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TBT Alters Bone Marrow Microenvironment and Suppresses Important Immune Cells

Researchers at the Boston University Superfund Research Program (BU SRP) Center reported that tributyltin (TBT) may promote aging-related problems in immune health. The team, led by Jennifer Schlezinger, Ph.D., found that TBT impacts bone marrow B cells directly by triggering cell death and indirectly by changing the microenvironment of bone marrow vital for supporting immune health.

TBT, best known for its use in reducing the growth of biological organisms on the undersides of boats and ships, started to be phased out in the late 1980s because of its persistence and toxicity. However, it still is used in industry today to control slime on masonry, to preserve wood, and to disinfect circulating industrial cooling water. TBT also is formed during production of polyvinyl chloride, or PVC, a widely manufactured plastic. Primarily introduced through diet, organotin compounds like TBT have been detected in human blood and in the liver. Previous studies have linked exposure to TBT to adverse reproductive, neurological, and immune outcomes.

TBT directly affects B cells

B cells are a type of white blood cell that develops and matures in the bone marrow and plays a critical role in the body's immune response to pathogens that may cause disease.

In experiments with B cells cultured from mice, the team demonstrated that even at low, environmentally realistic concentrations, TBT triggers cell death, or apoptosis, in three different models of developing B cells. Previous work had shown that TBT could trigger apoptosis at high doses, but the BU SRP Center team found that the underlying mechanism was unique at low doses.

TBT alters bone marrow microenvironment

The creation of B cells in the body is supported by multipotent mesenchymal stromal cells (MSCs) in the bone marrow. Bone marrow MSCs can differentiate into bone cells, or osteoblasts, and fat cells, or adipocytes. The balance of these cell types in the bone marrow microenvironment is important for B cell formation and development because osteoblast cells support B cell development and adipocytes suppress it.

Using cultured MSCs and B cells, the BU SRP team created a model of the bone marrow microenvironment. This model allowed them to study the influence of TBT exposure on B cell development as well as how changes to the microenvironment might alter these processes indirectly.

Their results showed that TBT suppressed the development of B cells in the model system. They also found that TBT exposure changed the way that B cells mature and differentiate. When MSCs and B cells were co-treated with TBT, the team observed a dose-response reduction in mature B cells and an increase in earlier B cells. They also found that when MSCs were pre-treated with TBT, untreated B cells did not develop and mature as expected. The authors suggest that in addition to direct effects on B cells, TBT alters the microenvironment by promoting MSC differentiation into adipocytes and, therefore, suppressing B cell development.

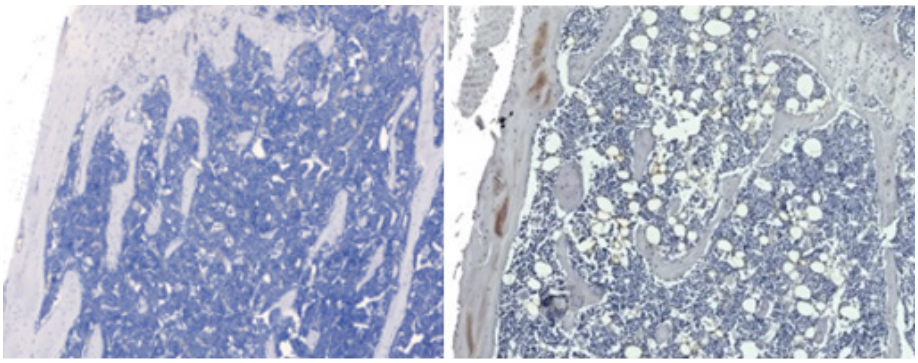
TBT reduces aging sensitive B cell population in mice

Using cells and a model bone marrow microenvironment cell system, the authors revealed how TBT negatively affects B cells. Their work also shows, for the first time, that low levels of TBT exposure over an extended period suppress B cells in mice.

The authors report that TBT-treated mice showed significantly reduced B cell numbers in the spleen. They also found that TBT-treated mice had more adipocytes in bone marrow than controls and fewer early stage bone marrow B cells.

Interestingly, specific B cells known to decrease with age, also referred to as "aging sensitive" B cells, were significantly reduced in the mice, leading the authors to propose that TBT exposure may intensify age-related problems of the immune system in people.

Increased adipocytes in bone marrow occurs with aging and is associated with decreased immune response. This may be contributing to the increased risk of more frequent and severe infectious diseases in the elderly. Although more studies are needed, results from the BU SRP Center team suggest that exposure to TBT may worsen age-related changes and risks for disease both by directly causing B cell apoptosis and by altering the bone marrow microenvironment toward adipocytes that suppress B cell development and maturation.



The image on the right shows an increased number of adipocytes in the bone marrow of TBT-treated mice, compared to the bone marrow of non-TBT-treated mice on the left. (Photo courtesy of Jennifer Schlezinger)

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To learn more about this research, please refer to the following source:

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