Immunology of BCG Vaccine*

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Since 1921, when the first experiments conducted on guinea pigs demonstrated that BCG (Bacille Calmette-Guérin) was an attenuated, non-virulent and genetically stable tubercle bacillus, the literature on the use of this vaccine has been prolific. The vaccine was originally developed by Calmette and Guérin at the Pasteur Institute of Lille by the sequential passage of virulent *Mycobacterium bovis* on a culture medium containing ox bile as an emulsifying agent. After 13 years of sub-culture, the strain was found to be attenuated, first in guinea pigs and subsequently in cattle. At that time, it was initially shown to confer protection against tuberculosis in cattle.[1]

It has been 60 years since BCG vaccine was first approved for human use in France. Since that time the vaccine has been administered to hundreds of millions of individuals. It has been subjected to numerous trials of efficacy as a vaccine for tuberculosis and more recently leprosy. It has also served as an immunological tool to help decipher how the immune system functions. Finally, it has been tested as an immunopotentiating agent in the treatment of both infections and neoplasms. This article will attempt to describe immune responses to BCG and their implications for clinical use. This is not intended to be a review of the entire literature, but is rather an overview of the most important points.

IMMUNOLOGICAL RESPONSE TO BCG

Pathological response

Following subcutaneous or intravenous injection of BCG, numerous pathological changes have been observed in laboratory animals. In rats, subcutaneous injection elicits a triphasic response. An initial simple granuloma is followed closely by necrosis and local mycobacterial multiplication at the site of injection. Subsequently, an epithelioid granuloma develops, mycobacteria disappear and the lesion heals.[2] The lymph nodes draining the area exhibit increased medullary vascularity and mononuclear infiltrates with the formation of granuloma.[3] Intravenous challenge has been shown to affect the lymphoreticular system diffusely. Hyperplasia of the thymic cortex associated with increased mitotic activity occurs.[4-7] In the lymph nodes, pronounced hyperplasia of the thymus-dependent areas is noted.[4,7,8] The splenic white pulp also becomes hyperplastic[4,6,9] and granulomatous inflammation is seen in both the lung and the liver.[4,10,11]

Cell-mediated immunity

The relationship of the observed pathological changes to immunological responses has been elucidated primarily through the study of BCG-induced non-specific immunity. Although BCG was presumed to protect against tuberculosis by virtue of the specific immune response it provoked, a direct examination of the immunological responses on challenge with tuberculosis was initially found to be technically difficult.[12] BCG was noted to have a stimulatory effect on the immune response to heterologous antigens[13-15] and subsequently to be a potent stimulant to the reticulo-endothelial system.[16] Further studies depended on the observations that when macrophages of a host infected with intracellular bacteria became highly resistant to re-infection, their activities were directed not only against the inducing agent but also against other intracellular bacterial parasites.[17-20]

Macrophage activation

Blanden *et al* studied the host resistance to *Listeria monocytogenes* in mice given primary and secondary infections with BCG.[21] *L. monocytogenes* was chosen because it is a facultative intracellular parasite, highly susceptible to inactivation by immune macrophages[17,18] and a highly sensitive measure of host resistance. Mice infected with 4×10^6 viable BCG developed increased resistance to *L. monocytogenes* in the liver and spleen within six days and demonstrated increased clearance of these and organisms from the blood.

Observations were made concerning the relationship between such resistance and the growth of BCG.

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The onset of resistance to *L. monocytogenes* (3-12 days) coincided with the growth of BCG in the liver and spleen and peak resistance occurred when BCG multiplication ceased (12-15 days). Although these findings suggest a parallel resistance to *L. monocytogenes* and BCG, continued inhibition of growth of BCG occurred during the period of declining resistance to *Listeria* (15-28 days). This observation can be explained by the concept of local immunity, as postulated by Dannenberg.[22] Systemic activation of macrophages has been shown to occur only during periods of intense antigenic stimulation.[17,22] As local lesions develop, the organisms within them become increasingly confined and their stimulatory effect restricted to macrophages in the vicinity. BCG immunity was thus sustained locally, but protection against systemic *Listeria* infection was found to diminish.

Increased resistance to *L. monocytogenes* and development of tuberculin sensitivity required exposure to living BCG organisms. Injections of heat killed organisms or concurrent vaccination with BCG and treatment with isoniazid failed to elicit host resistance.[21] Furthermore, studies on the effect of secondary infection with BCG demonstrated that host resistance in both liver and spleen was augmented. These findings were accompanied by the detection of striking morphologic changes in the peritoneal macrophages and enhanced killing of *Salmonella typhimurium* by these cells.[21] These macrophages have been found to develop increased spreading and metabolic activity,[23,24] namely, an increase in the rate of glucose oxidation resulting in enhanced phagocytosis and killing.[24]

Lymphocyte sensitisation

Understanding of the efferent limb of the host cell-mediated immune response, manifest by the production of what is now termed activated macrophages, preceded understanding of the afferent limb. In 1964, Mackaness[17] postulated that the induction of acquired resistance by BCG or other intracellular bacteria was due to an antibody adsorbed to the surface of host macrophages. Further studies in his laboratory, however, helped to elucidate the cellular basis of this phenomenon.[23] His studies were primarily done using the *Listeria monocytogenes* model. He demonstrated that infections with *L. monocytogenes* gave rise to a population of immunologically committed lymphoid cells which were capable of conferring both protection and delayed-type hypersensitivity upon normal recipients. These cells were most numerous in the spleen. They had to be alive in order to confer protection; they mediated resistance indirectly through the macrophages of the recipient. Studies examining the passive transfer of BCG-induced resistance to *Listeria* further showed that macrophage activation depended upon a specific interaction between immune lymphoid cells and the infecting organisms. BCG-immunised donors were highly and non-specifically resistant to *Listeria;* their lymphoid cells were unable to confer protection against a *Listeria* challenge unless the recipients were also injected with an eliciting dose of BCG.

Other investigators have since shown that the lymphoid cells responsible for this passive transfer of resistance are T lymphocytes.[26-29] They have also found that T lymphocytes not only activate macrophages but also lead to the accumulation of these cells in the liver and spleen of infected mice.[28]

Mackaness also made the observation that peritoneal macrophages were stimulated both morphologically and in their microbicidal function by the intravenous injection of immune lymphoid cells and BCG. He postulated that a circulating substance served as the mediator of macrophage activation. David[30] and Bloom and Bennett[31] demonstrated that lymphoid cells from tuberculin-sensitive donors, who were exposed *in vitro* to PPD, released a factor which was capable of modifying the migratory behaviour of macrophages from unsensitised subjects. Mackaness hypothesised that this substance, termed migration inhibitory factor (MIF), might be responsible for the activation of peritoneal macrophages.[25] More recently PPD sensitisation of lymphocytes has been found to lead to the production of MIF.[32] Re-exposure of sensitised lymphocytes to specific antigen has been found to lead to the production of numerous lymphokines, including macrophage activating factor (MAF), MIF, chemotactic factor, blastic factors, lymphotoxins and interferon.[33-35]

Humoral immunity

In addition to its role in macrophage activation, BCG appears to exert a broad influence on the immune system. Dienes and Schoenheit[14] first showed that the injection of antigen into a tuberculous focus stimulated both delayed-type hypersensitivity (DTH) and heightened antibody titres. Freund and McDermott[36] subsequently employed this observation by developing adjuvants which contained mycobacteria. More recent studies on the immune response to sheep red blood cells (SRBC) have demonstrated that BCG causes a marked enhancement of both T- and B-cell components.[37]

Studies on the host response to immunisation with SRBC, have shown that small intravenous doses elicit DTH. With larger doses however, antibody to SRBCs is formed and DTH is inhibited. This blocking effect of DTH is due to antigen-antibody complexes which accumulate in the serum of heavily immunised animals.[38]

Injection of BCG and SRBC into areas drained by a common lymph node leads to marked antibody formation and maintains DTH.[38] This is associated with a lymphoproliferative response in the paracortex

(T-cell area) and later the medulla of the regional lymph node.[40] Intravenous injection with BCG and SRBC leads to a similar response in the spleen of these animals.[38,40,41] The study of thymectomised mice, in which DTH responses are markedly diminished, has shown that the proliferating cells are T cells. These responses, however, can be restored with thymocytes.[27] It has been suggested that the coexistence of antibody formation and DTH in this experimental system is due to the increased clearing capacity of the reticulo-endothelial system of BCG-infected animals,[42] thus keeping the blood free of immune complexes which inhibit DTH.[43,44] BCG, therefore, not only clears the blood of immune complexes maintaining DTH, but it also enhances antibody formation in response to SRBC, presumably through the induction of T-helper cells.[44] The ability of BCG to activate non-specific T-helper cells has since been demonstrated.[45]

Suppressor cell stimulation

BCG has also been found to induce suppressor cells in several systems. The intravenous injection of killed BCG was shown to produce marked suppression of antibody responsiveness and delayed hypersensitivity to SRBC as well as a decreased proliferative response to PPD.[46] Intravenous BCG also suppressed both DTH and antibody responses to BCG[47] or SRBC,[48] normally observed following subcutaneous administration; BCG also activated natural bone marrow suppressor cells.[49] Suppressor cells elicited in this way are both specific[46,47,50] and non-specific.[46,48] This induction of suppressor cells has been found to be strain-dependent[46,50] and mediated by splenic cells[46,49,50] which are influenced by adherent I-J-positive cells.[53] It is also thought to be dose-dependent.[52]

Finally, BCG has been a useful tool in helping to illustrate how the genetic constitution of the host influences immunological responsiveness. In addition to suppressor cell induction, other BCG-induced phenomena have been found to be influenced by the mouse strain used. These include *in vivo* release[53] or *in vitro* production[54] of lymphokines, enhanced phagocytosis through stimulation of the reticulo-endothelial system,[55] enhancement of endotoxin sensitivity,[56] protection against unrelated intra-cellular infection[57,58] and parasitic infection.[59] The identification of the phenotypic expression at the cellular level of this genetic influence might accelerate the development of specific immunological therapy, once again establishing the prominent role BCG has played as a tool to help decipher the functions of the immune system.

CLINICAL APPLICATIONS OF BCG

Tuberculosis

Studies in 1921 showing that BCG protected cattle from tuberculosis infection preceded its use in humans which first occurred in 1924.[1] Although the initial studies to determine the immunological basis for BCG protection were fraught with technical difficulties,[12] our understanding of its augmentation of resistance to tuberculosis is more complete today.

Animal models

BCG vaccination has been shown to lead to resistance to tuberculosis in various models.[60,61] The mechanism of this resistance has been studied in several ways. In 1953, Suter determined that vaccination with BCG retarded or inhibited the intracellular multiplication of tubercle bacilli in rabbit and guinea pig monocytes.[62] Others observed a genetic dependence of granulomatous response to BCG and subsequent development of both DTH and acquired resistance in mice.[52,63] This has been used to decipher the immunological basis for protection.

C57BL/6 mice have been found to be susceptible to BCG infection and to develop protective immunity. C3H mice are resistant to infection and do not develop DTH or acquired resistance.[52,63] Investigations using adult thymectomised lethally irradiated bone marrow reconstituted C57Bl/6xC3H F1 mice have shown that splenic and pulmonary thymocyte proliferation is important in retarding and controlling bacillary multiplication.[64]

An examination of the response of mice, which are allogeneic or tetraparental bone marrow chimeras, has shown that development of resistance depends on bone marrow cells from C57BL/6 mice. C3H mice appeared to have an impairment in their ability to present antigen.[65] This finding might explain the observation of Pelletier *et al*[52] that, although C3H mice are naturally resistant to BCG, they do not develop a cellular immune response or acquired resistance. These observations confirm the experimental evidence that acquired resistance is dependent on the development of cellular immunity. Finally, several studies[61,66] have determined that BCG exerts its protective effect against tuberculosis by retarding and decreasing the hematogenous dissemination of virulent mycobacteria.

Human studies

The clinical studies done in humans have shown a variable (0-80%) BCG efficacy in protecting against TB. Excellent protection was demonstrated in studies by Stein and Aronson among North American Indian tribes (approximately 80% protective efficacy)[67] and by Rosenthal *et al*[68] in high-risk Chicago infants in whom 75 per cent protective efficacy was detected. In addition, the Medical Research Council (MRC) of Great Britain found 78 per cent protection in 14- to 15-year-old British school-leavers given BCG.[69] Treatment of children in Puerto Rico ranging in age from 1 to 18 years old was less successful (35% protection)[70,71] and in rural

South India[72] only 31 per cent were protected from infection with tuberculosis. In contrast, no protection was seen in the Muscogee County study in Georgia[73] and only 14 per cent protection was noted on treatment of the general population of Georgia and Alabama.[74] These studies were controlled field trials which have been judged to be methodologically correct.[75] Other uncontrolled or smaller scale studies showed equally contrasting results (0-80% efficacy).[76-79]

Several hypotheses were put forward to explain these disparate results. These included the possibility that infection with other atypical mycobacteria provided natural immunity to the population. Thus, the vaccinated group would receive only supplementation of the already existing immunity and the apparent effectiveness would be lower.[80] This hypothesis has been corroborated in the guinea pig model,[80] but does not fully explain the experimental results.[81] A second hypothesis was that the BCG products used had widely different immunising effects. In two field trials demonstrating no protection, however, experimental studies of the BCG products did not support this suggestion.[82,83] A third hypothesis put forward was that BCG efficacy is greater in areas where the prevalence of TB is high and low efficacy occurs where the incidence of TB is low.[84]

Based on this background of uncertainty about the efficacy of BCG, the South Indian trial was undertaken with the support of the World Health Organisation. This trial utilised several different BCG products in various dosages in their freeze-dried form. The trial was also intended to answer questions concerning the usefulness of BCG in the developing world where it is now most frequently used. Following the publication of the results after 7½ years of follow-up,[85,86] the issue of BCG efficacy continues to promote extensive discussion.[87] The South Indian trial found that BCG did not protect against tuberculosis in the study area. In addition, an unprecedented pattern of tuberculous infection had emerged suggesting the appearance of an organism of low virulence with a very low disease to infection ratio. In fact, only a fifth of the expected incidence was detected.[88]

In an experimental setting, several hypotheses were tested to explain these findings. The BCG used was found to be immunogenic and potent.[89,90] There was no demonstrable period of hypersusceptibility early after immunisation,[89] and the BCG product used led to good protection against the strain of low virulence from the study area.[90] Little information was obtained in this study regarding infection in children (the usual targets of BCG immunisation programmes) and protection against non-pulmonary TB, more frequently seen in children. The trial was continued; reevaluation at 12½ years identified 28 per cent protection.[86] The final results, however, will be evaluated following completion of this 15-year study. BCG has been shown to be effective in some settings and not in others. It is certainly possible that the third hypothesis cited previously[87] - - that BCG protects in areas of high prevalence and has little efficacy in areas of low endemicity - - accounts for the observations in India.

BCG vaccination in infants and newborns

In many programmes in the developing world, BCG vaccination has been directed at the youngest age groups of the population including newborn children. The rationale for this policy is that children would be vaccinated before being exposed to infection and that protection against the serious manifestations of TB in children, miliary tuberculosis and tuberculous meningitis, would be achieved. Although this is the current practice, there is little direct evidence concerning the degree of protection afforded to very young infants. In fact, the response to BCG among newborn children is not the same as that among adolescents and young adults. Suppurative lymphadenitis is a common side-effect and despite this the post-vaccination tuberculin sensitivity among newborn children appears to be lower than that elicited among older children.

Three controlled trials were carried out on newborn children in the 1930s. The first study began in New York City in 1926 and children from tuberculous homes were chosen to receive BCG by self-selection for seven years and subsequently by alternating assigment. Although the outcome in both groups was ,similar, there were several problems during the course of that study which made questionable the reported observations.[92] Ferguson and Simes[93] started a controlled trial among Saskatchewan Indians in 1933 and vaccinated infants intracutaneously within 10 days of birth. They observed an 80 per cent protective efficacy. A percutaneous multiple puncture method was used by Rosenthal *et al*[94] in this study. They noted 75 per cent protection from tuberculosis in the infants vaccinated with BCG within the first week of life. More recent publications describe retrospective studies which are well-known to be subject to observer bias. Bjartveit and Waaler[95] noted a strong association between the decline of TB in various age groups and the age of vaccination. This association was particularly strong for vaccination of newborn children. Ehrengut[96] compared two regions in Germany which differed with regard to vaccination policies for newborn children. In Hamburg, they were given BCG; there, the decline in mortality from tuberculous meningitis and miliary tuberculosis took place at a faster rate than in Bavaria where there was no newborn vaccination programme. Finally, the incidence of tuberculosis in the 0-1 year age group was found to double as a consequence of the temporary sus-

pension of BCG vaccination among newborn children.[47] These observations suggest that BCG vaccination of the newborn may offer protection from tuberculosis. However, because the products used in these studies are no longer available and in current immunisation programmes BCG is given a few months after birth rather than within the first few days, further evaluation is necessary.

Leprosy

Although there is no animal model for human leprosy other than the armadillo, *Mycobacterium lepraemurium* in mice is thought to bear many similarities to the human disease.[98] In this experimental model, BCG has been shown to confer protection against infection.[98-101] It leads to a decreased bacillary load and a delay in dissemination.[98] The protection conferred by BCG can be transferred with spleen cells[99] without the simultaneous boosting with BCG which is necessary in BCG-induced immunity to *Listeria* infection.[25] This confirms that its protective effect is due to immune responses to cross-reactive antigens and not to the non-specific immunity responsible for protection from listeriosis.[99] In addition, mice rendered tolerant to *M. leprae* could be partially sensitised by the intracutaneous injection of BCG.[101]

In 1939, Fernandez[102] reported that 90 per cent of children with a negative lepromin skin test became lepromin-positive following BCG vaccination. Upon confirmation of this finding in another study,[98] three vaccine trials were undertaken using BCG for primary prevention of leprosy. A study in Uganda[104,105] showed good protection (80-87%), while one in Burma[106] was less successful (29%). In Papua New Guinea,[107] 44 per cent protection was elicited and in the recent South India trial more than 30 per cent protection was detected.[88] Thus, variable protection is also observed with regard to the use of BCG immunisation for the prevention of leprosy. This may be due to numerous causes. Some may be similar to those postulated in cases of tuberculosis, and others may be due to specific features of leprosy such as the very long incubation period and the variable immunological and clinical spectrum which ranges from good to poor or non-existent cell-mediated immunity. Convit and his colleagues have shown that the injection of killed *M. leprae* and BCG into lepromatous patients led to bacillary clearance, an upgrading reaction and lepromin conversion which corresponds with increased cell-mediated immunity. It also elicited lepromin skin test positivity in lepromin-negative indeterminate patients and lepromin-negative contacts.[108,109] These observations have also been made in the experimental setting of murine *M. lepraemurium* infection.[100] Although BCG alone may not offer consistent protection,[100] there may be a role for BCG enhancement of a specific *M. leprae* vaccine.

Non-specific immunity

The initial studies on the effect of BCG on the immune system documented and investigated the stimulation of non-specific immunity to intracellular bacterial parasites such as *Listeria monocytogenes* and *Salmonella typhimurim*.[21] This immunity was mediated by activated macrophages which developed enhanced phagocytosis and killing.[23,24] In an animal model of a simulated surgical wound infection, BCG treatment was shown to improve tissue antibacterial activity.[110]

Non-specific acquired resistance has also been demonstrated in cases of various other infectious diseases. These include viral infections such as influenza,[111] protozoal diseases due to *Babesia, Plasmodium* and *Leishmania* species[112] and *Trypanosoma cruzi*[113,114] as well as various helminthic infestations which will be discussed later. BCG enhanced immunisation with the rabies vaccine[115] but offered no protection against recurrent *Herpes progenitalis*.[116] BCG given intravenously, but not by the retrobulbar route, protected rabbits against toxoplasma retinochoroiditis.[117] It offered no protection to mice which are susceptible to *Trypanosoma congolense*.[118] In cases of malaria, BCG treatment led to an enhancement of the normal antigen processing of macrophages and to the release of highly immunogenic "super antigens".[119]

In helminthic infestations, there is also experimental evidence that BCG affects the host-parasite relationship. It has been shown to suppress growth and metastasis of *Echinococcus multilocularis*,[120] to inhibit the development of secondary cysts of *E. granulosus*,[121] to decrease the systemic larval burden in cases of *Trichinella spiralis*[122,123] and similarly to reduce the worm burden in cases of *Schistosoma mansoni* infestation.[124] It offers no protection against *Fasciola hepatica*[125] and it decreases the volume of circulating microfilaraemia in cases of *Litomosoides carinii* infection without affecting adult worm viability or fecundity.[126]

In many of these settings, differences in the interval between BCG immunisation and effective protection were noted. Efficacy depended on the route of administration and BCG administration frequently led to a considerable duration of protection.[112,124] Protection against helminths has been found to be due to the generation of activated macrophages[127] by a T-cell-secreted lymphokine[128] or by coculture with macrophage activating factor.[129] Through the identification of genetic restriction of BCG induced macrophage activation,[59,130] arginase released by macrophages was identified in this setting as an important mediator of parasite cytotoxicity.[130] In humans, monocytes of subjects with active pulmonary tuberculosis also demonstrated enhanced *in vitro* killing of *S. mansoni* schistosomula.[131] Al-

though the experimental literature is extensive on the usefulness of BCG with regard to non-specific immunity to various infections, the clinical relevance to human disease has not yet been established. BCG might have a role in the enhancement of vaccine-induced specific immunity in these disease once vaccines become available.

Tumour immunity

The use of BCG as a potentiator of immunological defence against tumours was based on several observations. BCG has been shown to have a stimulatory effect on the immune reponses to heterologous antigens[13-15] and tumours were found to possess distinctive tumour-associated antigens not found in normal tissues.[133-135] Reticulo-endothelial system stimulation was also known to be associated with prevention of tumour growth[134] and BCG was found to be a potent stimulus of the reticulo-endothelial system.[16] In addition, bacterial toxins had already been used in patients with cancer and objective remissions and cure had been reported.[137]

Since those early observations, the literature surrounding the use of BCG in neoplastic disease has been extensive. BCG-activated macrophages are produced by similar mechanisms to those responsible for non-specific immunity to microbial pathogens[138] and they exert a non-specific cytostatic effect on human tumour cells *in vitro*.[139,140] The successful use of BCG as a preventive measure or a therapeutic tool in experimental animal tumours has been well documented. Although its use in treating human disease has been well examined, a discussion of these topics is beyond the scope of this article. The reader is referred to several excellent review articles.[141-147]

Complications of BCG therapy

Finally, one must examine the side-effects occurring because of treatment with BCG when assessing whether its use in various clinical settings should be promoted. The incidence of complications following BCG vaccination for tuberculosis is very low. The most frequent observations include localised abscesses[148] and regional lymphadenitis.[149] Rarer complications include systemic infection,[150] which rarely leads to clinical symptoms[151] or death,[152] liver granulomas[153] and anaphylaxis,[154] among others.

BCG immunotherapy, however, is associated more frequently with complications which are more serious. This effect is due to the larger doses and more frequent administration of BCG used in therapy for neoplasia. In addition, the immunological impairment of many cancer patients contributes[152] to this effect. Patients may develop local microabscesses, rash and pruritis, scarring or prolonged ulceration[152] at the site of injection. Systemic flu-like symptoms are common.[152] Disseminated infection,[155] hepatic toxicity,[152] anaphylaxis[149] and generalised cutaneous reactions[156,157] have all been reported. Finally, enhanced tumour growth[157] is a potential complication which has been well documented in animal studies,[44,149,150] but not yet documented in humans.[152]

Thus, in **summary**, since the development of BCG is 1921, it has proved to be a useful immunological tool in deciphering some of the mechanisms of cell-mediated immunity. In addition, it has played an important role in the prevention of tuberculosis and has been partially evaluated as an immunopotentiating agent in the treatment of other infections and neoplasms.

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