MYC is a transcription factor and an oncogene that drives the pathogenesis of Burkitt lymphomas (BL) and 30–50% of diffuse large B cell lymphomas (DLBCL) (1-3). MYC protein has critical functions that profoundly impact cell fate (reviewed) (4). These include regulation of transcription, translation, metabolism and cell cycle progression (4). Paradoxically, MYC over-expression induces genomic instability and can initiate apoptosis by increasing expression of the tumor suppressor P53 and the pro-apoptotic protein BIM (5). Inactivating P53 or over-expressing the anti-apoptotic protein BCL2 that neutralizes BIM are two effective mechanisms exploited by lymphoma cells to evade MYC-induced apoptosis, leading to unabated cell proliferation and therapeutic resistance (6,7). Mutations in TP53 and the co-expression of MYC and BCL2 proteins are associated with a poor survival in DLBCL patients treated with chemo-immunotherapy (2,3,8). Therefore understanding the mechanisms that deregulate MYC in aggressive lymphomas is clinically important.

MYC expression in DLBCL is heterogeneous and its mechanism of deregulation differs according to the molecular subtype (3). MYC expression is higher in the activated B cell (ABC) type of DLBCL as a result of transcriptional up-regulation of other oncogenic pathways. MYC expression in the germinal center B (GCB) type is most commonly detected in cases harboring MYC translocations that can involve different gene partners. In over half of the cases, the translocation juxtaposes MYC upstream of one of the immunoglobulin gene (IG) promoters, leading to constitutive transcription of MYC mRNA (9). However, the proximity to the IG increases the likelihood that MYC will become an inadvertent target of somatic hypermutation (SHM) driven by activation induced cytidine deaminase (AID) (10). Over 50% of BLs harbor MYC mutations, clustering in “hot spot” regions that appear to be “gain-of-function” (5,11). For instance, some mutants increase MYC mRNA stability and MYC protein expression (12). They also decrease pro-apoptotic function by preventing the activation of BIM and facilitate lymphoma progression in the absence P53 activation, ultimately leading to more aggressive lymphomas (5). However, the role of MYC mutations in DLBCL is unclear. In the February 2016 issue of Clinical Cancer Research, Xu-Monette et al. have addressed this question (13). They performed Sanger sequencing of the MYC gene in 750 well-characterized de novo DLBCL samples and report an association between the presence of MYC mutations, MYC protein expression and clinical outcome.

Xu-Monette reported that MYC mutations were common in DLBCL, being detected in 33% of samples. While this is comparable to a previous report (10), the rate of coding mutations was higher than what has been reported by exome sequencing (16% versus 5%) (10,14). The lack of germline DNA in the Xu-Monette study may in part explain this discrepancy, resulting in over-calling somatic mutations when the MYC variants could have been germline single nucleotide polymorphisms (SNPs) (13). Unlike BL, MYC mutations in DLBCL were distributed across the entire gene including the 5’ and 3’ untranslated regions (UTR), which include many regulatory elements. The most common mutations affected amino acid residues T58, S62, S67, P79, R83, F138, A141, P164, S175, and A185. The T58 or F138 mutations, previously identified as being “gain of function”, were only present in 0.5% of the
cohort. Thus, the incidence and pattern of MYC mutations in DLBCL is different than in BL.

The authors then demonstrated that MYC mutations, including SNPs (e.g., N11S), could impact MYC protein expression. Within the 16% of coding mutations, the T58 and F138 variants, known to increase mRNA stability, were associated with very high MYC protein expression. The other coding MYC mutations were associated with more variable protein expression. Interestingly, 2% of cases had MYC mutations predicting for a dysfunctional or truncated protein and had no or low MYC protein expression by immunohistochemistry (IHC). Within the non-coding mutations, the 5’UTR had the highest mutation rate in the entire gene (~20%). Mutations in this region have been previously shown to increase MYC protein expression by preventing the premature block in transcription elongation (15). In the Xu-Monette study, there was a trend for higher MYC protein expression in the 5’UTR mutants [38% versus 31% for MYC wild types (WT)], but this was not statistically significant (P=0.24). There was also no change in MYC protein expression with 3’UTR mutations, present in 6% of cases. Using an in vitro model, they then introduced different MYC mutants into the Rat1a cell line to directly assess the effect of mutations on protein expression. These embryonic fibroblast cells have been previously shown to be very sensitive to genomic instability upon transient increases in MYC expression (16). They demonstrated a marked variation in MYC protein expression depending on the mutation, ranging from the highest levels obtained with P57S and the lowest levels obtained with S159R and the SNP N11S. Thus, unlike BL, the MYC mutations detected in DLBCL resulted in more variable levels of MYC protein that were lower than the P57/T58 variants or WT MYC.

In addition to affecting MYC protein expression, Xu-Monette showed that MYC mutations were associated with other important prognostic factors in DLBCL. There was a significant association between the presence of a MYC translocation and MYC mutations, features associated with the GCB subtype. However, the presence of a MYC translocation is not a requirement for the acquisition of MYC mutations because it was only present in a third of the MYC mutant cases. In the ABC cases, MYC mutations were associated with the presence of a BCL6 translocation. Similar to what has been reported in BL, the presence of MYC mutations in DLBCL was associated with a WT P53. This is consistent with prior studies that showed that MYC mutations disable the pro-apoptotic function of MYC allowing cells to proliferate without having to inactivate TP53 (5).

With the exceptions of T58 and F138 variants, MYC mutations in the Xu-Monette study appeared to be associated with a favorable outcome in DLBCL. One of the biggest strengths of this work is the access to a large clinically-annotated cohort of DLBCL biopsies allowing to detect statistically significant differences in survival based on the presence of mutations that occur in only 0.5% to 2% of patients. T58 and F138 variants, which were associated with high MYC expression, were associated with a significantly inferior outcome. The remaining coding MYC mutations correlated with a favorable outcome, though in multivariate analysis, MYC protein expression and not MYC mutations, was significantly associated with overall and progression-free survival. Mutations in the 3’UTR were also associated with a poor outcome, though the mechanisms of this are unclear. The authors did not include factors that are known to be associated with a poor survival in their multivariate analysis, such as the co-expression of MYC and BCL2, cell of origin subtype or the presence of P53 mutations. Taken together, the positive clinical outcome observed in patients with MYC-mutant DLBCL is likely related to its association with known favorable features, such as low MYC protein expression, a GCB phenotype and a WT P53 status.

Given the proliferative advantage of expressing WT MYC, a key question is to understand why 33% of DLBCL harbor mutations in MYC. These occur as a consequence of aberrant SHM based on their pattern and features consistent with AID activity (10). Thus they could be beneficial (drivers) or non-deleterious (passengers). In the Xu-Monette study, the MYC mutant (P57S) was a clear driver mutation because it increased protein expression, increased colony formation in vitro, decreased apoptosis upon serum withdrawal and increased tumor volumes in immunosuppressed mice. The phenotype of non-P57S mutants appeared to be intermediate between clones expressing WT MYC and the empty vector controls that did not express any MYC. They all had impaired proliferative capacity compared to WT MYC as assessed by cell proliferation and tumor growth potential in vivo. However, they were significantly better at resisting apoptosis in the serum deprivation assay compared to WT MYC controls. While the authors conclude that these mutations were “loss of function”, these results imply that DLBCLs expressing mutant MYC protein could have a small advantage over DLBCLs that don’t express MYC, but not over DLBCLs that express WT MYC (Table 1). More importantly, the major selection advantage of expressing mutant MYC versus
WT MYC is to evade apoptosis, a feature consistent with some of these being potential “driver” mutations. Overall, the work by Xu-Monette et al. improves our understanding of the mechanisms that regulate MYC protein expression in DLBCL. Placed in clinical context, it provides a logical explanation as to why some cases harboring a MYC translocation don’t express high levels of MYC protein. It also implies that lack of MYC protein expression predicts for a favorable outcome, even in the context of a MYC translocation that has previously been associated with a poor outcome (17). Taken together, the data support the notion that most MYC mutations in DLBCL don’t have the prominent “driver” proliferative phenotype that is observed in BL. Rather, they have an intermediate phenotype that lacks the growth advantage conferred by WT MYC, but may nonetheless give DLBCL cells a survival advantage by escaping P53-mediated apoptosis. Given that these MYC mutant DLBCL cells retain WT P53 expression, they can still be sensitive to chemotherapy.

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Footnote

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