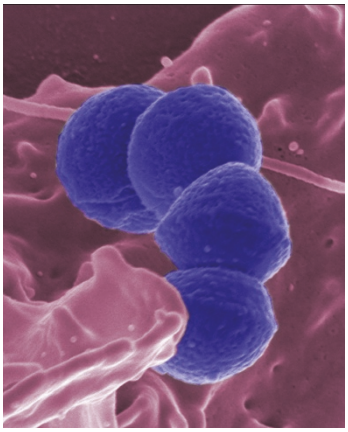
HOST RESPONSE

Controlling death

Human bacterial pathogens are exposed to a rapid innate immune response characterized by recruitment of polymorphonuclear leukocytes (PMNs or neutrophils) to sites of infection. One response to the onset of infection is acute inflammation caused by PMN activation and although highly beneficial to the host, control of infection-induced inflammation is critical for containing tissue damage. One important control mechanism to limit inflammation damage is PMN apoptosis following bacterial phagocytosis and a recent paper published in the *Proceedings of the National Academy of Sciences* sheds light on the molecular basis of this process.

By monitoring global changes in PMN gene expression, Kobayashi and colleagues investigated the molecular processes that are modulated by the phagocytosis of a diverse group of bacterial pathogens including *Borrelia hermsii*, *Burkholderia cepacia*, *Listeria monocytogenes* and *Streptococcus pyogenes*. The authors initially established that phagocytosis of bacteria by neutrophils resulted in changes to the global PMN gene expression profile, which were common to a broad range of bacterial pathogens – genes encoding key effectors of apoptosis were up-regulated, genes encoding antiapoptosis proteins were down regulated and receptors crucial to innate immune function were also down-regulated following initiation of phagocytosis-induced apoptosis. Together, these observations indicate that phagocytosis of bacterial pathogens modulates an apoptosis differentiation programme that facilitates PMN apoptosis, a process that is essential for resolution of infection. Consistent with the microarray data, was the additional observation that phagocytosis of pathogens accelerated PMN apoptosis.



A scanning electron micrograph that shows an early stage of phagocytosis of *S. pyogenes* by a human neutrophil. Image courtesy of Frank DeLeo (Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, Montana, USA).

Of course, not all bacterial pathogens succumb to this process and the resultant control of infection. Following phagocytosis by PMNs, *S. pyogenes* also alters the apoptosis differentiation programme elicted by other bacteria, however, this pathogen does it to survive. Unlike the common gene expression profile observed with other pathogenic bacteria, phagocytosis of *S. pyogenes* resulted in the altered regulation of 393 genes whose expression differed significantly from that induced by other bacteria. A significant difference included the down-regulation of 21 genes involved in responses to interferon. Interestingly, *S. pyogenes* was also found to induce rapid apoptosis, however, progression was significantly accelerated relative to other pathogens and was subsequently followed by significant necrosis. These observations suggest that key factors in the pathogenesis of *S. pyogenes* are the active alteration of inflammation signalling networks and apoptosis in PMNs.

Ultimately, increasing our understanding of how bacteria-induced apoptosis contributes to the resolution of infection, and how certain pathogens can subvert this process to enhance their survival is going to be crucial in our efforts to improve infectious disease treatment and outcome. The valuable insight gained from this study and potential targets identified for possible exploitation represent a significant step forward in this quest.

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References and links

ORIGINAL RESEARCH PAPER Kobayashi, S.D. *et al.* Bacterial pathogens modulate an apoptosis differentiation program in human neutrophils. *Proc. Natl Acad. Sci. USA* **100**, 10948–10953 (2003)

FURTHER READING Hornef, M.W. *et al.* Bacterial strategies for overcoming host innate and adaptive immune responses. *Nature Immunol.* **3**, 1033-1040 (2002)

WEB SITE
Frank DeLeo's laboratory:
http://www.niaid.nih.gov/dir/labs/lhbp/deleo.htm