Meeting report

The disease business

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Published: 6 November 2000

Genome ***Biology*** 2000, **1(5)**:reports4021.1–4021.2

The electronic version of this article is the complete one and can be found online at http://genomebiology.com/2000/1/5/reports/4021

A report on the 'Host-Pathogen Interactions' minisymposium at the first meeting of the European Life Scientist Organization (ELSO), Geneva, Switzerland, September 2-6, 2000.

The world of host-pathogen interaction is a complex and fascinating one. By focusing on a diverse variety of pathogens, this minisymposium dramatically illustrated the extremely elaborate specializations that have evolved during the long-running battle between pathogen and host.

Ejecting *E. coli* from epithelia

The proceedings opened with a familiar pathogen, *Escherichia coli*, demonstrating a familiar problem, the infection of epithelia. As the first line of defense, epithelia regularly repel the microscopic pirates that seek a home in the centrally heated comfort of the human body. Why, then, are pathogens vigorously ejected by some epithelia, but only weakly rebuffed by others?

Staffan Normark and colleagues (Karolinska Institute, Stockholm, Sweden) addressed this question by studying the interaction between *E. coli* and epithelial cells derived from bladder and kidney. As most urinary tract infections are caused by faecal *E. coli*, they reasoned that the bladder would be exposed to these opportunistic pathogens far more frequently than the kidney. Hence the bladder epithelium might be expected to have evolved more effective defences than the kidney, which was indeed exactly what Normark found. When exposed to bacterial lipopolysaccharide, epithelial cells from the bladder mount a vigorous inflammatory response, whereas the response of kidney epithelia is much weaker. This coincides neatly with the observation that kidney infections are far more likely to become chronic than those in the bladder.

Deciphering the emerging pathogen *Bartonella*

From the familiar ground of *E. coli*, the session moved to newer territory - the little-known pathogen *Bartonella*. Several members of this genus cause disease, ranging from localized inflammation (*B. henselae*) to fatal haemolytic anaemia (*B. quintana*). Christoph Dehio (University of Basel, Switzerland) presented his lab's recent progress in understanding their mechanism of infection. The pathogenic capacity of *Bartonella* stems from its ability to invade endothelia and red blood cells. After attaching to the endothelial cell membrane, the bacteria are gathered into a massive aggregate (the 'invasome') in a process that is apparently driven by the host cell. The invasome is then engulfed but, like many other intracellular pathogens, *Bartonella* avoids destruction by preventing its home, the phagosome, from fusing with lysosomes. Intriguingly, a much more dramatic manipulation of the endothelial host cell also occurs, as an unidentified bacterial membrane component stimulates the host cell to proliferate and eventually to form a new blood vessel.

Why ulcers are good for *Helicobacter*

Fortunately, *Bartonella*'s alarmingly clever technique is somewhat mitigated by its relative rarity. The same cannot be said for the lead player in the talk by Cesare Montecucco (University of Padova, Italy), *Helicobacter pylori*, which is infamous as the major cause of gastric ulcers. Indeed, it appears that it is an old enemy of ours, as the spread of this bacterium matches the early migration patterns of *Homo sapiens*.

H. pylori protects itself from the acidic stomach environment by burrowing within the mucus layer and holding fast to the epithelial cell surface. There, it secretes a toxin, VacA, which triggers massive vacuolation within the epithelial cells. At the same time, vesicle trafficking in these cells is

disrupted, blocking antigen presentation and redirecting acid hydrolases to the apical surface, where they hydrolyze the mucus layer. The concomitant weakening of tight junctions between epithelial cells by an unknown mechanism allows nutrients to leak out and diffuse rapidly through the newly weakened mucus towards the bacteria.

In addition, Montecucco discussed a second weapon that *H. pylori* has at its disposal, the toxin neutrophil activating protein (NAP), which, as its name suggests, activates neutrophils, triggering them to produce oxygen radicals. This defense response of the neutrophils, normally aimed at the invader, is now turned against the host, causing tissue damage and ulceration that further enhance the flow of nutrients to the bacterium.

Vaccinia takes the highway

Like several pathogenic bacteria, the *Vaccinia* virus moves within the host cell by using host proteins to assemble actin filaments at one pole of the viroid. As the filaments grow, they propel the virus within and between cells like a rocket. But Aspasia Ploubidou (European Molecular Biology Laboratory, Heidelberg, Germany) has now demonstrated that *Vaccinia* is not content with merely perturbing the actin cytoskeleton but also manipulates microtubules. The first clue came from the observation that newly assembled viral particles accumulate near the microtubule-organizing centre. This accumulation requires intact microtubules and the dynein/dynactin motor that walks along them, and microtubules are also required for the subsequent maturation of viroids. Later during the infection, microtubules are reorganized, losing their radial orientation and bundling into cortical arrays. This reorganization is due to two viral proteins (A10L and L4R), which act as microtubule-associated proteins, binding the viral core to microtubules. To complete the hijacking process, *Vaccinia* also disrupts the centrosome, preventing the cell from nucleating new microtubules.

Shigella - the complicated commuter

Shigella flexneri, the causative agent of bacillary dysentry, is certainly one of the best-studied pathogens, but its complex lifestyle means that the picture is certainly far from complete. Philippe Sansonetti (Institut Pasteur, Paris, France) discussed this infamous bacterium, and in doing so returned to the theme of epithelial interactions. *S. flexneri* invades gut epithelial cells, but cannot enter directly via the apical surface. Sansonetti has shown that, instead, it must initially pass the intestinal barrier by invading the 'immune surveillance' M cells in the associated follicular epithelium. The bacterium then emerges from the M cell at the opposite (basolateral) surface, from where it can successfully penetrate the basolateral surface of neighbouring epithelial cells.

Recent work has shown that during this process many bacteria are engulfed by macrophages, but this proves not to be a problem: *Shigella* induces a fatal case of indigestion in the macrophages, and they promptly undergo apoptosis, freeing the bacteria once more. The death of host macrophages triggers a massive inflammatory response, which recruits neutrophils to the infection site. They penetrate the epithelial layer, disrupting it and inadvertently increasing bacterial invasion. As with the earlier *Helicobacter* story, *Shigella* turns the host weaponry to its advantage.

This was a diverse and fascinating session at which one could sit back and marvel at the sheer complexity that exists in the interaction between pathogens and the organisms they feed upon.