The Origins and Maintenance of Host-Microbe Interactions

Angela E Douglas
The ancient origins of animal-microbe interactions

1. Our ancestors were multi-organismal before they were multi-cellular

Verrucomicrobia on Euplotidium

Legionella pneumophila in Hartmannella vermiformis

Bacteria in Blastocrithidia culicis (trypanosome)
The ancient origins of animal-microbe interactions

2. Key elements of animal signaling networks evolved in the context of pre-existing interactions with a resident microbiota

- perturbation of microbiota
- dysfunction in cell signaling and communication

Domazet-Lošo & Tautz 2008
Mol Biol Evol 25, 2699
The ancient origins of animal-microbe interactions

3. Fundamental principles of human interactions with the resident microbiota are conserved across animals

ANIMAL MODELS
perturbation of microbiota ↔ human disease

one microbe-one host

many microbes-one host

Images:
- [Image](news.wisc.edu/)
- [Image](uconn.edu/mcbstaff/graf)
- [Image](technewscentral.co)
- [Image](Adam Wong)
Axenic flies have elevated lipid and glucose levels

Ridley, Wong et al. 2012 & in press; Wong et al. unpub manuscript
The ancient origins of animal-microbe interactions

3. Fundamental principles of human interactions with the resident microbiota are conserved across animals

Bäckhed et al. 2004 PNAS 101, 157

Wong et al.
Low diversity microbiota in *Drosophila*

- *Lactobacillus fructivorans*
- *Acetobacter pomorum*
- *Lactobacillus brevis*
- *Acetobacter tropicalis*
- *Lactobacillus plantarum*
- Other

Wong et al. 2011 & under review
Bacteria and nutrient allocation

$Lactobacillus$ reduces sugar levels
$Acetobacter$ reduces lipid levels

- Microbial functions can be assigned to individual taxa
- Different microbiota-dependent traits can be functionally independent

Newell et al. in prep.
Interactions between animals and their microbiota is not uniform

Bacteria provide ile, phe, thr: shortfall in no-bacteria insects limits protein synthesis with accumulation of non-limiting AAs

Deficit of three amino acids
- Isoleucine
- Phenylalanine
- Threonine
in “no bacteria” insects
Nutritional Basis of Aphid-\textit{Buchnera} Symbiosis

<table>
<thead>
<tr>
<th>Sample type</th>
<th>% essential amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet (plant sap)</td>
<td>5-15</td>
</tr>
<tr>
<td>Aphid protein</td>
<td>50</td>
</tr>
</tbody>
</table>

The \gamma-proteobacterial symbiont \textit{Buchnera} 0.64 Mb (genomic decay & relaxed selection)
Animal-Microbial Metabolite Exchange

Buchnera bacteriocyte

33 ↔ 25

Klaas van Wijk  Anton Poliakov

METNET Consortium
Gavin Thomas
Sandy MacDonald
Metabolic network of *Buchnera*

Flux balance analysis to quantify flux through the metabolic network

**Metabolic Capabilities**

<table>
<thead>
<tr>
<th></th>
<th><em>Buchnera</em></th>
<th><em>E. coli</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. reactions</td>
<td>261</td>
<td>972</td>
</tr>
<tr>
<td>No. metabolites</td>
<td>255</td>
<td>609</td>
</tr>
</tbody>
</table>

MacDonald et al. 2011
Metabolite exchange between host and symbiont

<table>
<thead>
<tr>
<th>Flux</th>
<th>Input from host</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Glucose</td>
</tr>
<tr>
<td>46</td>
<td>Mannitol</td>
</tr>
<tr>
<td>32</td>
<td>Aspartate</td>
</tr>
<tr>
<td>21</td>
<td>Glutamine</td>
</tr>
<tr>
<td>13</td>
<td>Serine</td>
</tr>
<tr>
<td>8</td>
<td>Alanine</td>
</tr>
<tr>
<td>7</td>
<td>Guanosine</td>
</tr>
<tr>
<td>6</td>
<td>2-oxobutanoate</td>
</tr>
<tr>
<td>6</td>
<td>Glutamate</td>
</tr>
<tr>
<td>4</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>3</td>
<td>Proline</td>
</tr>
<tr>
<td>3</td>
<td>Asparagine</td>
</tr>
<tr>
<td>2</td>
<td>Tyrosine</td>
</tr>
</tbody>
</table>

... and 20 further metabolites

1. *Buchnera* is metabolically fastidious and inflexible, requiring multiple specific carbon and nitrogen sources
2. The bacteriocyte is enriched in enzymes mediating the synthesis of predicted inputs to *Buchnera* metabolic network

Poliakov, Russell et al. 2011; MacDonald et al. 2011
Metabolite exchange between host and symbiont

<table>
<thead>
<tr>
<th>Flux</th>
<th>Input from host</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Glucose</td>
</tr>
<tr>
<td>46</td>
<td>Mannitol</td>
</tr>
<tr>
<td>32</td>
<td>Aspartate</td>
</tr>
<tr>
<td>21</td>
<td>Glutamine</td>
</tr>
<tr>
<td>13</td>
<td>Serine</td>
</tr>
<tr>
<td>8</td>
<td>Alanine</td>
</tr>
<tr>
<td>7</td>
<td>Guanosine</td>
</tr>
<tr>
<td>6</td>
<td>2-oxobutanoate</td>
</tr>
<tr>
<td>6</td>
<td>Glutamate</td>
</tr>
<tr>
<td>4</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>3</td>
<td>Proline</td>
</tr>
<tr>
<td>3</td>
<td>Asparagine</td>
</tr>
<tr>
<td>2</td>
<td>Tyrosine</td>
</tr>
</tbody>
</table>

... and 20 further metabolites

Buchnera bacteriocyte

Output from Buchnera
25 metabolites, including 10 essential amino acids

BUT some essential amino acid biosynthesis pathways in Buchnera are incomplete

MacDonald et al. 2011
Loss of terminal transamination reaction in leucine synthesis

Bacterioocyte proteome enriched in BCAT, but no other enzymes in BCA degradation
Poliakov et al. 2011

Russell, Bouvaine et al. submitted
Evidence for shared metabolic pathways: BCAT and leucine synthesis

Dissection → Bacteriocytes → Homogenization & centrifugation → Isolated Buchnera

*Buchnera*-free bacteriocyte fraction (BF)

RE: recombinant enzyme

Russell, Bouvaine et al. submitted
Nutrient Acquisition from *Buchnera*

- Dietary non-essential amino acids
- Shared metabolic pathways in synthesis of 5/10 essential amino acids

**Coevolutionary changes:**
- Loss of *Buchnera* genes coding reactions which are also present in insect
- Expression of compensatory host genes in bacteriocytes
Conclusions

1. Metabolite exchange between animal cells and resident microbiota can be underpinned by coevolved animal and microbial metabolic networks

2. Microbiota influences metabolic configuration of animals: interacts with nutrient signaling network

3. Architecture of animal physiological systems is predisposed to modulation by microbial partners