Bcl-2 Expression in Anaplastic Large Cell Lymphoma

To the Editor-in-Chief:

Anaplastic large cell lymphoma (ALCL) is a distinct clinicopathological entity that has been individualized in the Revised European American Lymphoma (REAL) classification. This entity is defined as a T-cell or null-cell lymphoma expressing CD30 (Ki-1 antigen). Three different subtypes of ALCL have recently been identified: primary systemic anaplastic lymphoma kinase-positive (ALK+) ALCL, ALK− ALCL, and primary cutaneous ALCL. ALK expression is the consequence of chromosomal translocations involving the ALK gene at 2p23 and the protein is detectable by immunohistochemistry. The most frequent variant of the translocations implicating ALK is the t(2;5) translocation, which juxtaposes the ALK gene at 2p23 with the nucleophosmin (NPM) gene at 5q35. Recently, it has been shown that the NPM/ALK chimeric protein activated the phosphatidylinositol 3-kinase/Akt (PI-3K/Akt) anti-apoptotic pathway. Therefore, in case of NPM/ALK expression, one would expect the Bcl-2 protein to be overexpressed in association with other anti-apoptotic factors. In a previous report published in the Journal, we found in a short series of cases of NPM/ALK+ ALCL that the Bcl-2 protein was not expressed. The recent demonstration by Bai et al prompted us to extend our previous study confirming the preliminary data indicating the lack of Bcl-2 expression in ALK+ ALCL. These data strengthen the recent subdivision of ALCL into three distinct subgroups. Bcl-2 and ALK expression are mutually exclusive, and the lack of Bcl-2 expression may have diagnostic value, in some instances, in differentiating anaplastic cell lymphoma from Hodgkin's disease. As ALCL are sensitive to chemotherapy, our findings are also consistent with the concept that Bcl-2 expression is associated with chemoresistance.

Claire Villalva
Fethi Bougrine
Georges Delsol
Pierre Brousset
Centre Hospitalier Universitaire de Purpan
Toulouse, France

References

Formation of Granulomas in the Lungs of Severe Combined Immunodeficient Mice after Infection with Bacillus Calmette-Guerin

To the Editor-in-Chief:

It has been reported that T cells are involved in the process of granuloma formation and may be necessary to induce the formation of granulomas. However, in an issue of The American Journal of Pathology, North and Izzo showed the formation of granulomas in severe combined immunodeficient (SCID) mice, which are not able to generate efficient T and B cells, after infection with Bacillus Calmette-Guerin (BCG). These granulomas were found in spleen and liver. Moreover, the authors described a deficiency of these SCID mice to form granulomas in the lungs after inoculation with BCG. In an attempt to establish a granuloma model to analyze the process of granuloma formation, we intravenously inoculated SCID mice with BCG (strain Connaught) for means of control and examined the animals histomorphologically after 30 days. Three 10- to 12-week-old female C.B.17scid/scid mice were housed in filter-top cages in an incubator with a constant horizontal flow of filtered air and supplied with food and water ad libitum. The mice were inoculated intravenously with BCG (10⁸ CFU per animal; courtesy of E. Richter, National Reference Center for Mycobacteria, Borstel, Germany). The mice were sacrificed 28 to 30 days after inoculation, and the organs were kept in buffered formaldehyde solution (4% vol/vol). The tissue was paraffin-embedded, sliced, and hematoxylin-and-eosin-stained. Visualization of BCG in the tissues was performed by Ziehl-Neelsen staining.

With regard to the formation of granulomas in spleen and liver, we reproduced the results obtained in the study of North and Izzo. Furthermore, in accordance with previous results, we found isolated alveolar macrophages infected with BCG in the lungs of these mice. However, we also observed the generation of well formed granulomas in the lungs of these mice. These granulomas were not just aggregations of alveolar macrophages, but were morphologically comparable to the granulomas found in spleen and liver (Figure 1a). Inside the pulmonary granulomas, acid fast bacilli were detected by Ziehl-Neelsen staining (Figure 1b) and identified as mycobacteria from the Mycobacterium tuberculosis complex by means of polymerase chain reaction targeting mycobacterial 16S rDNA. This demonstrates that, upon infection with BCG, SCID mice can produce pulmonary granulomas.

Besides tumor necrosis factor-α release, the delivery of interferon-γ (IFN-γ) is an important prerequisite for granuloma formation and the eradication of the bacteria. In immunocompetent mice the most important source of IFN-γ is Th1 cells. In a recent publication, it was demonstrated that the development of T-cell-independent granuloma is reliant on the induction of IFN-γ release by natural killer (NK) cells. The induction of NK-cell IFN-γ release is dependent on the release of interleukin-12 and -10 by macrophages. In a model of Pneumocystis carinii infection, it was demonstrated that although alveolar macrophages are able to stimulate NK cells to release IFN-γ, they are inferior compared to splenic macrophages.

North and Izzo used the BCG strain Pasteur, so it can be speculated that there might be strain-specific differences in the induction of IFN-γ-inducing factors by macrophages in the lung, liver, and spleen, since the number of bacteria injected and the time spans of infection have been comparable.

Our experiments demonstrate that the presence of T cells is not mandatory for the generation of pulmonary granulomas in SCID mice. We conclude that SCID mice infected with BCG are capable of generating granulomas in the lungs.