Editorial
Angiotensin and Systems Thinking:
Wrapping Your Mind Around the Big Picture

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TODAY’S PROBLEMS COME FROM YESTERDAY’S SOLUTIONS

Systems thinking is a discipline for seeing wholes. It is a framework for seeing interrelationships rather than isolated things and events, for seeing dynamic patterns of change rather than static snapshots.1 Senge’s The Fifth Discipline emphasizes how systems thinking can help one understand the causes of and provide effective treatments for learning disabilities in organizations. The 11 laws of The Fifth Discipline are also applicable in many ways to problems of health and disease treatment and are recommended for problem solvers in this domain.

The challenges we face today for disease treatment are much different from those of the past. We are seeing growing incidences of autoimmune diseases, cancer, and neurodegenerative disorders. The most immediate factor in considering our current challenges is that we are simply living longer. This fact makes logical sense when considering cancer and diseases such as Alzheimer disease, but autoimmune diseases affect mostly the young and middle aged. The problem with autoimmune diseases is that we don’t yet fully understand the problem; our current understanding is that the immune system mistakenly attacks the very tissues it is intended to protect, but we don’t really understand the cause (the why) or the process. Some of the common factors proposed as potential contributors to the rise in autoimmune diseases include a decline in gut flora health,2 leaky gut,3 overuse of vaccines3 and antibiotics,4 environmental toxins such as pesticides,5 infections,6 reduced vitamin D,7 and environmental estrogen.8 Quite possibly, many of these factors are contributors or parts of a hidden bigger picture, but without an overall understanding of the cause and process of autoimmune diseases, we will continue to struggle to understand the problem and progress with a real solution.

This paper is based on published peer-reviewed literature, starting with the puzzle of chronic inflammation in disease. In an effort to solve this puzzle, the paper revisits a hormone system with capabilities that far exceed established expectations and explains how this system is corrupted in cancer to drive malignant processes and suppress the immune system. The cancer paradigm contributes to a greater understanding of how cells interact with their microenvironment and reveals a potentially clearer understanding of not only cancer but also many other diseases.

MENTAL MODELS DETERMINE UNDERSTANDING

Change in itself is not necessarily good or bad, but it is inevitable. Everything changes. In any system, the interaction and relationship between the system components and its environment are of supreme importance. In a system, things change due to time and circumstance as a result of interrelationships. Our minds, too, are systems, and perceptions are the result of numerous mental models we have built through our collective experience. These mental models help us to understand and interact successfully with our environment. Changes in thinking occur as a result of new knowledge or experience that expands and improves our understanding of how and why things work. During the process, the resultant changes in our mental models increase our success in life.

In 1900, Lord Kelvin famously stated, “There is nothing new to be discovered in physics now. All that remains is more and more precise measurement.”

While the accumulation of knowledge benefits from a reductionist approach, understanding of the why is only gained by considering the behavior of the whole in the context of its interaction with its environment. Five years after Lord Kelvin’s statement, Albert Einstein published his paper on special
Revolutions that cannot be explained by the current model. 9 of facts that seem significant and indisputably true but first signs that a paradigm is shifting is the discovery of comprehensive paradigm. He stated that one of the years. What Einstein had done was to provide a new way of looking at established data, new mental models that have revolutionized our understanding of the universe and our ability to interact with it. In 1970, T. S. Kuhn, in The Structure of Scientific Revolutions, argued that scientists work by creating a comprehensive paradigm. He stated that one of the first signs that a paradigm is shifting is the discovery of facts that seem significant and indisputably true but that cannot be explained by the current model.9

Discovery commences with the awareness of anomaly, i.e. with the recognition that nature has somehow violated the paradigm-induced expectations that govern normal science. It then continues with a more or less extended exploration of the area of anomaly. And it closes only when the paradigm theory has been adjusted so that the anomalous has become the expected. Assimilating a new sort of fact demands a more than additive adjustment of theory, and until that adjustment is completed—until the scientist has learned to see nature in a different way—the new fact is not quite a scientific fact at all.5,52

One such case is the puzzling role of inflammation: Inflammation is regarded as a key component of the immune system that ensures tissues of the body are free from invading organisms and pathogens. When an area is infected, it becomes red, swollen, hot, and painful. Another recognized function of inflammation is to support the healing process by removing cells that have been damaged through injury or by infection. In disease conditions, the immune system somehow malfunctions (develops an aversion to self). Instead of attacking invaders and destroying damaged tissue, inflammation starts to destroy healthy tissue, causing biological dysfunction, immune suppression,10–13 and ultimately death. Chronic inflammation is a critical feature of most diseases. Regardless of the underlying cause (infection, cancer, aging, autoimmunity), it is the chronic inflammation that ultimately damages the body.

When we try to understand inflammation and why inflammation can be immune suppressive, a useful mental model is to recognize that the biological manifestation of inflammation is a tissue state, and when tissue is inflamed, the involved white blood cells are participating in a wound, or tissue remodeling, response. While the immune and wound response systems share many of the same components (cells—in particular white blood cells) and many interface messengers (such as cytokines, chemokines, hormones, and other mediators), categorizing cells such as white blood cells simply as immune cells limits our ability to understand what is taking place because their function changes over time and depends on their environment. Many cells, including white blood cells, are better described as multifunctional. Much the same can be said for many of the messengers—such as interleukin (IL)-1 or tumor necrosis factor-alpha (TNF-α) (both considered strong proinflammatory mediators)—because their message and corresponding action depend on the state of the cells that receive the message. Simply put, an inflammatory response is not necessarily an immune response; indeed one key message from this paper is that inflammation (the tissue state) results in the suppression of adaptive immune responses.

Some new mental models presented here through words and pictures will challenge established mental models and inevitably conflict with the current ways of thinking. The old models are not bad; however, the new mental models may provide a better understanding of how and why biological systems do what they do. Through an improved understanding of the big picture, we create opportunities to work in harmony with these systems and better treat disease by addressing the causes and not just the symptoms. This is the power of systems thinking.

INTRODUCING THE CLASSIC RENIN-ANGIOTENSIN SYSTEM

In 1898, Tigerstedt and Bergman14 published their observation that kidney extracts produce pressor effects. They partially characterized the substance and named it renin. Although this observation began our understanding of the role of the kidney in hypertension and the renin-angiotensin system (RAS), their discovery lay dormant for nearly 40 years. Around 1936, 2 independent groups of researchers, using the Goldblatt technique to produce experimental hypertension, demonstrated renal secretion of a pressor agent similar to renin. They eventually concluded that renin acted enzymatically on a plasma protein to produce a new substance: angiotensin.15 The current widely recognized view is that the main effector of the RAS (Figure 1) is angiotensin II (AngII). AngII is generated from the precursor protein angiotensinogen by the actions of renin, angiotensin-converting enzyme (ACE), chymases, and various carboxy- and amino-peptidases. AngII exerts its pressor effects on the cardiovascular and renal systems via interactions with its 2 receptor molecules, AngII type 1 receptor (AT1R) and AngII type 2 receptor (AT2R). The receptors are viewed as mutually antagonistic in the control of blood pressure, water, and electrolyte homeostasis.
The angiotensin system is currently targeted primarily as a means of controlling blood pressure. The main drug targets are ACE inhibitors (ACEIs) or AT₁R blockers (ARBs).

REVEALING THE TRUE NATURE OF THE ELEPHANT

A contemporary model of the RAS is well described in a 2010 review of the emerging role of the RAS in cancer. This review also summarizes several aspects and new components of the system. The established view of the RAS being governed by the brain and the kidney is systemically being extended by the knowledge that many, if not all, components of the RAS can be produced as required by resident or infiltrating cells, such as mast cells, as a consequence of infection or injury. Also of great importance, an alternative pathway for angiotensin has been found whereby a new enzyme, ACE2, liberates angiotensin 1-7 (Ang1-7), which acts on the Mas receptor. Although the Mas receptor was originally identified in 1986 through the Mas proto-oncogene (protooncogenes code for proteins that help regulate cell growth and differentiation), only in 2007 did the ACE2/Ang1-7/Mas pathway come under consideration as a target outside of blood pressure control.

Could the 21 years that separate these 2 papers indicate how difficult moving from one mental model to another can be? This situation may be an example of how inertia regarding paradigm shifts constrains understanding and progress. Resistance to change in mindsets is a key point; not only is the researcher's ability to make the initial mental jump important, but the mindsets of the people who make decisions about funding also play a vital role.

When the RAS was first studied and its potent blood control effects were discovered, a mental model was established that the RAS controlled blood pressure with complementary effects in controlling thirst, salt retention, and fluid homeostasis. As additional components of the RAS are identified and characterized with properties including inflammation, immune modulation, tissue development, and tissue repair, this model is being challenged. In the fable of the blind men who came across an elephant, each of them had a different perception of what the elephant was (Figure 2).

In the case of the RAS, when researchers first came across the system (and grasped the tail of the elephant), they concluded that it controlled blood pressure. Our continued exploration of the RAS is revealing new biologically critical, yet puzzling facets, but they are only puzzling when not placed in the context of the big picture. Through a synthesis of newly established knowledge, the emergent picture (mental model) is that in an established animal, the RAS controls and manages the body's response to injury and wounding. When looking overall at the big picture, we can see that the properties of the RAS in the control of blood pressure, salt retention, and

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**Figure 1.** The classic renin-angiotensin system. AT₁, angiotensin II type 1; AT₂, angiotensin II type 2.

**Figure 2.** The elephant of understanding. (Adapted with permission from Himmelfarb et al.) ACE, angiotensin-converting enzyme; Ang1-7, angiotensin 1-7; AngII, angiotensin II; AT₁, angiotensin II type 1; AT₂, angiotensin II type 2.
Fluid homeostasis are simply important aspects of this wider function (Figure 3). The implications of this new understanding could revolutionize our approach to treating many chronic inflammatory diseases, including cancers, autoimmune diseases, neurodegenerative disorders, and infections.

The danger is that if we cannot adapt our thinking, then we will be slow, or worse still, will fail to take advantage of our new knowledge and understanding.

**YES, THE RAS REALLY DOES HAVE A KEY ROLE IN HEALING**

From a research perspective, the role of the RAS in healing has until recently perhaps been considered a peculiarity. However, with the discovery of the ACE2 enzyme and Ang1-7, commercial interest has increased and the role of the RAS in wound healing is becoming a hot topic. Several papers have now been published in the area of RAS and wound healing.

Inhibition of ACE has been found to promote healing in mouse models of bone fracture. Garcia et al. found that ACE inhibition increased AT2 presentation. Meanwhile, an analog of Ang1-7 has been found to facilitate enhanced healing in diabetic wounds. A review of aging and cardiac fibrosis highlighted the important role of AngII and AT1 in mediating fibrotic remodeling of the aging heart.

A recent study observed the change in the local level of AngII and the expression of AT1R and AT2R during wound healing. The results support the hypothesis that AngII participates in wound repair and remodeling in the late stage of wound healing through changes in the production of AngII and expression of AT1R and AT2R.

In an investigation of the role of AngII receptor subtypes in subconjunctival injury in mice, knockouts of AT1a and AT2 were found to have contrasting effects in collagen deposition, cell infiltration, and expression of collagen and tissue inhibitor of metalloproteinase-1 (a mediator that in general promotes tissue formation). Similarly, another AT1a knockout model found reduced wound-induced angiogenesis and wound healing. Results in these models support similar findings in human skin tissue, in which immunohistochemically stained skin sections showed a stronger expression of AT2R than of AT1R within the area of scarring. Enhanced AT2R expression was detectable as early as 24 hours after injury and lasted for up to 3 months.

A rabbit model of deep alkaline-induced corneal burn injury found a significant increase in ACE activity in the tear and internal ocular tissue structures, promoting microcirculatory disorders and tissue inflammation. The local use of ACEIs as instillations...
substantially reduced inflammation and the incidence of deep and extensive corneal ulcers.\textsuperscript{30}

Researchers modulating the response to local and systemic AngII in acutely injured skeletal muscle concluded that the clinical implications for the application of ARBs are potentially far reaching and include not only sports- and military-related injuries, but also diseases such as muscular dystrophy and trauma- and surgery-related injuries.\textsuperscript{31}

A search on PubMed in March 2012 showed 260 papers from a search of “angiotensin” and “healing” and 522 papers from a search of “angiotensin” and “repair.” These results include multiple organs and diverse types of insults, including infections, physical and chemical injuries, and radiation. Collectively, these published studies suggest that interest in the role of the RAS in injury responses and healing is growing.

A PubMed search in October 2012 found 4,684 papers in a search of “angiotensin” and “stress,” compared with 3,120 papers in a similar search of “stress” and “heme oxygenase,” a ubiquitous and well-documented stress-responsive protein. In injury models, skeletal muscle myoblasts have been reported to possess a stretch-responsive local angiotensin signaling system, in which angiotensinogen was transcriptionally expressed and ACE, AngII, AT\textsubscript{1}, and AT\textsubscript{2} were all locally evidenced.\textsuperscript{40} Renin transcripts were never detected. However, messenger RNA for the renin-like enzyme cathepsin D was observed, and Angl and AngII were identified in cell culture supernatants from proliferating myoblasts. The activation of a locally generated RAS has also been reported in hyperoxia (excess oxygen or higher than normal partial pressure of oxygen)-induced lung fibrosis in neonatal rats. In this study, RAS components including angiotensinogen, ACE, AngII, and the AT\textsubscript{1} receptor were significantly upregulated by hyperoxia.\textsuperscript{41} AT\textsubscript{1}R expression would appear to be a fundamental reaction by all cells to tissue stress and injury (Figure 5), glycemic stress,\textsuperscript{42} hypoxia,\textsuperscript{43} shear stress,\textsuperscript{44-46} and oxidative stress via oxidized low-density lipoprotein acting on the LOX-1 receptor.\textsuperscript{47-50} These reactions all lead to the transcription and presentation of the AT\textsubscript{1}R on cells. A spectrum of

![Figure 4. Angiotensin and disease. AIDS, acquired immunodeficiency syndrome; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SARS, severe acute respiratory syndrome.](image-url)
Important molecules involved in the cellular response to stress is induced by AT$_1$R.$^{21}$ These molecules include highly proinflammatory mediators such as IL-1$\beta$, TNF-$\alpha$, IL-6, and cyclooxygenase-2 (COX-2), as well as other agents that promote the influx and migration of white blood cells (such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1), the growth of new blood vessels (notably through vascular endothelial growth factor expression and signaling), and tissue remodeling (notably through matrix metalloproteinases and transforming growth factor-beta [TGF-$\beta$]).

A key question is what is the purpose of the activity promoted by the RAS through the AT$_1$ receptor? If cells are under stress and trigger changes in the environment of the cell, then the answer would seem to be a coordination of effort to remove or relieve the cause of the stress. In a healthy response to a wound, the damaged tissue is remodeled, dead and dying cells are cleared, a fibrous framework is laid down as the platform for tissue regeneration, and new blood vessels grow to support the new tissue. In disease conditions, the stress is not removed, the response continues unabated, and healthy tissue becomes subject to remodeling.

**EXPLAINING THE ROLE OF INFLAMMATION IN CANCER**

“The Hallmarks of Cancer,” the authoritative work by Hanahan and Weinberg,$^{51}$ described a new systems approach that analyzed the evolved capabilities necessary for cancer cells to become life-threatening tumors. Figure 6, adapted from this work, highlights some of the common defects in growth, antigrowth, and death controls that are necessary for normal cells to become cancerous and for tumors to form.

The key control signals that ensure that normal cells are maintained in relatively stable equilibrium (homeostasis) with their environment are presented in this cell circuitry. Figure 6 highlights some of the common genetic changes that must occur for cells to circumvent these controls and for carcinogenesis to happen. Inflammation pathways, such as radical oxygen species, overlap significantly with cancer circuits and increase the risk of genetic damage in targets that contribute to cancer initiation and progression. Inflammation from infection, injury, and stress or aggravators such as smoking or asbestos have been shown to induce cancers.$^{52-56}$ What is more surprising, however, is the emerging critical role of inflammation in the progression of the disease to
As cancer cells evolve to ignore programmed cell death, the uncontrolled proliferation causes a microenvironmental stress that provokes an inflammatory response. The resultant influx of inflammatory cells and immune cells into the microenvironment is ineffective against the cancer because those cells have developed resistance to death signals. Instead, the inflammation exerts lethal effects (apoptosis and phagocytosis) on healthy tissue and promotes many essential environmental support processes (angiogenesis, cell motility, and immune suppression) necessary for the cancer to flourish and disseminate.

This process is reflected in a direct relationship between systemic and chronic inflammation and patient mortality. Indeed, researchers have proposed that the reversal of these processes through microenvironment improvement could provide a new therapeutic approach.

The effects of unresolved stress and activation of the local RAS are perhaps most clearly observed in cancer (Figure 7). While the origin of cancer involves unrestrained growth in the cancerous cells, the stress of this unrestrained growth on all of the cells—both cancerous and healthy—drives malignant processes through the AT₁R. As previously reviewed, knockout and other models demonstrate that AT₁ expressed not only on tumor cells but also by the host stroma and on infiltrating white blood cells contributes to malignant processes. In knockout models, for instance, manipulation of various aspects of the angiotensin system can have significant consequences on cancer progression during tumorigenesis and malignancy. Additionally, what may appear to be conflicting influences are actually in keeping with the 2-phase view of the lifecycle of cancer. AT₂ knockouts inhibit tumorigenesis but promote malignancy, while AT₁ knockouts promote tumorigenesis (in cells that have already acquired prerequisite mutations) but inhibit malignancy.

ANGIOTENSIN MEDIATORS ARE CLINICALLY USEFUL IN CANCER

The previously reviewed promising prospects for the clinical use of ARBs and ACEIs in cancer prevention and treatment were challenged recently by a much-publicized metaanalysis of randomized controlled trials warning that ARBs were associated with a modestly increased risk of new cancer diagnosis. This publication resulted in a wave of press headlines—"ARBs Cause Cancer!" and "ARBs Increase the Risk of Cancer!"—and resulted in
several commentaries and follow-up publications. Many of these papers advised caution in interpretation of the results. One solid finding from the metaanalysis was a small increase in the risk of cancer with an ARB/ACEI combination, but no increase in death. Many studies concluded that ARBs carry no significant risk of worsening cancer incidence or progression, and one highlighted a reduced risk of cancer with ARB use.

What is interesting from a systems perspective is that all of these studies could be right, with the findings dependent on the circumstances and timing of the observations. From an understanding of the mechanistic perspective detailed so far in this paper, long-term (5+ years) ARB and ACEI use will progressively reduce cancer risk by reducing oxidative stress and genetic damage. Over fewer years, the drugs might slightly increase the risk, particularly when an ARB/ACEI combination is used in individuals such as smokers who already have precancerous nodules. The reason why ARBs and ACEIs have this effect is that they will push the RAS towards ACE2, Ang1-7, and Mas activation (the right-hand pathway in Figure 3) that will promote regenerative/growth processes and intracellular pathways that could facilitate the cell growth cycle. Mas activation by Ang1-7, for instance, might inhibit the downstream pathways of TGF-β receptor activators, such as the protein family that mediates intracellular TGF-β signaling (Smad), thus overriding TGF-β’s growth inhibition effects. Note the importance of TGF-β and Smad pathways in Figure 6.

While understanding the circumstances of cancer risk is important, the effect of ARBs/ACEIs (or indeed Mas agonists) from a mechanistic perspective should be of great significance in patient survival because these drugs would potentially block chronic inflammatory/tissue remodeling processes in the cancer microenvironment and thus reduce malignant processes. ARBs and ACEIs have many positive effects in advanced cancer, including increased survival, improved performance status, reduced reoccurrence, and reduced toxicity when used in conjunction with radiotherapy or chemotherapy. Additionally, synergistic benefits have been found when ARBs/ACEIs are used with surgery as well as with several new and existing agents under evaluation. Thus, it would be a great pity if the prospects for the use of angiotensin mediators as a therapy in cancer were dismissed as a result of a lack of system understanding.

CELL RESPONSE IN HEALTH AND DISEASE

The understanding that cells under stress promote a response intended to alleviate the stress led to the hypothesis that an overarching model taking into account other fundamental responses might be
useful in resolving puzzles such as inflammation. Smith and Missailidis introduced a mental model that provides an explanation of how cells interact with their tissue microenvironment (Figure 8). The model is based on 3 directional vectors that reflect 3 postulated adaptive cellular responses to injury, growth, and antigens. In addition, at the model center is an innate response that represents a very basic response to cell threat that evolved during the most ancient of times in single-cell organisms.

The components of this innate response are hard-wired in the cell circuitry and not subject to tailoring or adaptation through experience. This innate response forms the basic foundation for dealing with potential invaders and stress such as occurs with bacteriophages in bacteria. For multicellular organisms, these bacteriophages include the toll-like receptor and major histocompatibility complex recognition pathways.

In the cell response model, 3 adaptive responses are envisaged that provide specialist means whereby cells can respond to changes in their environment. Each of these responses involves a pressure, or force, that drives the response; an accelerator; and a brake for the process. Candidate drivers, accelerators, and brakes have been selected based on literature reviews using Occam’s razor (ie, use the simplest model to explain a phenomenon) and a qualitative most-true-associations approach.

A basic premise for this model is that all cells have multifunctional capabilities. This fact is perhaps most strongly observed in leukocytes but is also applicable to other cells that are often perceived as more fixed in their activities, such as epithelial cells, nerve cells, etc. The model predicts that although cells are indeed multifunctional, their degree of focus to a particular response is determined by their environment. In the cell response model, “He who shouts loudest gets the most attention.”

Wound response has been the main subject of this paper and provoked the systems thinking that led to the cell response model. The pressure or force behind the wound response is cellular stress, but the governance of the response is provided by the RAS. Analysis of the literature indicates that the AT$_1$ receptor appears primary to the acceleration of this response, whereas the Mas receptor acts as the brake.

In a normal healthy response to injury, tissue stress gradually leads to increased expression of AT$_1$R. Then, as dead or dying tissue is cleared away and the new fiber is laid down, AT$_2$R and then Mas receptor expression increase. Subsequently, over a period of weeks to a month, the activities of AT$_1$R decline, tissue regeneration takes place, and AT$_2$/Mas receptors are more gradually withdrawn.
disease conditions (a chronic wound response), the source of the cell stress is not resolved as a result of the wound response. Instead, tissue remodeling continues unabated through the dominant action of AngII on AT1R and is manifest as chronic inflammation of the tissue.

The second of the adaptive responses is the growth response. The pressure behind this response is provided by insulin-like growth factor-1 (IGF-1), which is mainly secreted by the liver as a result of stimulation by growth hormones. Importantly, IGF-1 is also expressed locally during wound healing and tissue regeneration.118 The accelerator for the growth response is tissue-specific growth factor receptors (glucocorticoid receptors and hormone receptors such as those for testosterone and estrogen) that steer the growth and replication of desired cells. A literature review suggests that the candidate brake to the growth response is the retinoic acid receptor. Teboul et al119 provide an interesting review of the role of nuclear hormone receptors, including key roles for glucocorticoid and retinoic acid receptors in the governance of the internal self-sustained circadian clocks present in virtually all cells. In a healthy growth response, the presentation of these receptors controls cell replication, but in disease conditions these processes fail and lead to uncontrolled proliferation.120,121

The adaptive immune response is driven by antigen presentation. This process has also been well described.122 The host cells express self-antigens. These antigens are different from those on the surface of bacteria or on the surface of virally infected host cells or cancer cells.

With the exception of nonnucleated cells (including erythrocytes), all cells are capable of presenting antigens and of activating the adaptive response. Some cells are specially equipped to present antigens and to prime naïve T cells. Dendritic cells, B cells, and to a lesser extent macrophages are equipped with special immunostimulatory receptors that allow for enhanced activation of T cells and are termed professional antigen-presenting cells (APC).

A key step in the adaptive immune response is the conditioning or maturing of the APC so it develops the ability to train T cells to recognize antigens in the lymph nodes. Several T-cell subgroups can be activated by professional APCs, and each type of T cell is specially equipped to deal with each unique toxin or bacterial and viral pathogen. The type of T cell activated and the type of response generated depend, in part, on the context in which the APC first encounters the antigen. Many cytokines have wide-ranging properties that steer either the early (innate) or the adaptive (antigen-derived) response. Candidate accelerators for the adaptive response included IL-4, interferon-alpha, IL-17, and IL-12, but these accelerators were specific for particular cell types. Because of its overarching presence in supporting immune cell population and function, whether inflammatory or regulatory,123 IL-2 was chosen as the accelerator. IL-10 was selected as the brake because it has an equally overarching suppressive role.

EXPLANATION, PREDICTION, AND GOALS

Established thinking has confined the RAS to the control of blood pressure, but through a process of experimentation and analysis of existing data we are discovering that the RAS is involved in cancer, chronic inflammatory diseases, autoimmune diseases, allergic diseases, and neurodegenerative disorders. Our existing mental models cannot accommodate this behavior of the RAS, nor the fact that inflammation is immunosuppressive. The cell response model explains that this otherwise puzzling behavior is caused by a failure mode of the wound response and unresolved tissue stress. Furthermore, the model predicts that this stress is caused by invaders such as cancer cells and infectious agents with the deliberate intent to avoid adaptive immune responses.

One cannot help but ask why such a chink in our biological defense exists. The logical answer would seem to be that in a healthy wound response, adaptive immunity is designed to be suppressed so when dead and dying tissue is phagocytized, the development of self-antigens is suppressed to avoid genuine autoimmune reactions. The model further predicts infection as a causative factor in autoimmune diseases and suggests that we should both look for and be more receptive to the wealth of evidence showing that dealing with the underlying ongoing chronic infection, rather than merely dealing with the symptoms, will lead to successful disease treatment.

Going beyond the ability of the cell response model to explain unexpected behavior and to make predictions about disease etiology, perhaps the model will become most useful in its ability to predict synergistic combinational approaches to disease treatment. Cancer is a complex disease; multiple processes at the cellular, tissue, organ, and super-system levels are at play, all changing over time. Opportunistic infections also lead to complications because strong growth and wound responses will further suppress the adaptive immune system and subject the patient to further attack and degradation. Defeating cancer will require more than just one silver bullet. Even if we identify intracellular approaches to overcoming one fault in the cell circuitry, the cancer cells will ultimately mutate to find an alternative pathway that will again allow the cancer cells to replicate uncontrollably. The cure for cancer will
inevitably be a combinational approach that will necessitate restoring the body’s ability to fight the cancer. The cell response model predicts that a combinational approach using ACEIs/ARBs or Mas agonists to suppress the wound response with retinoic acid agonists or hormone blockers in conjunction with immune stimulants such as low-dose IL-2 or dendritic cell vaccines could be synergistically effective. Finally, we must remember that we as living systems interact with our environment and with the microorganisms that both live within us and also sometimes incidentally prey on us. Changes to our environment and to these microorganisms have had unexpected effects in the past and will continue to do so until we are fully able to comprehend the big picture.

SYSTEMS THINKING AND ANGIOTENSIN

Established thinking has confined the RAS to the control of blood pressure, but through a process of synthesis of existing data we are on the cusp of recognizing its fuller role in maintaining organism, organ, and tissue integrity. One might say, “So what?” but this question is good to ask. The answer is that the fuller nature of the RAS is architecturally significant to the whole system; in other words, the RAS greatly influences the behavior of the whole. With a better understanding of the whole and of key effects such as inflammation and immune suppression, we significantly reduce the risk of unexpected and unwelcome side effects that occur because of interventions that do not take into account the systems context. Also with a better understanding of the whole, we significantly increase the probability of realizing the expected benefits of interventions by addressing the root causes of problems and not just the symptoms. Unexpected benefits and unexpected risks and problems are daily occurrences in the medical news, but these issues are only unexpected because we do not yet have a full understanding of the whole. In understanding the role of the RAS in its response to unstrained stress in chronic inflammatory disease, we can be better prepared to embrace the potential benefits of RAS manipulation, especially in synergy with other agents. Some might wonder if this review represents speculation, but when does speculation transition to established wisdom? One answer is when a consensus of opinion is established. From the perspective of the author and a growing number of peers in the angiotensin domain, many features of this paper are already established. If this new perspective is correct, then we need to hurry up and capitalize on it. Angiotensin is not just about blood pressure.

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REFERENCES


