Immuneresponsesinendocarditis

In1885WilliamOslerdeliveredtheGulstonianlectures
describingthebroadclinicalmanifestationsofbacterial
endocarditis.1Thepast30yearshaveseenconcerted
attempts to explain the pathogenetic mechanisms behind
thesyndrome: heart failure out of proportion to the valve
insufficiency; the presence of renal lesions in the majority
ofcases; arthritis, vasculitis, and splenomegaly as well as
theclassiccutaneoussigns. Whatisclearisthatan
encounter between a circulating bacterium and an abnor-
mal valve, with subsequent embolisation, can explain
nithertheinitialestablishmentofthevegetationnorthe
myriad of extracardiac sequelae. Moreover, in most cases
the microorganisms implicated are of low virulence, but
whensequesteredinavegetationtheyarecapableof
inducinguncharacteristicallyseveredisease.

Theunderstandingofendocarditisasanimmune com-
plexmediatedsyndromeandtheidentificationoffactors
necessary for the genesis of the vegetation have clarified
someofthesecondictions. Recentappreciationofthe
specific roles for cytokines in inflammation and control of
sepsisenablefurtherunderstandingofthediverse
pathophysiologicalfindingsininfectiveendocarditis.

Pathogenesisofthecardiacvegetation

The animal model of endocarditis, in which a polyethylene
catheter is passed across the aortic valve of a rabbit,
producing initially a non-bacterial thrombotic vegetation
and subsequently bacterial colonisation, has been a useful
pathophysiological tool.2,3Bacterial factors such as dex-
tran, slime, fibronectin binding, and teichoic acid have
been implicated in bacterial adherence to the platelet–
fibrin matrices on the damaged valve. Other studies, inves-
tigating the role of the host immune response in protection
againstendocarditis, employed whole cell vaccines with
varied results. In some cases, active (but not passive)
immunisation prevented endocarditis without accelerating
therateofbacterialclearancefromthecirculation,
suggesting a mechanism related to interference with bacte-
rial adherence to the vegetation. The requirement for active
rather than passive immunisation implicates additional
components of the immune system. Rabbits challenged
withEscherichiacoli
developendocarditisiftheyaregeneti-
cally deficient in C6, providing strong evidence for the
protectiverolesofcomplementagainstbacterialendocardi-
tis in this lupine model. Other studies in right sided lupine
experimental endocarditis demonstrated failure of sponta-
neous sterilisation in the presence of dexamethasone or
agranulocytosis. Recent work with viridans streptococci
has implicated platelet released bactericidal factors in the
clearance of bacteria early after adherence,4 and interest-
ingly reduction in vegetation weight and bacterial concen-
tration in rabbits treated with aspirin has been
demonstrated.5 The development of endocarditis depends
on a balance between the abilities of the organism to adhere
to vegetations and to resist the array of host responses.

Immunecomplexes

Necropsystudieshaveshownthepresenceofglomerulo-
nephritisinablаждportionofcasesofhumanendocard-
ditis, and immunofluorescence studies have characterised
thelesionasmediatedbyimmunecomplexdeposition.
The“lumpybumpy”distributionofimmunoglobulinand
complement components, typical of immune complex
mediated injury, is more common with streptococci, which
appear to involve the classic complement pathway. In con-
trast, staphylococci, which initiate the alternative pathway,
depositantigenandnotantibodywithcomplementinthe
kidney. Evidence suggests deposition of circulating
immunocomplexes (CICs) rather than formation intrare-
nally, and CICs have been identified in other sites, such as
thespleen and cutaneous lesions in endocarditis. Assays
developed to detect CICs have shown correlations between
CIC concentrations and duration of illness, extravalvar
manifestations, and hypocomplementaemia as well as a fall
in CIC in response to treatment.

Antibody specific to the infecting organism and bacterial
cell wall constituents have been identified within CICs.
Under normal conditions antigen–antibody complexes
should be solubilised and phagocytosed. Clearly other fac-
tors are acting to prevent solubilisation of these
complexes, with consequent deposition in tissues. Evi-
dence suggests that rheumatoid factors, detectable in 50%
ofendocarditis cases, mask the receptor sites for phagocy-
tosis and hence prevent clearance of CICs. This would
explain why patients with endocarditis may suffer long
termbacteraemadespitelonglevelspecificIgGantibody,
adequate complement, and functioning neutrophils.5

Antibodies directed against myocardialproteins

Another feature of endocarditis that has received attention
from immunologists is the presence of myocardial
dysfunction out of proportion to the valve lesion, often
even in the absence of significant valve destruction. Maisch
found that the polyclonal antibody response in endocardi-
tis included antimyolemmal and antisarcolemmal
antibodies.6 The antisarcolemmal antibodies could be
shown to cross react with streptococcal antigens, as
demonstrated previously in rheumatic fever and for viral
antigen in myocarditis. This may represent deliberate anti-
genic mimicry on the part of the bacteria, but the
pathological role of these antibodies in cardiac dysfunc-
tion, rather than just as innocent bystanders, is not proven.
The antimyolemmal antibodies (AMLA) were cytolytic
to cardiac cells in vitro in the presence of complement, and
cytolytic serum activity in some patients was present only
when AMLA were also found and correlated with AMLA
titre.

In addition, studies examining myocardial protein
synthesis in rats receiving endotoxin to simulate acute
phase response, demonstrated overall reduction in such
protein synthesis8 and a switch in myosin isoenzyme
transcription.9 Such profound changes in myocardial
protein synthesis in this rodent model may partially explain alterations in myocardial performance seen in inflammatory conditions such as infectious endocarditis.

**Lymphocyte activity**

White cell function in endocarditis has been analysed, until now fairly crudely, showing an increase in number of monocytes and granulocytes, but a decrease in number and activity of T helper, T suppressor, and natural killer cells during infection. The reduction in numbers in the peripheral blood may, however, be accounted for purely by trafficking to the site of injury. In some studies T suppressor cell activity corrected partially after treatment, suggesting a predisposition to endocarditis as a result of inherent reduced lymphocyte function in such patients, rather than lymphocyte dysfunction being purely a consequence of infection (note the increased risk of endocarditis in immune suppressed individuals).

A decrease in number of polymorphonuclear leucocytes in the circulation during severe bacterial infection may indicate consumption of these cells at sites of inflammation. However, in the setting of long term (four to six weeks) β lactam treatment for endocarditis, neutropenia is not unusual. Such neutropenia reverses spontaneously within days of stopping β lactam and is thought to be immune mediated. It is important to be aware of this iatrogenic phenomenon as its presence does not indicate uncontrolled disease but that antibiotic change is required.

**Cytokines and the mechanisms of inflammation**

The mechanisms of stimulation of phagocytosis and inflammation in general have come under more detailed scrutiny recently, with the study of cytokine responses to various organisms. Evidence suggests that interleukin 8 (IL-8), a member of the C-X-C chemokine family that has predominant neutrophil stimulatory and chemotactic activities, is an important mediator of acute inflammation in response to infection. Lipopolysaccharide, mycobacterium tuberculosis, and influenza A have been shown to induce production of IL-8, and increased plasma concentrations of IL-8 have been detected in acute bacterial infections. Bacterial endocarditis provides a useful tool for studying the mechanisms by which Gram positive organisms initiate activation of phagocytes and subsequent inflammation. Enhanced IL-8 expression in macrophages present in the inflamed endocardium of patients with *Staphylococcus aureus* endocarditis has been demonstrated. Furthermore, lipoteichoic acid, a constituent of the Gram positive cell wall and known to have important macrophage stimulatory effects, is a potent stimulus for IL-8 production.

IL-6, a cytokine involved in B cell stimulation, antibody production, and the release of acute phase proteins, has been found to be raised in streptococcal and Q fever endocarditis. In studies of patients with Q fever, tumour necrosis factor (TNF) and IL-1 are good markers of disease activity, concentrations being higher in patients with recent endocarditis than in those with stabilised endocarditis. In addition, immune complexes per se elicit release of eicosanoids and cytokines (for example, TNF from macrophages), and suppress protective cell mediated immunity by inducing IL-10 release from circulating phagocytes.

Plasma levels of TNF have been measured in streptococcal endocarditis. While lipoteichoic acid stimulates TNF production by macrophages in vitro, a study of 10 patients with subacute endocarditis showed normal plasma concentrations of TNF in all except those with complications. However, soluble TNF receptor (sTNF-R) concentrations were significantly raised. In contrast, control patients with falciparum malaria had high ratios of TNF to sTNF-R. The presence of high concentrations of sTNF-R suggests chronic constitutive TNF activity perhaps principally at the tissue level with little direct spillover of TNF into the circulation. The pro-inflammatory activity of TNF inducing the acute phase response may be pivotal in the systemic manifestations of infective endocarditis. The site of cytokine production is not yet established, but as the endothelium is known to be a rich source of such molecules, investigation of the endothelial factors released in infective endocarditis is a high priority in understanding the pathogenesis of this condition.

MICHAEL BROWN

GEORGE E GRIFFIN

Division of Infectious Diseases,
St George's Hospital Medical School,
Graham Terrace, London SW17 0RE, UK

1 Osler W. The Gulstonian lectures on malignant endocarditis. BMJ 1885;2;467-70,522-6,577-9.
15 Capo C, Zugun F, Stein A, Tardei G, Lepidi H, Falciparum malaria had high ratios of TNF to sTNF-R. The presence of high concentrations of sTNF-R suggests chronic constitutive TNF activity perhaps principally at the tissue level with little direct spillover of TNF into the circulation. The pro-inflammatory activity of TNF inducing the acute phase response may be pivotal in the systemic manifestations of infective endocarditis. The site of cytokine production is not yet established, but as the endothelium is known to be a rich source of such molecules, investigation of the endothelial factors released in infective endocarditis is a high priority in understanding the pathogenesis of this condition.

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