A real life example
Diabetes in Its Tracks

by Jon Cohen on 16 March 2012, 3:28 PM | 17 Comments

Michael Snyder has taken "know thyself" to the next level—and helped heal thyself.

Over a 14-month period, the molecular geneticist at Stanford University in Palo Alto, California, analyzed his blood 20 different times to pluck out a wide variety of biochemical data depicting the status of his body's immune system, metabolism, and gene activity. In today's issue of Cell, Snyder and a team of 40 other researchers present the results of this extraordinarily detailed look at his body, which they call an integrative personal omics profile (iPOP) because it combines cutting-edge scientific fields such as genomics (study of one's DNA), metabolomics (study of metabolism), and proteomics (study of proteins). Instead of seeing a snapshot of the body taken during the typical visit to a doctor's office, iPOP effectively offers an IMAX movie, which in Snyder's case had the added drama of charting his response to two viral infections and the emergence of type 2 diabetes.
Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

Rui Chen,1,11 George I. Mias,1,11 Jennifer Li-Pook-Than,1,11 Lihua Jiang,1,11 Hugo Y.K. Lam,1,12 Rong Chen,2,12 Elana Miriami,1 Konrad J. Karczewski,1 Manoj Hariharan,1 Frederick E. Dewey,3 Yong Cheng,1 Michael J. Clark,1 Hogune Im,1 Lukas Habegger,6,7 Suganthi Balasubramanian,6,7 Maeve O’Huallachain,1 Joel T. Dudley,2 Sara Hillenmeyer,1 Rajini Haraksingh,1 Donald Sharon,1 Ghia Euskirchen,1 Phil Lacroute,1 Keith Bettingger,1 Alan P. Boyle,1 Maya Kasowski,1 Fabian Grubert,1 Scott Seki,2 Marco Garcia,2 Michelle Whirl-Carrillo,1 Mercedes Gallardo,9,10 Maria A. Blasco,9 Peter L. Greenberg,4 Phyllis Snyder,1 Teri E. Klein,1 Russ B. Altman,1,5 Atul J. Butte,2 Euan A. Ashley,3 Mark Gerstein,6,7,8 Kari C. Nadeau,2 Hua Tang,1 and Michael Snyder1,*

1Department of Genetics, Stanford University School of Medicine
Glycated HgA1c (%): 6.4 (329) 6.7 (369) 4.9 (476) 5.4 (532) 5.3 (546) 4.7 (602)

Day Number (Relative to 1st Infection)

Glucose (mg/dL)

HRV Infection (Day 0-21)
RSV Infection (Day 289-311)
Life Style Change (Day 380-Current)
In human studies, we quantify ~120 plasma inflammation related proteins

**Monocytes**
- MMP9

**Macrophages**
- TNFα
- IL1β
- platelet derived growth factor
- IFNγ
- MMP1
- MMP8
- MMP13
- Myeloid Related Protein14
- CD40
- CD40L
- tissue factor

**Foam cells**
- IL18
- IL18Rα/β

**Endothelial cells**
- P-selectin
- VCAM1
- ICAM1
- MCP1/CCL2
- platelet derived growth factor
- CSF1
- NO
- CD40
- CD40L
- tissue factor
- PAI1
- NFκB
- adenine dinucleotide phosphate oxidase
- Cathepsin S

**Smooth muscle cells**
- collagen
- IFNγ
- IL6
- CD40
- CD40L
- tissue factor
- MCP1/CCL2

**Platelets**
- CD40L
- Myeloid Related Protein8
- Myeloid Related Protein14
- platelet derived growth factor
- CD40

**T helper 1 cells**
- IL1
- sCD40L
- INFγ
- RANTES
- MIF
- CD40

**Adipose tissue**
- adiponectin
- IL18
- PAI1

**Liver**
- CRP
- PAI1
- fibrinogen

**HDL**
**LDL**
oxLDL
Thrombin
Factor VII
paraoxonase 1
Angiotensin II
Lipoprotein lipase
Hepatic lipase
MPO
Lipoprotein associated phospholipase A2
Changes in proteins and metabolites in human plasma and gene expressions (in PBMC) related to inflammatory modulation by diclofenac

Van Erk et al
BMC Medicine
2010
The concept of nutrigenomics biomarkers

Level 1 - functional or ‘endpoint’ related biomarker (often not available)

Level 2 – biochemical reporters of processes (often non changed / not accepted)
(CRP, IL1, adiponectin, …)

Level 3 – biological networks that support the evidence of level 2 (both statistically and mechanistically)
Anti-inflammatory effect of supplement mix

› 36 overweight males (BMI 25-35) with low-grade inflammation (CRP 1-10 mg/L)

› Consumption of supplement mix for 5 weeks in a randomized cross-over trial

› Supplement mix: based on mediterranean diet, contains resveratrol, vitamin E, vitamin C, tomato extract, green tea extract, fish oil

› Designed to exert effect on different inflammatory pathways (based on literature)
Extensive phenotyping

‘omics’ analysis allows quantification of enormous # of parameters

110 cytokines
78 lipids
198 metabolites
11,000 genes
~ 30 parameters
Eicosanoid related inflammation (but no effect PGE2)

fish oil $\uparrow$ PUFA

endothelial inflammatory factors

plaque formation / coagulation

increased expr prostaglandin metabolism genes in adipose tissue

anti-inflammatory effects in adipose tissue: adiponectin, IL10RA, SOCS3

Bakker, AJCN 2010
Effect on inflammation: part of the Inflammatory profile in plasma

![Graph showing % change in inflammatory markers](image)
Anti-inflammatory effects of supplement mix  
Postprandial challenge

Oral Lipid Tolerance Test:

Plasma measurements over time (up to 6 hours) after consumption of lipid-rich dairy product

120 Inflammatory proteins  
246 Metabolites (GC-MS)
Homeostasis versus perturbation

Inflammation markers at baseline and during an oral lipid tolerance test

Adiponectin

Placebo and intervention graphs showing changes in concentration over time.
Homeostasis versus perturbation

Inflammation markers at baseline and during an oral lipid tolerance test

% change

inflammatory markers

- adiponectin
- IL-18
- Beta-2 Microglobulin
- Ferritin
- ICAM-1
- VCAM-1
- 8-iso prostaglandin F2-alpha

Time (min)

Concentration

Beta-2 Microglobulin

placebo

intervention
Homeostasis versus perturbation

Inflammation markers at baseline and during an oral lipid tolerance test

![Graph showing changes in inflammatory markers over time]
Homeostasis versus perturbation

Inflammation markers at baseline and during an oral lipid tolerance test

Inflammatory markers
- adiponectin
- IL-18
- Beta-2 Microglobulin
- Ferritin
- ICAM-1
- VCAM-1
- 8-iso prostaglandin F2-alpha

% change

Time (min)

Concentration

ICAM-1

Placebo

Intervention
Homeostasis versus perturbation

Inflammation markers at baseline and during an oral lipid tolerance test

![Graph showing changes in various inflammatory markers over time](image)
Plasma metabolomics and proteomics profiling after a postprandial challenge reveal subtle diet effects on human metabolic status

Linette Pellis · Marjan J. van Erk · Ben van Ommen · Gertruud C. M. Bakker · Henk F. J. Hendriks · Nicole H. P. Cnubben · Robert Kleemann · Eugene P. van Someren · Ivana Bobeldijk · Carina M. Rubingh · Suzan Wopereis

Metabolomics  
Received: 31 March 2011 / Accepted: 12 May 2011
Same “anti-inflammation food cocktail” in transgenic CRP mice

basal CRP at various doses food mix

mix does not influence inflammatory homeostasis in mice
CRP-mice (expressing human CRP) Challenge with interleukin-1 (IL-1)

Supplement mix attenuates IL-1 induced CRP response

Challenge tests as more powerful way to quantify modulation of inflammation?
Effect of anti-inflammatory diet on inflammation in mice

- ApoE3L mice on high cholesterol diet develop atherosclerosis
- Supplementation with food mix inhibits atherosclerosis development

HC: plaque in aorta
HC + food mix: no plaque in aorta

Verschuren, J Nutr 2011
Visceral adiposity

LDL elevated

Glucose toxicity

Fatty liver

Gut inflammation

Inflammation

Hypertension

IBD

Dyslipidemia

High cholesterol

LDL elevated

Muscle metabolic inflexibility

Adipose IR

Hepatic IR

Insulin resistance

Systemic inflammation

Inflammation

Myocardial infarctions

Heart failure

Myocardial infactions

Cardiac dysfunction

Brain disorders

Nephropathy

Retinopathy

Strol

Atherosclerosis

Microvascular damage

Hypertension

β-cell failure

Glucose toxicity

Systemic inflammation

β-cell pathology

Risk factor

High glucose

High cholesterol

Ectopic lipid overload

Adipose inflammation

Visceral adiposity

Hepatic inflammation

Fibrosis

IBD

Endothelial inflammation

Metabolically healthy

Systems flexibility is the key!
- What does “optimal inflammatory flexibility indicate?"
- Are there organ specific messages?
Nutrition and maintaining robustness?

The energy pulse and the control mechanisms

Decreased flexibility
- linked to ‘metabolic syndrome’
- may result in damage
Nutrition and maintaining robustness?

The energy pulse and the control mechanisms

Optimal flexibility depends on:
- optimal damage control phenotype
- micronutrient levels
- antioxidant status
- anti-inflammatory elasticity
Gut
- Host-microbe interaction
- Absorption, intestinal integrity, barrier function
- Gut-mediated inflammation control
- Chylomicron production

Brain
- Gut-Brain axis
- Endocrine responses
- HPA axis

Adipose tissue
- Lipoprotein metabolism
- Lipid metabolism
- Energy metabolism
- Macrophage infiltration
- NEFA
- Expandibility
- Lipokine/Adipokine production
- Insulin sensitivity

Pancreas
- Systemic insulin sensitivity
- b-cell failure

Vasculature
- NO metabolism
- chronic low-grade inflammation
- Endothelial flexibility/integrity
- Reversibility of inflammation
- Microvascular damage
- Lipid droplet formation
- Arterial stiffness

Liver
- Adaptation carb/lipid switch
- Oxidative stress
- ER stress
- Tissue injury
- Fibrosis
- Toxicity
- Insulin sensitivity

Muscle
- Protein metabolism
- Oxidative stress
- ER stress
- Tissue injury
- Energy metabolism
- Insulin sensitivity

Kidney
- (re)absorption
- urea cycle
- Tissue injury

Diagnosis assay: organ flexibility

TNO innovation for life
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- Gut hormones (Ghrelin, GIP, etc)

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- Lipid metabolism (MG, TG)
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- Microvascular damage
- Lipid droplet formation
- Arterial stiffness
- Systolic/Diastolic BP
- Heart rate (BPM)
- Lipotoxicity

OGTT (plasma)
**OLTT (plasma): dairy, incl. carbs and proteins**

- **Gut**
  - Host-microbe interaction
  - Absorption, intestinal integrity, barrier function
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- β-cell integrity

OLTT (plasma):
sunflower oil

Kidney
- (re)absorption
- Urea cycle
- Tissue injury
role of local and systemic inflammatory control in metabolic health
The challenge concept:
Stress response curve of glucose
Health is maintained by a complex interaction of processes, each maintaining “homeostasis”, elasticity and robustness.
4 weeks + 1300 kcal

Comparable response?

Figure 1a. Study design - fat challenges in healthy (10) and metabolic syndrome (10) subjects
High-fat challenge

500 ml shake consisting of 53% whipping cream, 3% sugar and 44% water

<table>
<thead>
<tr>
<th>500 ml contains:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>775 kcal</td>
</tr>
<tr>
<td>Protein</td>
<td>8 g</td>
</tr>
<tr>
<td>Fat</td>
<td>80 g</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>45 g</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>16 g</td>
</tr>
</tbody>
</table>
Figure 1b. Study design High-fat high-caloric diet

- **Day 1**: HF challenge
- **Day 8**: Body composition, Dietitian consult
- **Day 15**: Dispensing study substances, Compliance check
- **Day 22**: HF challenge
- **Day 29**: Body composition, Blood sampling

**Pre-study**: food intake diary (3-day)
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  \((CRP, \text{ IL1, adiponectin, ...})\)

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