**Microbiology Comment** provides a platform for readers of *Microbiology* to communicate their personal observations and opinions in a more informal way than through the submission of papers.

Most of us feel, from time to time, that other authors have not acknowledged the work of our own or other groups or have omitted to interpret important aspects of their own data. Perhaps we have observations that, although not sufficient to merit a full paper, add a further dimension to one published by others. In other instances we may have a useful piece of methodology that we would like to share.

The Editors hope that readers will take full advantage of this section and use it to raise matters that hitherto have been confined to a limited audience.

**Jon Saunders, Editor-in-Chief**

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**Hypothesis – can UV produced by intracellular bacteria cause cancer?**

In earlier contributions to *Microbiology Comment* I discussed (with others) the possibility that, by producing UV, microorganisms might influence the growth of adjacent cells (1), and that there is considerable evidence to suggest that bacteria and other non-viral micro-organisms may cause cancer (2). An interesting hypothesis develops when these two possibilities are joined together, namely, that some cancers result when bacteria produce mutagenic UV light in situ.

Considerable historical and recent evidence suggests that bacteria and other non-viral micro-organisms can readily be isolated from human tumours (3) and that rather than being harmless contaminants, they may cause cancer. Such so-called ‘cancer germs’ often lack cell walls, exhibit extreme pleomorphism and apparently reside within cancerous cells (4,5). The link between cancer and bacterial infection has been strengthened by the recent findings that *Helicobacter pylori*, the cause of stomach ulcers, is also involved in the aetiology of gastric cancer (6,7). *H. pylori* shows limited pleomorphism in having a coccoidal phase; a filamentous species of *Helicobacter* has also been isolated recently (8).

Most authors have assumed that if bacteria induce cancer they would do so by causing inflammation, or by producing mutagenic carcinogens *in situ*. For example, Ohshima & Bartisch (9) suggested that tumours result from DNA damage when bacteria generate active oxygen species and nitric oxide.

An alternative hypothesis, which I wish to propose, is that by producing UV light when growing within or between body cells, bacteria cause DNA mutations which in turn cause cancer.

This hypothesis firstly requires that bacteria are present in pre-cancerous cells and tumours. As mentioned above there is considerable historical, as well as recent, evidence to show that this is the case. Chan et al. (10), using a sensitive PCR-ELISA method, have shown that mycoplasma conserved DNA is prevalent in malignant ovarian cancer. It is noteworthy that these authors describe mycoplasmas as ‘tiny polymorphic prokaryotic organisms that lack a cell wall and reside ubiquitously at the cell membrane or internalized within the cell’. That is they correspond to what historically has been termed the ‘symplasm’ or hidden phase of the ‘cancer germ’.

A second, obvious requirement of the hypothesis is that bacteria must be able to produce UV light.

The ability of living cells, including bacteria, to produce UV and visible light as part of their normal metabolism is now well-established (11). Tilbury & Quickenden (12), for example, have shown that *Escherichia coli* produces weak luminescence during aerobic growth, the first period of emission occurring during exponential growth and comprising a UV band (210–330 nm) as well as a visible region (450–620 nm). Similar emissions have also been reported in *Saccharomyces cerevisiae* (13). As yet, however, no one has tested the possibility that (a) bacteria isolated from cancers can emit UV or visible light and (b) if they do, whether such emissions are produced by bacteria when growing *in situ* in the body. It would also be interesting to know if *H. pylori* produces UV when growing in the stomach lining; such emissions might induce cellular changes that lead to the formation of ulcers as well as tumours.

Could this UV, produced by bacteria, induce cancers? The mutagenic properties of UV are of course well-known. Kielbassa *et al.* (14) found that DNA damage to Chinese hamster cells was induced by UV and visible light (290–500 nm). Such emissions, if produced *in situ*, might induce DNA damage and ultimately the formation of cancers. Illingworth (15) also suggested that cancer may result when body cells themselves produce potentially mutagenic UV. While this may be the case, UV and visible light produced by bacteria, growing within cells and in close proximity to the nucleus, might be expected to be more intense and cause more damage to DNA than would cellular UV.

Bacteria can live within cells for extended periods, as so-called ‘persistors’, in which form they can avoid the immune system and the effects of antibiotics. In terms of DNA damage, the ability of bacteria to grow intracellularly and emit UV over long periods might help compensate for the ultra-weak nature of bacterial UV emissions.

It is also worth noting that polyaromatic hydrocarbons (PAHs, which incidentally are produced in cigarette smoke) can induce cancers, including those of the breast (16), and secondly, that UV light (300–400 nm) is known to enhance the carcinogenic effects of UV light.
of these compounds (17). It is therefore possible that cancer may result from synergistic interactions between normal cellular UV light, bacteria-produced UV emissions and pollutants such as PAHs.

The suggested hypothesis would help explain why cancer is not infectious in the normal sense, since it implies that the UV produced by bacteria growing within the cell would operate as a 'cancer switch', which would also be influenced by both hereditary and environmental factors. The internal production of UV might be one of many ways by which intracellular bacteria might influence the operation of such a 'switch'.

Of course, 'the devil lies in the detail' and the main problem with this hypothesis relates to dose-effect. That is would sufficient UV be produced by intracellular bacteria to effect DNA mutagenesis, bearing in mind that any UV emissions would be subject to adsorption by cellular contents, including membranes?

Should the present hypothesis be correct, then vaccines might be developed to prevent the growth of intracellular bacteria. Alternatively, other agents might be found which could prevent such bacteria from emitting UV, or counteract its mutagenic effects. Such agents would be invaluable in preventing both the development or spread of cancer.

Milton Wainwright
Department of Molecular Biology and Biotechnology, University of Sheffield, Sheffield, S10 2TN, UK.
Tel: +44 114 222 4410.
Fax: +44 114 272 8697.
e-mail: M.Wainwright@shef.ac.uk


**Reviewer’s Comments**

At first sight, this hypothesis appears unlikely. However, if it is an established fact that micro-organisms do produce UV light, then it is worth considering.

One possible way of testing this hypothesis is to look at the profile of mutations induced in a gene such as p53 in tumour cells. Skin cancers show significant levels of mutations at adjacent pyrimidines indicative of UV-damage. If this was shown to be the case for internal tumours this would suggest UV-damage at di-pyrimidine sites, a finding that would strongly support the hypothesis. However, the prevailing data do not show this, certainly not at significant levels. For example, lung tumours, associated with smoking, most often show transversions at G residues, consistent with UV-damage. If this was shown then it is worth considering.

**Intracellular location of mycoplasmas**

Mycoplasmas associated with animals have generally been regarded as extracellular and their specific attachment to the surface of eukaryotic cells has been widely reported. However, in recent years evidence has accumulated that certain species, including *Mycoplasma fermentans*, *Mycoplasma genitalium* and *Mycoplasma hominis*, may have an intracellular location, and *Mycoplasma penetrans*, isolated from the urine of AIDS patients, has been shown to penetrate a wide range of cultured animal cells (1). The ability of mycoplasmas to survive within host cells is significant and might help explain the chronic nature of many mycoplasma infections and the persistence of asymptomatic carriers. Furthermore, their survival within professional phagocytic cells might lead to dissemination within the host.

*M. fermentans* has been implicated in human diseases affecting diverse body tissues. We have obtained electron micrographs of *M. fermentans* (PG18) with human polymorphonuclear leukocytes (PMNL) which show mycoplasmas clustered within phagosomes and also single mycoplasma cells apparently free within the cytoplasm (Fig. 1). There is an apparent interaction between the cytoplasm and these intracytoplasmic mycoplasmas that leads to the formation of an electron-dense layer completely enclosing the mycoplasma cell and approximately 30 nm in thickness. This electron-dense layer may be surrounded by a membrane. The frequency with which intracytoplasmic mycoplasmas were seen was greater where mycoplasma cells were non-opsonized than when non-specifically opsonized by incubation for 45 min in 10% human serum. In contrast, when mycoplasma cells were opsonized, intracellular mycoplasmas were almost always internalized within phagolysosomes.

It has been argued that in electron microscopic studies the appearance of mycoplasmas within cells might be artefactual and due to the presence of the mycoplasmas within imaginations of the cell membrane. Thus, Taylor-Robinson et al. (2) claimed that unequivocal evidence of the intracellular location of mycoplasmas required specific staining of both the mycoplasma and host cell surface. This was achieved in their study using gold-labelled anti-mycoplasma antibody and ruthenium red, which bound to the exposed polysaccharide surface of both mycoplasma and eukaryotic cell surfaces, but not to the membranes of cell vacuoles. Jensen et al. (3) found ruthenium red staining of the Vero cell membrane to be weak and of little value in confirming the apparent intracellular location of *M. genitalium* cells. They argued that where mycoplasma cells appeared close...