Development of bronchus associated lymphoid tissue (BALT) in human lung disease: a normal host defence mechanism awaiting therapeutic exploitation?

The lung is continuously subjected to a barrage of agents carried in the air we breathe, many of which are antigenic and hence capable of eliciting potentially tissue damaging immunoinflammatory reaction in the lung and airways. To deal with these challenges we have developed a series of overlapping defence mechanisms with increasing levels of complexity. Mucociliary clearance and alveolar macrophage ingestion represent front line "exclusion" mechanisms in the respiratory tract, and these are bolstered by immune surveillance involving lymphocytes and local accessory cells responsible for trapping inhaled antigens for presentation to the immune system. This "adaptive" immunity confers a higher level of specificity onto local defences, the clearest example being the role of secretory IgA antibodies in increasing the efficiency of antigen exclusion at the epithelial surface. In addition, the adaptive immunity makes available a broader range of effector mechanisms (such as cell mediated cytotoxicity) which are specialised for dealing with incoming antigens that successfully broach front line exclusion barriers.

However, the same immune defence mechanisms have the potential for damaging host tissues and the increased appearance of activated lymphocytes in some respiratory diseases, such as asthma and sarcoidosis, have prompted suggestions that they may play a direct part in the pathogenesis of these diseases.

The distribution of lymphocytes in the normal and diseased lung has been the subject of intense investigation over many years. About 20 years ago Bienenstock and colleagues suggested that lymphoid aggregates in the bronchial wall were a potentially important focus for immune surveillance in the respiratory tract.[1 2] These structures resembled the Peyer's patches in the gut, commonly referred to as gut associated lymphoid tissue (GALT), and were accordingly named "bronchus associated lymphoid tissue" (BALT).[1 2] These initial studies and a subsequent series of experiments on the function of BALT derived lymphocytes (reviewed by Bienenstock[3]) led to the development of the concept of the common mucosal immune system. This scheme envisaged the selective migration of B lymphoblasts (particularly those involved in IgA production) between mucosal associated lymphoid tissues (MALT) throughout the body, effectively focusing the immune response to antigens encountered at these sites into the precise areas where they are required.

The progeny of B lymphocytes which are "sensitised" to microbial antigens encountered in the gut and subsequently clonally expand will therefore preferentially seed back to mucosal sites, not just in the gastrointestinal tract, but also in the mammary gland, salivary gland, the cervix, and also the lung, imparting protection to mucosal surfaces throughout the body in the form of secretory antibodies. This concept has since been expanded to include subpopulations of mucosal "homing" T lymphocytes which are originally sensitised at mucosal sites.

The molecular mechanisms by which this complex cellular system operates are steadily being unravelled and include the expression of mucosal tissue specific "homing" molecules on the surface of T and B cells which mature in MALT, together with expression of complementary tissue specific receptors on MALT high endothelial venules which function to selectively bind recirculating lymphoblasts displaying the appropriate "homing" ligands.

The overall MALT concept continues to provide a valuable theoretical framework for analysis of the cellular and molecular basis for host defence at all mucosal surfaces, but it nevertheless remains a model and, as such, requires updating as relevant new information becomes available. In particular, it is now clear that significant structural differences exist between MALT tissues in organs such as the gastrointestinal tract and lung, both within and between species.[4 5] Secondly, it seems increasingly possible that MALT may perform a different range of functions in different organs. For example, while it is evident that GALT plays an important part in the maturation of the IgA B cell system, a corresponding role has not been demonstrated for the equivalent BALT tissues of the respiratory tract. Additionally, while GALT in rodents is involved in the initiation of primary immunity and tolerance to a range of both soluble and particulate antigens,[6–8] challenge studies involving administration of antigen to the upper respiratory tract suggest that the appearance of antigen specific lymphocytes in BALT is the result of recruitment from other lymphoid organs rather than local activation.[9 10]

Thus, while active surveillance for antigens in the steady state appears to be a prime function of MALT in the gut, the participation of respiratory tract BALT in the immune response to antigen instilled into the airways is apparently focused on later stages of the humoral response. Surveillance for inhaled antigens in the steady state appears vested in the dendritic cell populations which occur as highly developed networks throughout the airway epithelium and the alveolar septa,[11] the function of which is to "shunt" antigen from the airway surface to the regional lymph nodes for presentation to the T cell system.[12–14]

The study of BALT in man has lagged behind that in experimental animals, and indeed the very presence of BALT in the normal human lung has been questioned.[15] In this issue of *Thorax* (pp 1130–1134) Richmond and colleagues report a thorough investigation on the distribution of human BALT, examining a total of 256 sites in 31 lungs.[16] BALT was seen in only two of 14 non-smokers. This suggests that the development of human BALT is actively "driven" by inflammatory stimuli, a view consistent with findings from most animal species.[4 5] It may be that the essential differences between species do not lie in the structure and function of BALT, but rather in the relative stimulation thresholds required to initiate its development.

What then is the function of human BALT? The striking correlation reported in this issue of *Thorax* by Richmond *et al* between the occurrence of BALT and cigarette smoking, a habit associated with biphasic changes in immune function in the respiratory tract,[17] is unlikely to be trivial and may reflect an attempt on the part of the immune system to bolster local defences in

the face of stress. Similarly, the occurrence of large areas of BALT in children and young adults with chronic or recurrent pneumonia[18] may point to a similar compensatory response. It is also noteworthy that, in the only comprehensive paediatric study reported in this area, "lymphoreticular aggregates within the bronchial mucosa and just deep to the epithelium" were detected in about half of the tissue samples from 316 lungs taken from children under the age of 10 months, but were absent from more than 90% of stillborn samples.[19] Whether this points to a special (and perhaps transient) role for BALT like structures in local humoral immune defence during the "high risk" period of infancy, or perhaps in "education" of the immature immune system to newly encountered inhaled environmental antigens, remains to be determined. This issue will not be resolved until comparative data are available from tissues of normal neonates.

Despite these uncertainties the key consistencies in the literature on BALT bear re-emphasising: (1) in the majority of species BALT develops entirely postnatally; (2) its rate of development reflects the degree of local antigenic (particularly microbial) stimulation in the airways; (3) in the adult BALT can expand significantly in response to local inflammation or immunostimulation. Thus, under conditions of stress, particularly chronic inflammation associated with infection, the generation of signals (yet to be defined) within the bronchial mucosa stimulate the seeding or expansion of local BALT elements, or both, ultimately providing the means to harness more effectively the cellular resources of the body's common mucosal immune system.

Could such a system be exploited therapeutically in chronic lung disease? A possible pointer to the future may be found in recent studies of chronic bronchitis, a disease in which BALT development (presumably in response to local microbial stimulation) appears to be a common feature.[20] The incidence of acute episodes of bronchitis in chronic sufferers has been shown to be reduced by oral immunisation with *Haemophilus influenzae*.[21 22] The theoretical basis for this vaccine strategy involves activation of the common mucosal immune system via initial antigenic stimulation of GALT, and the presence of developed BALT structures in the lung would provide the portal for recruitment of antigen primed "mucosal homing" T and B lymphocytes into the inflamed bronchial mucosa.

The ability to effectively control such a process—that is, by optimising the antigenic priming signals delivered to the common mucosal immune system via GALT while, at the same time, enhancing the traffic of resulting populations of lymphocytes to the bronchial mucosa via stimulation of BALT function—could provide novel opportunities for therapeutic intervention in chronic infectious diseases of the lung. Such possibilities justify further detailed research on the underlying mechanisms responsible for the generation of human BALT within the airway mucosa and its occurrence in chronic disease states.

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