Neutrophils are early wound healing and inflammation regulators that, due to functional plasticity, can adopt either pro- or antitumor functions. Until recently, beclin-1 was a protein known mainly for its role as a critical regulator of autophagy. In this issue of the JCI, Tan et al. describe the effects of the beclin-1 conditional myeloid cell–specific deletion in mice, in which immunostimulation resulted in hypersensitive neutrophils. The chronic proinflammatory effect of these neutrophils triggered spontaneous B cell malignancies to develop. Such tumorigenic effects were mediated primarily by IL-21 and CD40 signaling, leading to the upregulation of tolerogenic molecules, such as IL-10 and PD-L1. The authors went on to examine samples derived from patient lymphoid malignancies and showed that beclin-1 expression in neutrophils positively correlated with pre–B cell leukemia/lymphoma. Overall, the study provides an elegant model for neutrophil-driven carcinogenesis and identifies potential targets for immunotherapy of B cell malignancies.
Beclin-1 as a neutrophil-specific immune checkpoint

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Neutrophils are early wound healing and inflammation regulators that, due to functional plasticity, can adopt either pro- or antitumor functions. Until recently, beclin-1 was a protein known mainly for its role as a critical regulator of autophagy. In this issue of the JCI, Tan et al. describe the effects of the beclin-1 conditional myeloid cell-specific deletion in mice, in which immunostimulation resulted in hypersensitive neutrophils. The chronic proinflammatory effect of these neutrophils triggered spontaneous B cell malignancies to develop. Such tumorigenic effects were mediated primarily by IL-21 and CD40 signaling, leading to the upregulation of tolerogenic molecules, such as IL-10 and PD-L1. The authors went on to examine samples derived from patient lymphoid malignancies and showed that beclin-1 expression in neutrophils positively correlated with pre-B cell leukemia/lymphoma. Overall, the study provides an elegant model for neutrophil-driven carcinogenesis and identifies potential targets for immunotherapy of B cell malignancies.

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identified a population of tumor-promoting neutrophils with so-called B cell helper phenotype assisting in the transition from autoimmune manifestations to chronic lymphocytic leukemia or lymphoma (13, 14).

Tan et al. next investigated the molecular mechanisms driving B cell lymphomagenesis in \textit{Becn1}\textsuperscript{ΔM} mice. The interaction of B cells with \textit{Becn1}-deficient neutrophils resulted in increased activity of STATs (STAT1, STAT3, and STAT5) as well as ERK and JNK kinases downstream from IL-21 and/or CD40 receptors. The B cells from \textit{Becn1}\textsuperscript{ΔM} mice upregulated expression of several STAT1/3 targets, such as \textit{Cd274} (PD-L1), \textit{Cxcl9}, \textit{Irf1}, \textit{Socs1} or \textit{Socs3}, and B cell activation markers (\textit{Il10}, \textit{Saa3}) (15).

Also upregulated was a gene encoding a key cytosolic DNA sensor (\textit{Mb21d1}), better known as cyclic GMP-AMP synthase (cGAS), which shows dichotomous pro- and antitumor effects (16). Both Jak/STAT3 and ERK signaling contributed to PD-L1 expression through direct promoter activation and potential transcript stabilization (9).

To validate the therapeutic implications of these findings, Tan et al. used antibodies to neutralize PD-L1 or IL-21R in lymphoma-bearing \textit{Becn1}\textsuperscript{ΔM} mice. The elimination of IL-21 as well as PD-1 immune checkpoint blockade triggered tumor infiltration by cytotoxic CD8\textsuperscript{+} T cells, thus supporting the role of both molecules in the neutrophil and B cell crosstalk (9).

Finally, Tan et al. provided enticing evidence for beclin-1 as an immune checkpoint regulator in human B cell malignancies, such as pre-B acute lymphoblastic leukemia/lymphoma (ALL). The neutrophils in tested pre-B cell ALL patients showed lower on average expression of beclin-1.
with increased neutrophil activation as measured by formation of neutrophil extracellular traps (NETs). Correspondingly, the gene expression analysis using publicly available databases confirmed the correlation between the expression of neutrophil marker (LY6G) and upregulation of both IL-21 and PD-L1 in a large group of recurrent pre-B cell ALL patients (9).

Remaining questions and therapeutic implications

The report by Tan et al. sheds light on the new role of beclin-1 as a potential neutrophil-specific immune-checkpoint molecule operating in inflammation and cancer (9). At the same time, the study raises a number of questions warranting further investigation. Is beclin-1 dynamically regulated in neutrophils by inflammatory mediators, as suggested by studies demonstrating the role of NF-kB and various miRNAs in Becn1 expression (17)? Would STAT3 counteract these effects in TANs and repress Becn1, as shown before in cancer cells (18)? Which innate immune receptors in neutrophils (TLRs, cGAS/STING, RIG-I) are controlled by beclin-1 to prevent inflammatory and tumorigenic effects? More in-depth studies should evaluate further the contribution of neutrophils and beclin-1-controlled IL-21 production in the pathogenesis of human B-ALL. Due to direct cytotoxic effects on malignant B cells, IL-21 is being broadly explored for therapy of B cell lymphomas, albeit with limited success as a monotherapy (19). The current study indicates that IL-21 can have an opposite, tumor-promoting effect in mice, thus underscoring the importance of testing immune mediators in the broader context of the immune cell network. The neutralization of IL-21 alone or together with PD-L1 could provide new immunotherapeutic approaches to recurrent adult pre-B cell ALL, since the emerging anti-

body and CAR T cell immunotherapies are often hampered by the emergence of CD19- or CD20-negative cancer clones (20). Interestingly, the correlation of high neutrophil infiltration and poor patient outcomes have been previously reported in brain, breast, or lung cancers (21), which are also known for reduced beclin-1 levels (17). Thus, it is tempting to suggest that the role of beclin-1 as a neutrophil-specific checkpoint and tumor suppressor could reach beyond B cell malignancies.

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