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Apoptosis in chronic inflammation, with specific reference to airway disease

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Abstract

Mechanisms governing the normal resolution processes of inflammation in the lung are poorly understood, yet their elucidation may lead to a greater understanding of the pathogenesis of several pulmonary inflammatory disorders. The elimination of activated lymphocytes by apoptosis is one prerequisite for resolution, and knowledge concerning the role of apoptosis in chronic inflammation is still far from complete. A complicating fact is that apoptotic pathways seem also to be involved in cellular proliferation.

The aim of this project was to study the relationship between apoptosis and inflammation with special regards to mitochondrial apoptosis and chronic inflammation in the airways .

In the first two studies we showed that tributyltin (TBT) effectively induces mitochondrial apoptosis in resting human peripheral blood lymphocytes (PBL), by the release of cytochrome-c and caspase-3 activation. Interestingly, when peripheral blood T lymphocytes were anti-CD3 activated, we observed a time-dependent induction of caspase-3 activity in the absence of an apoptotic morphology. Moreover, at the observation point when the activity of caspase-3 had reached its maximum, an insensitivity against TBT induced apoptosis started to develop. Finally, co-culture with dexamethasone (DEX) inhibited caspase-3 activity as well as proliferation, suggesting a role for caspase-3 in the activation differentiation process in these cells.

Our goal in the third work was to investigate whether the increased airway inflammation, seen in individuals with asthma, exposed to airborne allergen, was associated with a altered apoptotic phenotype of lymphocytes. Here we found a reduced sensitivity to apoptosis in broncho-alveolar lavage (BAL) fluid lymphocytes, following airway allergen exposure, which was accompanied by an increased amount of cells expressing the anti-apoptotic protein Bcl-2.

In a previous study, an increased apoptosis resistance was observed in lung T lymphocytes from sarcoidosis patients. Based on this, in the last study we further studied the mechanisms behind the observed apoptosis-resistance by investigating whether the sarcoidosis associated cytokines IL-12/IL-23 and IL-18 could influence the apoptotic phenotype of these lymphocytes. The results suggest a pro-survival role of IL-12 and/or 23 whereas IL-18 appear to have a pro-apoptotic function in the lungs of sarcoidosis patients. We also found a difference in apoptosis-inducing capacity between the anti-TNF- α drugs, infliximab and etanercept, with infliximab being the more effective in killing BAL fluid lymphocytes. This finding may be related to the differences in drug efficacy between these two compounds in the treatment of sarcoidosis.

In the present studies, we have shown that the activation state of the cell influences the sensitivity to apoptosis and that caspase-3 might participate in the early activation/proliferation machinery of T-cells. Moreover, allergen inhalation renders BAL fluid lymphocytes from asthmatic individuals more resistant to apoptosis, suggesting an association between the degree of inflammation and apoptosis. We have also identified cytokines affecting the apoptosis susceptibility of BAL fluid lymphocytes from sarcoidosis patients. Together these results might help to shed more light on the role of apoptosis in chronic inflammation.

Keywords: Apoptosis, asthma, chronic inflammation, lung, sarcoidosis, tributyltin (TBT)

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