MYC mutations in Burkitt lymphoma uncouple MYC from mTOR to bypass germinal center selection bottlenecks

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Abstract

Somatic gene mutations in B cell non-Hodgkin lymphomas (B-NHLs) can be tell-tales of basic principles in germinal center (GC) biology. In Burkitt lymphoma (BL), a clinically aggressive GC-derived B-NHL, recurrent missense mutations target the MYC gene in >50% of cases. These mutations typically cluster at specific hotspots, i.e. Threonine 58 (T58), of immunoglobulin translocated MYC alleles. Mutant MYC proteins have enhanced oncogenic potencies, but the mechanistic basis for these observations and relevance to BL pathogenesis are unclear. In fact, current knowledge on the biology of these mutations comes exclusively from experiments in non-B cells.

To solve these questions, we studied a set of genetically engineered mouse models where a MYC T58A mutation was specifically targeted to germinal center B cells. In vitro and in vivo analyses demonstrated that MYC mutations allow B cells to bypass a critical mTOR-dependent checkpoint monitoring the initiation of cell division upon positive (affinity) selection. Unlike wildtype counterparts, MYC T58A mutant B cells could effectively grow and expand in presence of rapamycin by engaging alternative energy sources and cellular biosynthesis programs independent of mTOR activity. Simple MYC overexpression did not overcome mTOR blockade. The metabolic programs sustained by T58 mutations were also activated in normal germinal center B cells undergoing positive selection, and endowed MYC mutant B cells with a competitive advantage, regardless of antigen affinities. Mechanistically, we found that in B cells receiving positive selection signals (i.e. CD40), mTORC1 became the sole regulator of GSK3 activity. GSK3 phosphorylated MYC at Threonine 58, and MYC mutations specifically exploited this signaling ‘shunt’. We surmise that these findings explain the elusive functional link between MYC and mTOR that fuels GC positive selection. Specific genetic co-option of this circuitry in lymphomas may support the clonal expansion of precancerous B cells outside the constraints of affinity selection.