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**ASSIGNMENT**

Discuss the involvement of T- and B-lymphocytes in the pathogenesis and progression of Osteomyelitis and osteoarthritis.

T cells and cellular immunity in Osteoarthritis

Mononuclear cell infiltrates in synovial tissues have been reported in OA (Smith et al., 1997; Lindblad & Herdfos 1987) and have been shown to contain primarily CD3+ T cells (Ishii et al., 2002). Both CD4+ and CD8+ cells were found in OA synovium at similar levels as in RA synovium. The Th1 subset of T cells were found to be about 5 times more than Th2 cells (Ishii et al., 2002) and higher levels of Th1 cytokines, IL-2 and IFNγ, were detected in most of OA patient (Sakkas et al., 998). T-cells in lymphocytic aggregates in OA synovium were shown to bear early (CD69), intermediate (CD25 and CD38) and late (CD45RO) activation markers. These observations suggest the presence of an active cell-mediated immune response in majority of OA patients. Analysis of α/β T cell receptor diversity revealed the presence of oligoclonal populations of T cells in OA patients (Nakamura et al., 1999). This suggested that those cells were undergoing clonal expansion in response to specific antigens within the synovium. Although there are no conclusive data on the antigens, which drive the immune response in OA, several candidate antigens have been proposed. T cells derived from peripheral blood and synovial fluid of OA patients showed a strong response to autologous chondrocyte and fibroblast membrane preparations (Alsalameh et al., 1990). In another study OA chondrocytes were shown to stimulate autologous T cell response in vitro (Sakata et al., 2003). Cellular immunity to type III collagen and proteoglycan was detected after partial meniscectomy in rabbits (Champion and Poole 1982). Higher cellular immunity was observed in OA patients compared to normal subjects when their peripheral blood lymphocytes were stimulated with human cartilage link protein and G1 globular domain of proteoglycan (Guerassimov et al., 1999).More specifically, peptides representing amino acid regions 16–31 and 263–280 located in G1 domain of proteoglycan were more frequently recognized by PBMCs isolated from OA patients compared to healthy controls (de Jong et al., 2010). These studies suggest a role for cartilage components as autoantigens responsible for oligoclonal T cell response observed in OA patients. The role of CD4+ T cells in OA was highlighted by a recent study in anterior cruciate ligament-transection (ACLT)-induced OA mice where these cells were found to be involved in increased production of MIP-1γ followed by increased infiltration of macrophages in synovium and increased expression of MMP-9 ( Shen et al., 2011). In another study, when chondrocytes from OA patients were co-culture with autologous T cells, they produced higher amounts of RANTES and MMP-1, MMP-3 and MMP-13 (Nakamura et al., 2006).

B cells and humoral immunity in Osteoarthritis

Cellular infiltrates in the inflamed OA synovium have been reported to contain activated B cells along with other cell types (Revell, Mayston & Mapp, 1988). A clonal analysis of B cells in OA synovium revealed their oligoclonal nature suggesting an antigen driven activation instead of non-antigenic activation (Shiokawa, Matsumoto & Nishimura, 2001). Moreover, several studies found antibodies against cartilage components highlighting the activation of humoral adaptive immune response in OA. When cartilage cell surface proteins were used as substrate in an ELISA and sera from OA patients were applied, an elevated antibody titer was detected compared to controls (Mollenhauer et al., 1988). Similarly, autoantibodies were found in OA patients against cartilage derived proteins osteopontin (Sakata et al., 2001) cartilage intermediate layer protein (CILP) (Tsuruha et al., 2001), YKL-39, (Tsuruha et al., 2002) fibulin-4 (Xiang et al., 2004) and collagen (Charrière et al.,1988) Anti-CCP antibodies were detected in 7 out of 136 OA patients (Du et al., 2005) while another group also detected them in OA patients but at significantly lower levels compared to RA patients (Caspi et al., 2006) Antibodies against native G1 domain of aggrecan core protein were found in synovial fluid of OA patients (Karopoulos, Rowley, Ilic & Handley, 1996) Using proteomic approach, Xiang et al identified triosephosphate isomerase (TPI) as an important antigen with autoantibodies present specifically in OA but not in RA (Xiang et al., 2004). Other studies have reported autoantibodies in animal models of OA including horses (Niebauer, Wolf, Yarmush & Richardson 1988) and dogs (de Rooster, Cox & van Bree 2000). The role of the autoantibodies against cartilage components in development of OA has been further highlighted by studies showing their deposition (Jasin, 1985) and cytotoxic effects on cartilage (Takagi & Jasin, 1992) which may be one of the mechanisms playing important role in cartilage degeneration in OA.

Osteomyelitis

Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), is a major global health threat, resulting in over 2 million deaths each year. M. tuberculosis is a remarkably successful pathogen due to its ability to modulate and to evade immune responses ( Flynn & Chan 2003) Cell-mediated immunity effectively regulates bacterial containment in granulomatous lesions in the lungs, usually without completely eradicating the bacteria, which persist in a latent state (Kaufmann, 2002). However, reactivation of TB can occur when the host immune system is compromised by various factors, such as HIV infection and the use of tumor necrosis factor (TNF) blockade therapy for a variety of inflammatory diseases (Sperber & Gornish 1992). The ability of M. tuberculosis to manipulate and evade immune responses presents a major challenge for the development of efficacious therapies and anti-TB vaccines (Cooper, 2009). Bacillus Calmette-Guèrin (BCG), an attenuated strain of Mycobacterium bovis, is the only anti-TB vaccine that is currently administered (Kaufmann, 2010). Although BCG protects adequately against pediatric TB meningitis, its protective effect for adult pulmonary TB, a most common form of the disease, is inconsistent at best (Kaufmann, 2001). A more thorough understanding of protective immunity and the ways by which M. tuberculosis manipulates these responses will aid in the control of TB (Kaufmann, 2010).

It has been well established that cell-mediated immunity plays critical roles in defense against M. tuberculosis (Cooper, 2009); by contrast, B cells and antibodies generally have been considered unimportant in providing protection (Casadevall & Pirofski 2011). This notion has derived, at least in part, from inconsistent efficacy of anti-TB passive immune therapies tested in the late nineteenth century, which possibly could be due to the varied treatment protocols and reagents employed (Glatman-Freedman & Casadeval 1988). In the late nineteenth century, the development of the concept of cell-mediated immune response based on Elie Metchnikoff starfish larvae observation as well as antibody-mediated immunity derived from Ehrlich’s side-chain theory (Kaufmann, 2008) set the stage for the subsequent emergence of the view that defense against intracellular and extracellular pathogens are mediated by cell-mediated and humoral immune responses, respectively (Collins, 1978). Guided by this concept of division of immunological labor, the role of humoral immune response in defense against M. tuberculosis, a prominent intracellular pathogen, is generally thought of as insignificant (Casadevall & Pirofski 2011). However, accumulating experimental evidence derived from studying intracellular and extracellular pathogens suggest that the dichotomy of niche-based defense mechanisms is not absolute (Casadevall & Pirofski 2011). A more comprehensive unbiased approach to evaluate the contribution of both the cell-mediated immune response and B cells and humoral immunity to protection against pathogens regardless of their niche could further advance our knowledge of host defense that may eventually influence on the development of efficacious vaccines. The importance of this comprehensive approach is further reinforced by the advancement of our knowledge in immunology and vaccine development that highlights the significance of the interactions between innate and adaptive immunity, as well as those between various immune cells and subsets in the development of effective immune response against microbes (Pulendran & Ahmed 2011). This approach may be particularly important for pathogens, such as M. tuberculosis, for which consistently protective vaccines are still lacking.

Do B Cells and Humoral Immunity Contribute to Defense Against Intracellular Pathogens?

Based on the concept of division of labor by the cell-mediated and the humoral arm of the immune response in controlling pathogens, protection against intracellular microbes is generally thought to be mediated exclusively by cell-mediated immunity (Casadevall, 2003). This has led to the use of highly T cell-centric strategies for the development of vaccines against intracellular pathogens including M. tuberculosis (Seder & Hill 2000). Complete exclusion of a role for B cell and humoral immune response in defense against microbes that gravitate to an intracellular locale is, however, problematic. Indeed, emerging evidence supports a role for B cells and the humoral response in protection and in shaping the immune response to pathogens whose life cycle requires an intracellular environment such as Chlamydia trachomatis, Salmonella enterica, Leishmania major, Francisella tularensis, Plasmodium spp., and Ehrlichia chaffeensis (Culkin, Rhinehart-Jones & Elkins 1997). Interestingly, humoral immunity has been shown to contribute to protection against E. chaffeensis, a bacterium classified as an obligate intracellular pathogen (Li, 2003). This observation has led to the discovery of an extracellular phase in the life cycle of E. chaffeensis (Li, 2003). The Ehrlichia study suggests that even a brief extracellular sojourn may expose an obligate intracellular organism to antibody-mediated defense mechanisms operative in extracellular milieu. Indeed, it is likely that many intracellular pathogens exist in the extracellular space at some point in the infection cycle, making them vulnerable to the actions of antibodies (Casadevall, 2003); and evidence exists that this notion is applicable to M. tuberculosis (Grosset, 2003). In the control of viruses, the quintessential class of obligatory intracellular pathogen, antibodies have been shown to play an important role in disease control and virion clearance from infected tissues involving mechanisms that are independent of neutralization resulting from direct interaction of immunoglobulins with viral particles. For examples, binding of antibodies to membrane-associated viral antigens of infected cells have been shown to attenuate transcription and replication of the virus (Fujinami & Oldstone 1979). Additionally, immunoglobulins (e.g., certain anti-DNA (Yanase et al., 1994) and anti-viral IgA antibodies ((Mazanec, Coudret & Fletcher 1995) have been shown to be able to enter cells.

B cells can shape the immune response by modulating T cells via a number of mechanisms based on antigen presentation and the production of antibodies and cytokines (Maglione & Chan 2009). B cells and humoral immunity contribute to the development of T cell memory (Elkins. Bosio & Rhinehart-Jones 1999) and vaccine-induced protection against a secondary challenge (Maglione & Chan 2009) (two components critical to development of effective vaccines) with intracellular bacteria such as Chlamydia (Igietseme, Eko, He & Black 2004) and Fransicella (Rawool, 2008). Thus, infections with intracellular microbes where cell-mediated immunity is central to protection may also require humoral immunity for optimal clearance and vaccine efficacy. This dual requirement for both the cell-mediated and humoral immunity also applies to the development of optimal immune response to extracellular pathogens. For example, it has been reported that cellular immunity contributes to defense against Streptococcus pneumoniae (Weber, Tian & Pirofski 2011) and T cells shapes the host response to Escherichia coli infection (van Schaik & Abbas 2007); furthermore, the antigen-presenting attribute of B cells plays an important role in host defense against extracellular helminthes (Wojciechowski et al., 2009). Together, these observations have provided evidence that, regardless of the preferred niche of the pathogens in the host, the immune response against invading microbes is shaped by the collaborative effects of cellular immunity and the B cell and humoral immunity. In the context of intracellular microbes such as M. tuberculosis, and particularly those for which efficacious vaccines are lacking, understanding how B cells regulate the immune response to the pathogens, and how these immune cells and antibody-dependent immunity interact with the cellular arm of the host response to mediate protective effectors will likely aid in the development of strategies to enhance anti-microbial immunity and vaccine efficacy.

B Cells Can Influence T cell Responses

The interaction of T cells and B cells in response to an antigenic challenge has been well studied. These studies, however, have mostly focused on the characterization the mechanisms by which T cells provide help to B cells (Vinuesa, Tangye, Moser & Mackay 2005). It has been firmly established that T cells play an important role in modulating the response of B cells to antigens, affecting biological functions as diverse as antibody production and cytokine secretion (Vinuesa, Tangye, Moser & Mackay 2005). In contrast, the role of B cells in regulating T cell responses is less well-defined; and this is particularly the case for CD8+ T cells. This line of investigation has yielded conflicting results (Gray, Gray & Barr 2007), which are likely due, at least partially, to the complexity of the experimental systems employed, which use varied antigens and mouse models. For example, a much used model involves mice rendered deficient in B cells genetically, although non-B cell immunological aberrancy is known to exist in these strains (Lund & Randall 2010). The use of the B cell-depleting agent Rituximab in the treatment of a variety of human diseases have provided an excellent opportunity to study the role of B cells in shaping immune responses (Czuczman & Gregory 2010). These studies have provided compelling evidence that B cells regulate CD4+ T cell responses (Lund & Randall 2010). Although less well studied, accumulating evidence suggests a role for B cells in regulating CD8+ T cell responses including through antigen presentation (Shen et al., 2003), even though, as in the case for CD4+ T cells, the results derived from these studies are not entirely congruent (Asano & Ahmed 1996).

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