancer or AD. Moreover, aging is clearly linked to chronic inflammation; aging is associated with increased levels of chronic inflammation and with inflammatory activity reflected by increased circulating levels of cytokines, such as tumor necrosis factor (TNF) and interleukin (IL) 6, and acute phase proteins (16). Various inflammatory processes and cytokines may also have a role in the pathology of AD. Inflammation is a general marker of tissue damage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response (17).

## Inflammation as a Common Risk Factor for AD and Cancer

Inflammation is a common risk factor for cancer and AD. Liver cancer is frequently associated with such pre-existing

inflammation and fibrosis. Between 60 and 90% of hepatocellular carcinoma occur in patients with hepatic macronodular cirrhosis (18, 19). Chronic liver disease of any type is a risk factor for liver cancer. Evidence for a cause-effect link between cirrhosis and hepatocellular carcinoma is lacking. The relation may often be one of chance alone, since not all cirrhotics develop cancer. Nonetheless, diseases that cause cirrhosis also increase the risk of hepatocellular carcinoma (19). Furthermore, the more disorganized the liver becomes, the higher the risk of hepatocellular carcinoma (18, 19). The same is true for lung cancer, which is very often preceded by chronic bronchitis (inflammation of the main bronchi). Chronic bronchitis paves the way toward lung cancer. Long-term usage of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced likelihood of developing AD (20) and cancer (21). In addition to long-standing evidence from observational studies, evidence from randomized trials of the effectiveness of aspirin for chemoprevention of colorectal cancer has increased substantially in recent years. Trials have shown that daily aspirin for about 5 years reduces incidence and mortality due to colorectal cancer by 30–40% after 20 years of follow-up, and reduces the 20-year risk of all-cause cancer mortality by about 20%. Human post-mortem studies, in animal models, or *in vitro* investigations also support the notion that NSAIDs can reduce inflammation related to amyloid plaques (20). However, trials investigating their use as palliative treatment have failed to show positive results while no prevention trial has been completed (20).

## Inflammation is Synonymous to Increased Osmotic Pressure

The word “physician” is a reminiscence of the time when medicine was a part of Physics. But today, the role of physical forces in the development of disease has been largely neglected (to the notable exception of orthopedics). Inflammation is characterized by *tumor*, *dolor*, *rubor*, and *calor* as stated by Galen 2000 years ago. Inflammation can be caused by factors as diverse as heat, freezing temperature, trauma, or chemicals. The capillary hydrostatic pressure drives fluid out of the capillary (i.e., filtration), and is highest at the arteriolar end of the capillary and lowest at the venular end. The oncotic pressure drives the liquid back into the capillary. Because the capillary barrier is readily permeable to ions, the osmotic pressure within the capillary is principally determined by plasma proteins that are relatively insoluble. Therefore, instead of speaking of “osmotic” pressure, this pressure is referred to as the “oncotic” pressure or “colloid osmotic” pressure because it is generated by colloids. Albumin generates about 70% of the oncotic pressure. This pressure is typically 25–30 mmHg.

During inflammation, there is extravasation of proteins from the vascular space to the extracellular space. It is known to the clinicians that there is an increase of protein content in the inflammatory fluid, such as a pleural effusion or a pericarditis. This increased protein content and the resulting increased osmotic pressure is the reason for inflammation. We have previously shown both *in vivo* and *in vitro* that hyperosmolarity can induce pro-inflammatory cytokine responses in epithelial cells (22–24). Our group and others recently demonstrated that inflammation

results from increased interstitial pressure (16, 22–24). There is increased osmotic pressure in the inflammatory fluid due to the presence of a large quantity of proteins. This increased extracellular osmolarity results in the secretion of pro-inflammatory cytokines, such as TNF, IL 6 and 8, and numerous other cytokines. Monocytes exposed to hyperosmolarity doubled their half life (24). It is probable that inflammation (a disease) is synonymous to increased osmolarity pressure (a force).

## Mechanical Stress as a Critical Factor in Cancer

Many solid tumors show an increased interstitial fluid pressure (IFP), which forms a barrier to transcapillary transport. This barrier is an obstacle in tumor treatment, as it results in inefficient uptake of therapeutic agents. There are a number of factors that contribute to increase IFP in the tumor, such as vessel abnormalities, fibrosis, and contraction of the interstitial matrix. It is this increased pressure that the physician tries to feel when doing a clinical exam, such a rectal exam when searching for a prostate cancer.

The role of increased pressure in carcinogenesis has been poorly investigated. There is a continuum of increased pressure from normal tissue to inflammation fibrosis and cancer. The pressure of the hepatic parenchyma is 4 mmHg. The parenchyma is under increased pressure in liver cirrhosis (13 mmHg) and in primary or metastatic cancer (between 15 and 25 mmHg). The increased interstitial pressure may be responsible for the most common features of cirrhosis and/or cancer, such as hepatocyte necrosis, extensive fibrosis, connective tissue deposition, vascular distortion, infiltration by immune cells, and nodular regeneration of the remaining tissue parenchyma. Increased pressure is known to induce collagen deposition and modulate cell proliferation either by cell death or by cell multiplication (25). Exposure of immune cells to increased osmotic pressure doubled their half-life (23).

Increased pressure is responsible for cancer invasion. Cancer invades preferentially soft tissues such as glands or muscle rather than fascia or bone (15). It is also because of increased pressure that cells can escape, reach the blood vessels to form distant metastasis. Physical forces play also a major role in cell proliferation (25–27). Mechanical deformation induces cell proliferation (26). Cell proliferation of colon carcinoma cell line, HCT116, is increased by 30% after 2 days of deformation (30 cycles/min). But solid stress (45–120 mmHg) inhibits multicellular tumor spheroid (27). Changes in physical constraints has another consequence (28), the probability of a wrong plane of cell division is increased. Transition from normal, well stratified epithelium, to an invasive, fractal, dendritic pattern is observed. This transition shows a sequence of morphologies in the following order as a function of loss of polarity: first, an apparently normal but already diseased tissue, then, metaplastic followed by a dysplastic tissue, and eventually carcinoma first *in situ*, then invasive. In fact, most normal cells, and especially the epithelial cells are organized along a structural plane (29), which allows cell adhesion to the mesenchyme on one side, and epithelium function on the lumen side.

Changes in physical constraints explain the stellar dendritic shape of cancer, enabling the cells to escape physical constraints from their neighbors (25, 28). This functional polarity is most often lost during carcinogenesis (29). In normal tissue, it is maintained by the cytoskeleton, by vesicular trafficking that proceeds along the microtubules (30), by organelles, such as the centrosomes, and in general terms, by the interpretation of cues coming from the surrounding tissue. In particular, mechanical forces coming from neighboring cells are able to induce a polarity of the cell, and influence cell divisions in specific directions. This question has already been studied in plants, where it is known that one can induce deterministically the position of the plane of division by a mechanical stress (31).

## Interactions Between Mechanical Stress and AD

### Mechanical Stress may Influence AD Pathophysiology

Several authors have already suggested the hypothesis that AD pathology is driven by mechanical forces. Wostyn et al. and Silverberg et al. were the first to bring up the causative link between intracranial pressure and AD (32–36). It has been shown that mechanical impedance (a measure of how much a structure resists motion when subjected to a given force) of the intracranial cavity and vessels plays a role in the pathophysiology of AD (37). Some have set forth that the strength of the pulse waves induced by the vascular tree in the craniospinal cavity is the underlying vascular pathophysiology behind AD and other conditions, such as vascular dementia and normal pressure hydrocephalus (NPH) (38–41). Barz (42) set forth that mechanical changes accumulate in neuronal membranes and cytoplasm in old age, in a similar fashion to how vessel walls stiffen and change in arteriosclerosis. Hachiya et al. (43) suggested that continuous and repetitive exposure to environmental mechanical stress, mostly in an unrecognized and inevitable manner in daily life, becomes a potential driving force for A $\beta$  and tau aggregation (43).

A great number of studies have suggested that amyloid cascade may occur in parallel and their onset and rate could be under the influence of a series of environmental risk factors (44). Mechanical stress has been positioned as an environmental factor that may provoke disturbances in the cellular quality control systems and molecular chaperones that target misfolded proteins, such as tau and A $\beta$  (43). Computational simulations have shown that A $\beta$  structure could be twisted, flexed, and bent by the imposition of shear forces (45), which suggests that shear stress may influence A $\beta$  misfolding and aggregation. Tau proteins, in turn, may resist and accumulate elastic stress, which seems to protect axonal microtubule from mechanical deformation (46). Amyloid peptides, others than A $\beta$ , have been described in mechanical loading environments, such as heart valves exposed to high shear stress (47) or in the joint cartilage (48). Amyloid adhesion and nucleation, critical events in A $\beta$  aggregation, can be mechanically induced by tensional forces exerted in amyloid nanofibers (49, 50). Atomistic simulations also showed that helical nanostructure of A $\beta$  oligomers may induce neurotoxicity by mechanical damage on membrane structure (51).

## AD Risk Factors may be Linked to Mechanical Stress Exposure

Epidemiological and neuropathological data suggest a tight association between AD and the exposure to mechanical stress factors. Extracranial mechanical stressors predisposes an individual to AD later in life, as observed in traumatic brain injury (TBI) (52) and occupational exposure in athletes (boxers, football, and soccer players) and military personnel (53). Neuropathological analysis of TBI tissues in humans has led to notable findings regarding AD pathological features. Abnormal accumulation of A $\beta$  deposits (54) and cytoskeletal tau proteins, pathological hallmarks of AD, has been constantly detected after isolated or/and repetitive cranial impacts (55, 56).

Mechanical energy can also exert stress within intracranial environment. Cerebrovascular blood flow accompanying every heartbeat generates forces that can displace the brain tissue by tens of micrometers (57). Similarly, mechanical interactions constantly occur between brain parenchyma and cerebrospinal fluid (CSF) (58). These mechanical stressors interacting with brain compartments are confined within the rigid structure of the skull. Changes in intracranial hydrodynamics may result in an increased risk of AD as seen in NPH, since several studies have demonstrated neuropathological evidence of AD in NPH patients (59–62). NPH is characterized by transient intracranial pressure peaks, while CSF pressure measurements usually remain within the normal range. The accumulation of hydrodynamic loads leads to chronic mechanical stress on the ventricular walls, and ultimately on the brain parenchyma (63). The frequency of tau-amyloid deposits through cortical biopsies taken during shunt placement has been shown to be greater than that of the general population, suggesting that NPH and AD may occur as a result a coexisting hydrodynamic pathophysiology (64–66).

Cerebrovascular hemodynamic stress, caused by atherosclerosis, heart diseases, and arterial hypertension, also affects cognition and are among the most important risk factors for AD (67).

These vascular conditions interact with intracranial mechanical constraints, and so could be considered as “mechanical” risk factors (68). Arterial hypertension increases brain hemodynamic stress as a result of pulsating shock waves (some 30 million/year) produced by the external surface of the arterial wall in contact with the brain parenchyma (69). Atherosclerosis can increase brain arterial stiffness, increasing mechanical damage of the perivascular tissue (70) and leading to accumulation of A $\beta$  plaques (71) and cognitive decline (40, 72).

## Mechanical Stress Models of AD-Like Pathology

Effects related to endogenous mechanical energy in AD pathology have been widely overlooked in hypotheses involving a postulated molecular amyloido-centric pathway, such as the amyloid cascade theory (73) derived from reductionistic transgenic animal mutation models that do not account for the principles of mechanics. Extracellular accumulation of A $\beta$  and intracellular accumulation of tau in brain tissues and neuroinflammation have been described not only in transgenic animal models of AD but also in mechanical stress-based diseases of different mechanisms, such as TBI, arterial hypertension, and NPH. As observed in humans, AD-like pathology is also present in numerous experimental models of TBI using mice, rats, rabbits, pigs, and monkeys (74). Animal models of NPH have revealed accumulation of tau and A $\beta$  deposits in brain tissues subjected to hydrodynamic stress (75, 76). It have been also found that rodent models subject to high levels of blood pressure, or hemodynamic stress, demonstrate an accumulation of A $\beta$  and tau aggregates (77, 78). These mechanical stress models may increase our knowledge of how different mechanical factors, from both the external and the internal environment, could influence pathophysiological mechanisms underlying AD. **Table 1** compares five hallmark features from transgenic and mechanical stress rodent models of AD pathology. Amyloidosis, tauopathy, gliosis, neuronal loss, or cognitive impairment could be present in at least four of the five selected mechanisms of mechanical stress.

**TABLE 1 | Selected transgenic and mechanical stress-based models displaying AD pathological hallmarks.**

Rodent models	Transgenic			Mechanical stress			Arterial hypertension	HPN
	APP	Tau	APPxTau	Traumatic brain injury				
				CCI	FPI	Mild/WD		
Amyloidosis	++	–	+	++	+	++	++	+
Tauopathy	? <sup>a</sup>	++	+	++	+	? <sup>b</sup>	+	+
Neuroinflammation	++	+	+	++	+	+	++	+
Neuronal loss	? <sup>c</sup>	? <sup>c</sup>	–	++	+	++	? <sup>d</sup>	+
Cognitive impairment	++	++	+	++	++	++	? <sup>d</sup>	+
Reference	(79–81)		(79–82)	(83–91)	(92–97)	(83, 90, 98, 99)	(77, 78, 100)	(75–106)

Comparison between transgenic and mechanical stress rodent models as a function of five hallmark features of AD pathology.

(+) Feature present in mice or rat models.

(++) Feature present in both mice and rat models.

(?) Unknow.

<sup>a</sup>Only increased p-tau but no tau deposits.

<sup>b</sup>Tau transgenic mouse.

<sup>c</sup>Only present in a few models.

<sup>d</sup>Only when associated with white matter and focal lesions.

APP, amyloid precursor protein; CCI, controlled cortical impact; FPI, fluid percussion injury; Mild, mild repetitive trauma; WD, weight drop; NPH, normal pressure hydrocephalus.

## Mechanics Related to Brain Atrophy and Brain Amyloidosis in AD

In general, biological tissues adapt to higher levels of stress by changing cross-sectional area, density, or volume. In a recent work, our group estimated increments of mechanical stress undergoes by the tissues during brain shrinkage. Selecting AD as a primary model of a non-linear dynamic, chronically progressive degenerative disease, pressure equivalents were related to atrophy and found to be 42% higher in AD brains comparatively to normal aging brains (5.92 versus 3.43 mmHg, respectively). The phenomenon of mechanical brain fatigue, or the increased amplitude of oscillations generated by arterial, hydraulic, or external shock waves, was suggested to mainly contribute to the accumulation of mechanical stress in AD (107). Another example of how organs adapt to stress consists in changes in its mechanical properties. In AD, slow cumulative changes in the microarchitecture of the brain could impact its mechanical properties (108, 109). The elasticity and stiffness of the brain vary substantially in normal humans as well as with age and the state of the disease (110). Cerebral stiffness, which can be measured by magnetic resonance elastography (MRE) (111), decreases when AD pathology is present in both humans and transgenic mice models (108, 112). However, the extent to which mechanical dynamics influence AD pathophysiology, and vice-versa, remains a mystery. AD deposits could increase the resilience of neuronal tissues to mechanical stressors and consequently increase the tolerance to subsequent stresses. Like muscle fibers, neuronal tissues may adapt to physical stresses by altering their structure and composition to better meet the biological requirements of routine energy loads. It raises the possibility that mechanical stress levels, which exceed the maintenance range of brain tissues, could trigger and accelerate protein misfolding, aggregation, and deposition. The higher the exposure to mechanical stress, the more likely an early onset of the disease will be (43).

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**TABLE 2 | Core hypotheses linking mechanical stress and the pathophysiology of cancer, inflammation, and Alzheimer's disease (AD).**

Condition	Hypothesis
Cancer	Increased interstitial pressure may accelerate carcinogenesis Mechanical forces may induce cell polarity, and consequently modulate cell divisions in specific directions
Chronic inflammation	Increased interstitial pressure (hyperosmolarity) may drive inflammation
AD	Accumulation of mechanical energy during lifespan may accelerate amyloid cascade, tauopathy, and microarchitectural changings in brain tissues

## Conclusion

The role of mechanical forces in the pathogenesis of chronic inflammation, AD, and cancer has been overlooked. In addition to genetic factors, the accumulation of mechanical energy could underlie biological cascade pathways in inflammation, cancer, and AD (Table 2). This hypothesis has to be tested before any conclusion can be drawn. The extent to which mechanical energy influences the pathophysiology of these conditions, and/or whether mechanics is just an effect of biological processes, remains a mystery. Mechanical stress could be the cause, the consequence, and/or might also simultaneously interact with biological processes. We point to the importance of accumulated mechanical stress as an environmental and endogenous factor that pushes cell and tissue functioning over the disease threshold.

## Author Contributions

All the authors contributed equally to this manuscript.

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