Unraveling the molecular events leading to the genesis of large granular lymphocytic leukemia reveals a new treatment strategy

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The link between chronic inflammation and the development of cancer has long been understood, and the mechanisms that connect these two events are areas of intense scientific scrutiny.[1] One contributing factor, the excessive production of pro-inflammatory cytokines, is a known piece of the puzzle. However, precisely how such cytokine signals fit into the bigger picture of malignant transformation has been unclear. Large granular lymphocytic (LGL) leukemia is a rare disease thought to arise from transformed NK cells or NK-T cells[2] and is one example of where chronic exposure to a pro-inflammatory cytokine, IL-15, has been clearly implicated in cancer genesis. LGL leukemia patients have increased levels of serum IL-15, and a mouse model engineered to aberrantly over-express IL-15 develops a clonal leukemia resembling human LGL after several months of life.[3] While IL-15 mediated signals are known to be critical for normal NK cell physiology and promote proliferation and survival, the question of why and how long-term exposure to IL-15 results in NK or NK-T cell transformation has remained unanswered.

A recent report by Mishra *et al*. from the Caligiuri laboratory identified a complex interaction of two pathways downstream of prolonged IL-15 receptor signaling that co-operate to transform both human LGL *in vitro* and mouse NK cells in the IL-15 transgenic model.[4] Through a series of complementary experiments, the authors identified that NF-κBp65 activated by IL-15 receptor signals results in increased Myc expression. Via Myc overexpression, two independent pathways are affected: microRNA (miR)-29b and the aurora kinases. In the first, Myc overexpression results in miR-29b down-regulation which in turn leads to enhanced expression of its target Dnmt3b. Increased Dnmt3b is responsible for hypermethylation of the LGL genome,[5] resulting in gene silencing, and contributes to chromosomal instability. Notably, the transformation of LGL *in vitro* was decreased by forced overexpression of miR-29b, and enhanced by inhibitors of miR-29b. In the second pathway, Myc overexpression results in increased expression of the aurora kinases A and B that leads to chromosomal instability likely due to their kinase activity at the centrosome. After clarifying these interacting pathways, the authors sought to target the aberrant upregulation of Myc and NF-κB using the proteasome inhibitor bortezomib. While conventional proteasome inhibitor preparations proved too toxic, a novel liposomal formulation of bortezomib was not, and treatment of mice with established LGL leukemia cleared leukemia cells and greatly improved survival. Since STAT3 is also activated by the engaged IL-15 receptor, and patients with LGL leukemia with activating STAT3 mutations have been reported,[6] it remains possible that the story is more complex, with STAT3 also playing a yet to be defined role, perhaps in cases without excessive IL-15 driving constitutive activation.

These findings are important because they open up a way to explore novel targeted therapies for a disease with a poor overall prognosis and limited standard treatment options. The most direct clinical translation of these findings will be to investigate treatment with proteasome inhibitors in patients with LGL leukemia, especially novel formulations that include liposomal packaging. However, aurora kinase inhibitors, agents that target NF-κB signals, miR-29b mimics, and STAT3 inhibitors may also be promising therapeutic options for this rare but often fatal disease.

References

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