Insulin Receptor Activation in Deletion 11q Chronic Lymphocytic Leukemia

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The chromosomal abnormalities characteristic of chronic lymphocytic leukemia (CLL) are well studied, but the mechanisms underlying their contribution to pathogenesis are only partially elucidated. Integrated genomic profiling focused on deletion 11q has identified elevated expression of the insulin receptor in a subgroup of CLLs, and associated it with worse outcomes.
In this issue of *Clinical Cancer Research*, Saiya-Cork et al use integrative genomic profiling to identify that the insulin receptor is significantly overexpressed in about 25% of CLLs, many of which carry deletion 11q(1). Deletion 11q has been associated with marked lymphadenopathy and rapid disease progression in CLL, leading to short overall survival(2,3). At diagnosis or initiation of first therapy, deletion 11q is the most common high-risk abnormality in CLL. Although the molecular pathogenesis of CLL with each characteristic chromosome abnormality is being intensively studied, much remains to be understood. Most interest in 11q deletion has focused on loss of the ataxia telangiectasia mutated (ATM) gene, a well-known tumor suppressor gene involved in cell cycle checkpoint signaling and DNA repair. Since 11q deletion generally only affects one of the two chromosomes, the other ATM allele would be expected to be mutated if ATM is a key target for CLL pathogenesis. One report found mutations in the other ATM allele in 36% of 11q CLLs and found that having such a mutation was associated with worse survival than 11q deletion alone(4). Even if reproducible, those findings imply that two-thirds of 11q deletion CLLs do not have mutation of the other ATM allele, suggesting either a gene dosage effect or the involvement of other genes in pathogenesis. Providing support for the involvement of other genes is the observation that families with ataxia telangiectasia due to germline mutation of the ATM gene do not have high rates of CLL.

Saiya-Cork et al use array-based expression profiling to identify the insulin receptor as a significantly differentially expressed gene between CLLs with and without deletion of 11q, and they confirm this finding with quantitative PCR as well as FACS analysis and Western blotting. They find that insulin receptor expression varies continuously across a large cohort of CLLs, with about 60% of CLLs showing some INSR mRNA expression, and deletion 11q CLLs enriched in the highest expressing group. Approximately two-thirds of the deletion 11q CLLs show elevated insulin receptor expression. Importantly, deletion 17p CLLs are not enriched in the highest expressing groups, suggesting that INSR expression is not merely a proxy for aggressive or proliferative disease. Saiya-Cork et al are not able to identify a candidate gene or a common pattern of deletion within 11q that explains insulin receptor overexpression, although they do not comment on microRNAs. The importance of microRNAs in CLL has become increasingly clear(5,6), and certainly deletion of a microRNA in 11q that could target the insulin receptor might lead to its overexpression. However, since only about two-thirds of the deletion 11q patients demonstrate insulin receptor overexpression, and some patients in the other
cytogenetic groups also demonstrate overexpression, the mechanism of insulin receptor expression is undoubtedly complex, likely involving either multiple mechanisms, or one mechanism with multiple regulators.

Saiya-Cork et al further demonstrate that the insulin receptor expressed in these CLLs is functional, in that insulin is able to induce activation of the AKT and RAS/RAF/ERK pathways as well as tyrosine phosphorylation of IRS1. These signals provide survival support to the CLLs, which show a reduction in apoptosis in response to insulin. In fact, insulin leads to AKT phosphorylation at about the same levels as stimulation through the B cell receptor (BCR), which is well known to provide survival signals to CLL cells(7). These findings of activated signaling suggest a possible mechanism of rapid clinical translation, since direct potent inhibition of the insulin receptor itself would presumably be clinically problematic. Multiple drugs already in the clinic inhibit PI3 kinase, which is downstream of the insulin receptor and upstream of AKT, and at least to date these PI3 kinase inhibitors have not been reported to cause substantial clinical problems with hyperglycemia(8).

The PI3 kinase inhibitor most tested in hematologic malignancies and which has very significant activity in CLL is CAL-101(9). CAL-101 is a specific inhibitor of the p110 delta catalytic subunit of PI3 kinase. The p110 delta isoform shows restricted expression in leukocytes and is not thought to be involved in insulin signaling, which is usually mediated by the ubiquitously expressed p110 alpha or beta catalytic subunits. In CLL, inhibition of the p110 delta isoform with CAL101 has been shown to block the signaling effects of stimulation through the B cell receptor (BCR) or CD40(10,11), but insulin signaling has not been investigated. The PI3 kinase isoform involved in insulin signaling in CLL cells will need to be determined experimentally, since the alpha and delta isoforms are both expressed. If insulin signaling in CLL cells is mediated by the p110 alpha subunit as it is in other cell types, then a pan-PI3 kinase or PI3 kinase alpha inhibitor would be required to inhibit insulin signaling, and would be expected to have better clinical activity than CAL101 in the CLL subgroup that overexpresses the insulin receptor, albeit at a possible cost of hyperglycemia not seen with CAL-101. Of course, if insulin signaling in CLL is actually mediated by the delta isoform, then insulin receptor overexpression might be associated with very good response to CAL-101. Whether the variable sensitivity of different CLLs to PI3 kinase inhibitors is related to insulin receptor
expression can easily be tested in vitro. Analysis of insulin receptor expression levels in the CLLs of patients enrolled on clinical trials of these inhibitors is also simple. Depending on the results, these data could lead fairly quickly to rational selection of patients for a prospective clinical trial.

Finally, Saiya-Cork et al find that increasing expression of insulin receptor is associated with lymph node disease, as well as shorter time to first treatment (TTFT) and overall survival (OS). The association with lymph node disease may be related to the known association of lymph node disease with 11q deletion(3). However, the findings for TTFT and OS are true even when CLLs with deletion 11q are excluded, demonstrating that the higher risk associated with INSR overexpression may apply more generally in CLL. The size of their study makes it difficult to determine definitively whether these effects are truly independent of unmutated IGVH and positive ZAP70, which are enriched in the high INSR CLLs. Interestingly, however, they observe that in the ZAP70 negative CLLs, high INSR expression is predictive of steady progression to treatment, similar to that of ZAP70 positive CLLs. Given that ZAP70 expression has been associated with higher BCR signaling in CLL(12), this finding suggests that perhaps activation of the INSR is substituting for ZAP70 by activating shared signaling pathways leading to disease progression. The clinical utility of this finding as a prognostic marker will depend on its reproducibility, the availability of accurate ZAP70 testing, and the number of CLLs that express high INSR but lack other adverse prognostic markers associated with short TTFT. Future large studies will be required to clarify these points.

The results of Saiya-Cork et al are intriguing and raise many questions for future work: What is the mechanism of INSR overexpression in CLL and how does it relate to 11q deletion? Is INSR overexpression truly an independent prognostic marker? Which PI3K isoform mediates insulin signaling in CLL and does a drug already available for clinical trials inhibit it in vitro? Can a clinical trial of the most appropriate PI3K inhibitor be designed selectively for those patients with high INSR-expressing CLLs? These results provide an excellent beginning for a bench-to-bedside story......
Figure Legend

Figure 1. The figure demonstrates BCR signaling through the PI3 kinase p110 delta isoform in CLL, leading to AKT activation. The presence of ZAP-70 in a subset of CLLs amplifies the signal downstream of the BCR. The insulin receptor is also illustrated on the surface of the cell, signaling through PI3 kinase, but it is unknown whether this occurs through p110 delta or alpha. Given that both the BCR and INSR pathways converge on AKT activation, CLLs that lack ZAP-70 but overexpress the insulin receptor may show enhanced AKT activation compared to those that lack both ZAP-70 and insulin receptor expression, thereby compensating for the lack of ZAP-70.
References

Akt activation

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Clin Cancer Res Published OnlineFirst March 22, 2011.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-11-0295

Supplementary Material
Access the most recent supplemental material at:
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