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. Clin Cancer Res; 17(9): 2605–7. ©2011 AACR.

In this issue of Clinical Cancer Research, Saiya-Cork and colleagues used integrative genomic profiling to identify that the insulin receptor (INSR) is significantly overexpressed in about 25% of chronic lymphocytic leukemias (CLL), 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. Because 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 and colleagues used array-based expression profiling to identify the INSRA as significantly differentially expressed gene between CLLs with and without deletion of 11q and they confirmed this finding with quantitative PCR as well as FACS analysis and Western blotting. They found that INSR expression varied 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 showed elevated INSR expression. Importantly, deletion 17p CLLS were not enriched in the highest-expressing groups, suggesting that INSR expression is not merely a proxy for aggressive or proliferative disease. Saiya-Cork and colleagues were not able to identify a candidate gene or a common pattern of deletion within 11q that explains INSR overexpression, although they did 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 INSR might lead to its overexpression. However, because only about two thirds of the deletion 11q patients showed INSR overexpression, and some patients in the other cytogenetic groups also showed overexpression, the mechanism of INSR expression is undoubtedly complex, likely involving either multiple mechanisms, or one mechanism with multiple regulators.

Saiya-Cork and colleagues further showed that the INSR expressed in these CLLs was functional, in that insulin is able to induce activation of the AKT and RAS/RAF/extracellular signal regulated kinase (ERK) pathways and 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, because direct potent inhibition of the INSR itself would presumably be clinically problematic. Multiple drugs already in the clinic inhibit phosphatidylinositol 3-kinase (PI3K), which is downstream of the INSR and upstream of AKT, and at least to date, these PI3K inhibitors have not been reported to cause substantial clinical problems with hyperglycemia (8).

The PI3K inhibitor most tested in hematologic malignancies and that has very significant activity in CLL is CAL-101 (9). CAL-101 is a specific inhibitor of the p110α
catalytic subunit of PI3K. The p110δ isoform shows restricted expression in leukocytes and is not thought to be involved in insulin signaling, which is usually mediated by the ubiquitously expressed p110α or p110β catalytic subunits. In CLL, inhibition of the p110δ isoform with CAL-101 has been shown to block the signaling effects of stimulation through the BCR or CD40 (10, 11), but insulin signaling has not been investigated (Fig. 1). The PI3K isoform involved in insulin signaling in CLL cells will need to be determined experimentally, because the alpha and delta isoforms are both expressed. If insulin signaling in CLL cells is mediated by the p110α subunit, as it is in other cell types, then a pan-PI3K or PI3Kα inhibitor would be required to inhibit insulin signaling and would be expected to have better clinical activity than CAL-101 in the CLL subgroup that overexpresses the INSR, albeit at a possible cost of hyperglycemia not seen with CAL-101. Of course, the authors observed that, in the ZAP-70–negative CLLs, high INSR expression was predictive of steady progression to treatment, similar to that of ZAP-70–positive CLLs. Given that ZAP-70 expression has been associated with higher BCR signaling in CLL (12), this finding suggests that perhaps activation of the INSR is substituting for ZAP-70 by activating shared signaling pathways leading to disease progression (Fig. 1). The clinical utility of this finding as a prognostic marker will depend on its reproducibility, the availability of accurate ZAP-70 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.

Finally, Saiya-Cork and colleagues found that increasing expression of INSIR was 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, showing that the higher risk associated with INSIR 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 ZAP-70, which are enriched in the high INSIR CLLs. Interestingly, however, the authors observed that, in the ZAP-70–negative CLLs, high INSIR expression was predictive of steady progression to treatment, similar to that of ZAP-70–positive CLLs. Given that ZAP-70 expression has been associated with higher BCR signaling in CLL (12), this finding suggests that perhaps activation of the INSIR is substituting for ZAP-70 by activating shared signaling pathways leading to disease progression (Fig. 1). The clinical utility of this finding as a prognostic marker will depend on its reproducibility, the availability of accurate ZAP-70 testing, and the number of CLLs that express high INSIR 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 and colleagues are intriguing and raise many questions for future work: What is the mechanism of INSIR overexpression in CLL, and how does it relate to 11q deletion? Is INSIR 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.

References


Disclosure of Potential Conflicts of Interest

J R. Brown has served as a consultant for Calistoga Pharmaceuticals.
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