Infection, inflammation, and cancer

Richard Darveau

The award of the Nobel Prize in Medicine to Johannes Fibiger[1] in 1926 for his discovery that stomach cancer in rats was caused by a nematode parasite represented the first official recognition of the controversial link between cancer and infectious agents. Since then, it has become clear that infection, inflammation, and certain cancers are intimately linked, and rapid progress has made in our knowledge of the interactions between pathogens and tumors.

In this issue, Low et al.[2] exploit that expanding knowledge to build a new weapon to fight cancer. In their report, they engineer a *Salmonella typhimurium* strain that has lost its ability to induce a systemic tumor necrosis factor (TNF)-α based inflammatory response, but retains both its tumor targeting and its tumor-retarding properties.

The relationship between infection and cancer was recognized over two hundred years ago when it was observed that neoplasms often regressed following acute infections[3]. Therapeutic studies with bacterial fractions led to the discovery of "hemorrhagic necrosis" of tumors[4], with bacterial lipopolysaccharide being identified as the active component and the eventual discovery of the potent cytokine TNF-α[5]. With the demonstration that TNF-α (known as cachectin at the time) was responsible for the systemic lethal effects of lipopolysaccharide[6], efforts to separate the lethal from the beneficial antitumor effects of TNF-α were born.

Independently, it was discovered that attenuated vaccine strains of *Salmonella,* when administered to tumor-bearing mice, would retard tumor growth and prolong mouse survival[7]. Live, but not acetone-killed, bacteria retarded tumor growth, leading the authors to conclude that lipopolysaccharide alone was insufficient to induce tumor cytotoxicity. In addition, it was found that lower doses of *Salmonella* were more effective in prolonging mouse survival, demonstrating that the line between the beneficial and detrimental effects of bacterial treatment could be crossed, even with attenuated strains.

Prior to their present paper, Low and coworkers[8] modified this approach to create *Salmonella* strains that would be suitable for gene delivery by isolating hyperinvasive, multiple auxotrophic attenuated strains of *Salmonella*. They determined that these strains demonstrated bacterial dose-dependent reductions in tumor growth and prolonged mouse survival. Interestingly, they also found that the auxotrophic strains preferentially accumulated in the tumors, where they achieved tumor to liver ratios of as high as 9000:1. The reasons for the tumor localization are not well understood, but it is possible that the tumors provide the mutant *Salmonella* strains with their necessary growth requirements in an immune-privileged environment.

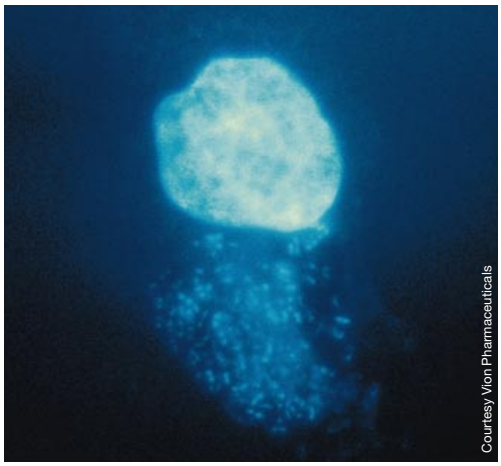

Figure 1. DAPI-stained DNA of *Salmonella* internalized into a human melanoma cell. Doublets of the bacteria can be seen throughout the cytoplasmic region of the cell, indicating bacterial replication. The nucleus can also be seen, stained with DAPI.

The concern that *Salmonella* lipopolysaccharide, with its potent ability to induce TNF-α and other host-derived inflammatory mediators, would be too toxic for use in animals, let alone humans, remained a major stumbling block. Without addressing this drawback, the beneficial properties of the new *Salmonella* antitumor weapon, hyperinvasion and auxotrophy, were irrelevant. In the present paper, Low et al. engineer *Salmonella* to circumvent the problem of lipopolysaccharide toxicity.

Several breakthroughs in the field of inflammation have made their work possible. First, a long history of structure–activity relationship studies and the complete chemical synthesis of lipid A confirmed that this lipopolysaccharide component contained most of the host inflammatory activity. Next, the almost complete genetic and biochemical elucidation of the lipid A biosynthetic pathway in *Escherichia coli* provided a framework to understand how bacteria assembled this essential component of their cell wall. Finally, a gene (*msbB*), was identified that added a key fatty acid responsible for the majority of host cell activation, including TNF-α secretion by macrophages[9,10].

Unlike all previous lipid A biosynthetic mutants, *msbB* mutant strains were able to grow at mammalian host cell temperatures[9]. This permitted Khan et al.[11] to examine the effects of lipid A in *Salmonella* infections. By employing a *msbB* lipid A mutant strain of *Salmonella*, they concluded that death of mice from *Salmonella* infection was indeed due to the toxic nature of lipid A and postulated that it was related to its ability to promote inflammatory mediator secretion.

The *Salmonella* strains described in this issue contain the *msbB* mutation along with the hyperinvasive and auxotrophic phenotypes. These strains retain their ability to retard tumor growth and fail to induce systemic TNF-α. It is possible, however, that this cytokine or other inflammatory mediators were produced locally, rather than systemically, and that accounts for the beneficial antitumor effect.

Our understanding of the relationship between infection, inflammation, and cancer will undoubtedly deepen. In time, it might even turn out that Fibiger's worms were infected with bacteria.

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