Why Do We Need RNA?

Dr. Amy Yasko
April 2005
Many factors influence our susceptibility to disease. These include our stress load, our environment and the toxins we absorb from it, the total number of infectious agents we are exposed to as well as our underlying genetic susceptibility to these diseases. It is important in this day and age to address all the contributing factors to these multifactorial diseases.
Multifactorial Disease

“What do schizophrenia, diabetes and autism have in common? The answer is that many different factors act together to influence their development. As well as fundamentals like age and gender, other genetic and environmental factors...may play a role in the onset of these so-called multifactorial diseases.”

Multifactorial Diseases: Choose your targets
BIOPEOPLE, Summer 2004
In recent years, a number of chronic diseases have been linked, in some cases definitively, to an infectious etiology: peptic ulcer disease with *Helicobacter pylori*, cervical cancer with several human papilloma viruses, Whipple's disease with *Tropheryma whippelii*, Lyme arthritis and neuroborreliosis with *Borrelia burgdorferi*, AIDS with the human immunodeficiency virus, liver cancer and cirrhosis with hepatitis B and C viruses, to name a few. The proven and suspected roles of microbes does not stop with physical ailments; infections are increasingly being examined as associated causes of or possible contributors to a variety of serious, chronic neuropsychiatric disorders and to developmental problems, especially in children.
Infectious Agents and Schizophrenia

• “Most cases of schizophrenia are caused by infections and other environmental events occurring in genetically susceptible individuals.”

• “Infections relating to schizophrenia occurring in this context would not...lead to disease in individuals who do not have the appropriate genetic susceptibility.”

• There was an association between infection with HSV2 and higher rates of schizophrenia.

• The authors found increased levels of antibodies to *Toxoplasma gondii* in individuals with recent onset schizophrenia.

On a related note:

• Parasitic infection impairs the immune response to the tetanus vaccine.

  (Infection and Immunity May 2004 )
Multifactorial Disease

- Environmental
- Genetic
- Infectious
- Stress

DISEASE
“I disagree with labeling those individuals who are ‘genetically susceptible’ as ‘having a genetic disease’ because they are the first injured on exposure to modern toxicants.”

Dr. Boyd Haley
Autism as a Multifactorial Disease

• Multifactorial Diseases are caused by a combination of factors acting together. This can include infections and environmental events occurring in genetically susceptible individuals. Basic parameters like age and gender, along with other genetic and environmental factors, play a role in the onset of determining vulnerability to these diseases.

• What we currently call "autism" is actually a medical condition caused by infections and environmental events occurring in genetically susceptible individuals. Infections would only lead to autism if they occur in individuals with the appropriate types of genetic susceptibility that render them vulnerable.

• The basis for this susceptibility in autism may result from single or multiple mutations in the methylation pathway, combined with complex interactions between thimerosal and this pathway. These imbalances in methylation lay the appropriate groundwork for the further assault of environmental and infectious agents to result in autism.

• As a result of the decreased activity in the methylation pathway, there is a shortage of methyl groups in the body for a variety of important functions.
• All of these changes, when they occur in utero or in very young children, can alter brain development, and can also set up metabolic changes that cause ongoing compromise of brain function.

• The metabolically caused changes in brain function can, however, be treated if problems driving these metabolic changes are treated and corrected.

• This would suggest that autism is a medical condition associated with a defect in the methylation pathway, with brain and behavior changes that lead to observable autistic behaviors occurring as a downstream consequence of these medical abnormalities. and that it should be characterized as such.

• Continuing with this analogy, perhaps autism should be reclassified as a defect in methylation that results in neuroinflammatory disease.
Atherosclerosis vs. Autism

- Genetic
  - MTHFr
- Infectious
  - Chlamydia pneumonia
  - Streptococcus
- Stress
  - Inflammatory Mediators
  - Glutamate
    - Improper Calcium Regulation
    - Improper CO₂ Regulation
- Environmental
  - Cholesterol
- Cardiovascular Inflammatory Disease

- Genetic
  - MTHFr
- Infectious
  - Viral: MMR, Herpes
  - Bacterial
- Stress
  - Inflammatory Mediators
  - Glutamate
    - Improper Calcium Regulation
    - Improper CO₂ Regulation
- Environmental
  - Heavy Metals
- Neuroinflammatory Disease
Stress + Infectious agents + Toxins + Underlying genetic susceptibility = Disease
Implications of Stress, Psychosocial Factors on the Immune System

by Arline Kaplan
Stress

MAP38 Kinase

cell death

Mg    Ca

IL6

methylation

myelination

Bacterial infection
Antibiotics
Lack normal flora
Pancreatic malfunction
Improper fat absorption

Vit K
Psychology

Chronic stress and age-related increases in the proinflammatory cytokine IL-6

Janice K. Kiecolt-Glaser *,†, Kristopher J. Preacher §, Robert C. McCallum ‡, Cathie Atkinson *, William B. Malarkey † ‡ and Ronald Glaser * † ‡ † ‡

Departments of *Psychiatry, † ‡ Internal Medicine, and * ‡ Molecular Virology, Immunology, and Medical Genetics, Ohio State University College of Medicine, Columbus, OH 43210; §

Department of Psychology, † Institute for Behavioral Medicine Research, and ‡ Comprehensive Cancer Center, Ohio State University, Columbus, OH 43210; and ‡ Department of Psychology, University of North Carolina, Chapel Hill, NC 27599

Edited by Burton H. Singer, Princeton University, Princeton, NJ and approved June 3, 2003 (received for review April 2, 2003)

Abstract

Overproduction of IL-6, a proinflammatory cytokine, is associated with a spectrum of age-related conditions including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, certain cancers, periodontal disease, frailty, and functional decline. To describe the pattern of change in IL-6 over 6 years among older adults undergoing a chronic stressor, this longitudinal community study assessed the relationship between chronic stress and IL-6 production in 119 men and women
MAP38 & Stress

Stress: Osmotic Shock, γ radiation, Anisomycin

FASL, Inflammatory Cytokines, UV, etc.

Growth Factors, UV, Trophic Factors, etc.

Extracellular

Cytoplasm

MAP2K6

MEKK1

MLK1

TAK1

ASK1

APOPTOSIS

TRANSLATION

PLA2

SB203580

p38 MAPK

MNK1

PRAK

HSP27

MAPKAP-2

DNA Transcription

Cytokine Production, Apoptosis, etc.

STAT1

MAX

C-MYC

ELK1

CHOP

MEF2

ATF-2

HMG-14

HISTONE H3

CREB
How worms tackle stress

JNK and p38 pathways are used and integrated in response to pathogen stress in *C. elegans*

By David Secko

*July 14, 2004*

When an animal cell encounters a bacterial or chemical toxin, it needs to respond to ensure its survival, but how it does this is still poorly understood. Now, two independent studies clarify the involvement of the c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) signaling pathways in these responses in *Caenorhabditis elegans*.

Both JNK and p38 are well known mediators of stress responses in mammalian cells, and in *C. elegans*, these proteins, other components involved in their signaling pathways, and their involvement in stress responses are conserved. The two new papers, reported in the July 12 issue of *PNAS*, together reveal an evolutionarily interconnected mechanism for responding to bacterial stress.
Stress

MAP38K  IL-6

Inflammation
IL-6 May be Stress-Health Link

You don’t need research to tell you that stress can make you sick. However, a new study may have discovered the link between stress and health – interleukin-6 (IL-6).\(^1\)

IL-6 is a proinflammatory cytokine (small protein released by cells) that directly affects the behavior of other cells in the body. It is associated with many diseases, including arthritis, cancer, diabetes, osteoporosis, Alzheimer’s dementia, periodontal disease and cardiovascular disease. IL-6 has also been linked to frailty and functional decline in old age.

Perhaps one of the most important concerns about IL-6 is that it is directly linked to cardiovascular disease. This is due, at least in part, to the fact that it plays a central role in promoting the production of C-reactive protein (CRP), a marker of inflammation that, when elevated, is a significant risk factor for older adults, accelerating host of age-related diseases.\(^7\)

It is important to note that research has shown that poor habits can also raise levels of IL-6, including smoking, lack of exercise, sleep habits, and being overweight. These findings suggest that reducing stress is important for better health, may healthy lifestyle is imperative.

“The bad news is that we are experiencing chronic stress, caregiving or another difficult situation, you need to be aware that the significantly impact your health.”

author Dr. Ronald Glaser, the Institute for Behavioral Research at the Ohio State University College of Medicine, told Life magazine.

“The good news is you can impact stress has on yo
IL6 Inflammation
Inflammation and Stress

- It is not sufficient to simply address inflammation.
- It is necessary to also address the underlying physical or chronic stress that leads to further inflammation.
Chronic Inflammation is like a house of cards
Inflammation
Inactive NMDA receptor

Activated NMDA receptor

Healthy brain cell

Injured brain cell

-70 mV

0 mV

GY

Glu

MAP kinase cascade

Cell death

Apigenin

Nutrition Industry Executive,
Nov/Dec 2002
Andrius Baskys, MD, PhD
Effect of Nerve Calm RNA NutriSwitch™ on Excitotoxins

26 month old Female

Seizure Activity

Avg. # Seizures/Day

Example graph showing seizure activity over time.
Chronic Inflammation
The Epidemic Disease of Aging

Why do aging people suffer from so many seemingly unrelated disorders? Mainstream medicine attributes these multiple diseases to old age and fails to adequately address them. The sad fact is that people are needlessly suffering and dying from a common problem that is easily correctable.

In what will soon become a medical breakthrough, Life Extension has identified a reversible culprit (systemic inflammation) that is involved in the development of age-related diseases.

This role of inflammation has been overlooked by the medical establishment, yet persuasive scientific evidence exists that correcting a chronic inflammatory disorder will enable many of the infirmities of aging to be prevented or reversed.

Conventional doctors often tell their patients to accept the fact that they are not young anymore. Now that we know that systemic inflammation is a prime reason for the development of degenerative disease, safe steps can be taken to suppress the inflammatory cascade that destroys cells throughout the aging body.

Aging and inflammation

Chronic inflammation inflicts devastating effects, especially as humans grow older. The pathological consequences of inflammation are fully documented in the medical literature. Regrettably, the dangers of systemic inflammation continue to be ignored, even though proven ways exist to reverse this process.

Many people join The Life Extension Foundation (LEF) because they suffer from various degenerative diseases. A common culprit we find in these frail individuals is systemic inflammation.
### Diseases Related To Chronic Inflammation

Seemingly unrelated diseases have a common link. People suffering from multiple degenerative disorders often exhibit excess levels of pro-inflammatory markers in their blood. Here is a partial list of common medical problems associated with chronic inflammation:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Chronic inflammation causes most cancers</td>
</tr>
<tr>
<td>Heart Attack</td>
<td>Chronic inflammation contributes to coronary atherosclerosis</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Chronic inflammation destroys brain cells</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>Chronic inflammation causes heart muscle wasting</td>
</tr>
<tr>
<td>Stroke</td>
<td>Chronic inflammation promotes thromboembolic events</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Inflammatory cytokines destroy joint cartilage and synovial fluid</td>
</tr>
<tr>
<td>Aortic Valve Stenosis</td>
<td>Chronic inflammation damages heart valves</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>Inflammatory cytokines restrict circulation and damage nephrons</td>
</tr>
<tr>
<td>Lupus (SLE)</td>
<td>Inflammatory cytokines induce an autoimmune attack</td>
</tr>
<tr>
<td>Asthma</td>
<td>Inflammatory cytokines close the airways</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Inflammatory cytokines induce dermatitis</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Inflammatory cytokines induced pancreatic cell injury</td>
</tr>
<tr>
<td>Allergy</td>
<td>Inflammatory cytokines induce autoimmune reactions</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Inflammatory cytokines attack traumatized tissue</td>
</tr>
<tr>
<td>Surgical complications</td>
<td>Inflammatory cytokines prevent healing</td>
</tr>
<tr>
<td>Anemia</td>
<td>Inflammatory cytokines attack erythropoietin production</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Inflammatory cytokines are elevated in fibromyalgia patients</td>
</tr>
</tbody>
</table>
Inflammation, Hypertension, and the Metabolic Syndrome

Scott M. Grundy, MD, PhD

In this issue of The Journal, Sesso and colleagues report a positive relationship between increased serum levels of C-reactive protein and the risk for development of incident hypertension in participants of the Women's Health Study. A total of 20525 women were followed up prospectively for a median of 7.8 years, during which time approximately one fourth of the women acquired elevated blood pressure; those with higher levels of C-reactive protein were more likely to develop hypertension. C-reactive protein levels in the upper ranges of the normal distribution (high-normal levels of C-reactive protein) are widely believed to reflect a state of low-grade chronic inflammation; therefore, the association between higher C-reactive protein levels and new-onset hypertension led Sesso et al to suggest that hypertension may be an inflammatory disease.

The term inflammation is applied by Sesso et al because higher levels of C-reactive protein are thought to result from activation of cells characteristic of an inflammatory response (ie, cells of the immune system and vascular endothelium). Although the response denoted by high-normal levels of C-reactive protein is of a very low-grade chronic brinogen and plasminogen activator inhibitor-1). It is well recognized that high-normal levels of C-reactive protein are common in persons with the metabolic syndrome, thereby leading to inclusion of a proinflammatory state as one of the syndrome's components.

Sesso et al did not specifically address the question of what proportion of individuals with high-normal levels of C-reactive protein actually met criteria for the metabolic syndrome. A previous report from their laboratory showed the proportion to be high. Some investigators have questioned whether elevated blood pressure truly is a component of the metabolic syndrome because blood pressure is known to be increased by several nonmetabolic factors (eg, increasing arterial stiffness with aging). Nonetheless, the present demonstration of an apparent connection between low-grade inflammation and hypertension supports the concept that elevated blood pressure should be listed as one of the components of the metabolic syndrome.

Obesity is one of the major underlying causes of the metabolic syndrome. The mechanisms whereby obesity elicits or worsens metabolic risk factors are not fully understood but several potential links exist. Obesity is accompanied by high plasma levels of nonesterified fatty acids that cause insulin resistance in skeletal muscle and overload the liver with lipid,
THE SECRET KILLER

- The surprising link between INFLAMMATION and HEART ATTACKS, CANCER, ALZHEIMER'S and other diseases
- What you can do to fight it
strained silicon speeds chips
hardest diamonds developed
coin tossing not random
shedding light on dark energy

too plump
AN INFLAMMATORY SURPRISE
Inflammation Versus the Brain

Evidence mounts that inflammation is involved in neurodegenerative diseases.

Chronic inflammation is getting a bad name for its presumed role in several diseases—and new research shows that its notoriety may be well deserved.

A team led by Jeffery W. Kelly, a chemistry professor at Scripps Research Institute, suggests that abnormal cholesterol and lipid metabolites produced as a result of inflammation bond with normal amyloid β peptides in the brain. These reactions increase the peptides' hydrophobicity, predisposing them to misfold. The misfolded peptides then aggregate into the neurotoxic fibrils characteristic of Alzheimer disease [Proc. Natl. Acad. Sci. USA, published online March 15, http://www.pnas.org/cgi/doi/10.1073/pnas.0400924101].

The inflammatory process involves several types of cells and signaling compounds in a complicated cascade. In the peripheral nervous system, one control point for the cascade centers on the binding of acetylcholine to macrophages, which curtails the cells' inflammatory response. Last year, Kevin J. Tracey and colleagues at the North Shore Long Island Jewish Research Institute in Manhasset, N.Y., identified the binding
Effect of RNA on Inflammation
57 yr. old Female, A.F., Polymyalgia Rheumatica

Initial CRP = 14
Prednisone = 15mg

Start Health Foundation &
Hyper Immune RNA NutriSwitch

CRP = 0
Prednisone = 0 mg
Glutamate $\rightarrow$ Reactive Oxygen Species (ROS) $\rightarrow$ Inflammatory Mediators:

- COX2
- NFkB
- TNF
- LO
Inflammatory Mediators:
- COX2
- NFkB
- TNF
- LO

Glutamate leads to Reactive Oxygen Species (ROS), which amplifies excitotoxin damage. Lead also amplifies excitotoxin damage and leads to increased Inflammatory Mediators.
Inflammatory Mediators:
- COX2
- NFKB
- TNF
- LO

Glutamate Reactive Oxygen Species (ROS)

Lead amplifies excitotoxin damage

Inflammatory Mediators:
- COX2
- NFKB
- TNF
- LO

Nerve Calm RNA NutriSwitch™

Health Foundation RNA NutriSwitch™ & Stress Foundation RNA NutriSwitch™

Metals RNA NutriSwitch™ & EDTA
We are all familiar with the game of “telephone” where one child whispers a message to the child sitting next to him, who in turn whispers the message to the child sitting next to her, who in turn whispers the message to yet a fourth child and so on until the message has been whispered to the last child in the circle. By the time the message reaches its destination, the final child, it has undergone significant changes.
Think of RNA as the mediator that ensures that the initial message is not distorted. RNA helps to facilitate our cell:cell communication by ensuring that the messages in our genes (our DNA) are accurately converted into the structural building blocks for our body (our proteins) in spite of the stresses, the toxins and the infectious diseases in our lives.
One area or variable that has been sorely overlooked is enhancing our natural cell: cell communication. As we attempt to facilitate the communication between our cells we can reduce some of our underlying genetic susceptibility to disease.
While specific RNAs can help us to address Stress and Inflammation, more importantly they help us to address proper cell: cell communication that is necessary to address multifactorial disease.
Neurological Research Institute Newsletter

Topic of Interest for the Month: Methylation

- S-adenosyl-methionine serves as a methyl donor to convert cytosine to methyl cytosine.
- In humans, 5 methyl cytosine is only seen on cytosines that precede guanosine in CpG dinucleotides.
- Methylation of cytosine is generally correlated with silencing of genes.
- Methylation of cytosine may maintain the large amount of noncoding DNA in an inert state.
- Under-methylation in normally silent regions of the DNA could cause harmful expression of inserted viral genes.
- S-adenosylmethionine can serve as a methyl donor for phospholipid methylation.
- In addition, single carbon folates can serve as methyl donors for phospholipid methylation. S-methyl THF appears to be the donor for this process.
- Dopamine stimulates phospholipid methylation.

Topic of the Month Continued

- S-methyl THF increases dopamine stimulated phospholipid methylation.
- Single carbon folates are generally interconvertible, with the exception of 5 methyl THF which is not directly reversible.
- Decreases in the level of 5-formyl THF result in decreases in 5 methyl THF, suggesting a regulatory relationship.
- Phospholipid methylation may be involved in modulation of NMDA (glutamate) receptors.
- RNA silencing may be a means of targeting DNA methylation, which may indicate how sequence specific epigenetic gene silencing is established.
- RNA dependent, DNA methyl transferases may serve to monitor methylation.

Chemical and Engineering News February, 2004

- It has been assumed that mercury levels in the fetus are similar to mercury levels in the mother. A new study shows that mercury in the fetus can be nearly twice that of the mother.

Nature Reviews Immunology February, 2004

- Intestinal cells respond to pathogenic bacteria by increasing the level of various inflammatory mediators like NFκB and IL8.
- Conversely, normal bacteria otherwise known as commensals or normal flora decrease the level of inflammatory mediators.
The Puzzle of Autism: Putting It All Together
A Guide to Transforming the Treatment Of Autism

For Parents and Physicians

Garry F. Gordon MD, DO, MD(H) and
Amy Yasko PhD, ND, NHD, AMD, HHP, FAAIM
Dr. Amy Yasko: Neurological Research Institute

I know that it is a long, hard and lonely journey trying to recover your child from autism. I am often asked why I work in the field of autism, as my own children are not autistic. Many doctors work in this field because they have family members that are autistic. It is precisely because of the fact that I am blessed to have three healthy children that I want to help others to have that same gift in their lives. In addition, I am blessed to have the luxury of taking on a limited number of patients with whom I am able to spend a great deal of time to customize and individualize their recovery programs. This affords me the opportunity to gain an intimate understanding of some of the issues in autism. Finally, I am blessed to have a diverse practice that specializes in neurological and chronic inflammation. This enables me to learn from individuals with single imbalances in the body, and then apply these principles to the more complex issues that are encountered in autism.

I have been researching and working with inflammatory pathways in the body since my doctoral work at Albany Medical College. I have always felt that it is critical to understand why something is happening in order to make informed choices directed at correcting the imbalance. It is my belief that the more one understands the pathogenesis that leads to a particular condition, the easier it is to ascertain effective strategies to truly resolve the problem rather than simply eliminating symptoms. This is especially true for autism where every child is so unique. Autism is a broad category which, for the most part, is based on developmental and behavioral characteristics. Within this broad category are children with a great diversity of biochemical imbalances. In most cases it is incumbent upon the parent to make individualized decisions about their own child’s welfare. The better that parents understand the causes and the processes that underlie the condition we call autism, the easier it is for them to make informed choices for their child’s individual needs.

One of my goals is to share my knowledge, observations and experience so that others might have the tools they need to aid in their own healing process. Every time I give a talk I begin where I left off with the prior talk. In that way the talks and the tapes build on each other, and individuals coming to the talks or listening to the tapes do not hear the same content over and over. They get the benefit of the newest information as we move forward to uncover all the pieces of this puzzle of autism.

There are several videos that are available that help to lay the basic groundwork for the autism book. These include the Neurological...
Typed by a 30 year old non verbal autistic male. He was using RNAs and GABA.

“Sometimes I just can’t stand much going on around me like sounds, people moving, smells and food tastes, Visual stuff is entertaining if the other sense are not bothering me. Sometimes Mother’s voice drives me crazy. It’s not all the time, but when I’m keyed or on edge it’s awful. Your voice isn’t that bad, but you won’t sit still. That body motion of throwing myself if saying stop. I made that body motion because I wanted her to stop talking because I wanted to hear one of my favorite songs. She turned the radio off which really upset me, but I didn’t dare show it because I wanted to hear music.

How else can I show my frustration if I don’t use my body motions? Then I can’t express how I fell when I am angry, frustrated, keyed or impatient because the only way I can express myself now is with my body motions and that’s not OK. That mellow med (GABA) really helps me with my control and processing my feelings and thoughts. I need that mellow med more often on a consistent schedule. No skipping med times Please give me my meds (RNAs) at the same time every day. Please don’t take any away from me. It makes me feel very up and down. “

D.S. May 17, 2002