

STAT3: The double edged molecular sword in Chronic Lymphocytic Leukemia cells

The common denominator of different types of cancers is an ever expanding clone that originates from a single cell. In acute leukemia the clonal expansion may be very rapid and the clone double its size sometimes within hours. In other types of cancers the clone may grow very slowly and sometimes the doubling time takes years.

Chronic Lymphocytic Leukemia (CLL) is the most common leukemia in the Western world. CLL is characterized by a slow increase in blood lymphocytes over time. The increase in lymphocyte counts is slower than what is expected by the rate lymphocytes are born, suggesting that a fraction of these lymphocytes die and disappear from the blood.

In this study we investigated what regulates the growth rate of CLL lymphocytes over-time. Specifically, we attempted to define whether a "lymphostat" that senses the clonal size and prevents the rapid expansion of the CLL clone actually exists.

STAT3 is a protein found in mammalian cells, usually in non-active form that normally requires additional modification to be activated. We have previously reported that in CLL cells STAT3 is *a/ways* active. Scientists found that once STAT3 is active, it shuttles to the nucleus, binds DNA and activates a genetic program which prevents cell death (apoptosis) and promotes proliferation.

We confirmed that in CLL, STAT3 activates this genetic program. However, we found that once levels of STAT3 reach a certain threshold it activates a suicidal program and the switch in the function of STAT3 determines the cell fate. Once the suicidal program is activated CLL cells undergo rapid spontaneous apoptosis.

How does this switch happen?

It occurs because STAT3 binds with high affinity to genes that promote survival and with low affinity to the caspase 3 gene, a suicidal gene that activates apoptosis. Because the affinity of STAT3 to Caspase3 is low, activation of Caspase 3 occurs only once STAT3 levels are sufficiently high.

Unlike their normal counterpart, the resting B-cells, CLL cells proliferate. However clonal expansion is regulated and the clonal growth rate is usually slow. STAT3, the same molecule that provides the CLL cells with survival advantage also activates pro-suicidal program once cellular levels are sufficiently high.

Thus, STAT3 could be viewed as an on/off switch controlling malignant cell proliferation in CLL. The switch is turned on at lower levels of STAT3, however once levels reach a certain threshold, STAT3 acts to reduced cell proliferation.

Currently we are studying how CLL cells sense the clonal size and how this information is used to tune the levels of cellular STAT3 ultimately leading to apoptosis.

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