Published in final edited form as:
Leukemia. 2009 August ; 23(8): 1374. doi:10.1038/leu.2009.75.

NOTCH inhibition and glucocorticoid therapy in T-cell acute lymphoblastic leukemia

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Abstract

Inhibition of NOTCH1 signaling with gamma-secretase inhibitors (GSIs), has been proposed a molecularly targeted therapy in T-cell acute lymphoblastic leukemia (T-ALL). However, GSIs seem to have limited antileukemic activity in human T-ALL and are associated with severe gastrointestinal toxicity resulting from inhibition of NOTCH signaling in the gut. Inhibition of NOTCH1 signaling in glucocorticoid-resistant T-ALL restored glucocorticoid sensitivity and cotreatment with glucocorticoids inhibited GSI-induced gut toxicity. Thus, combination therapies with GSIs plus glucocorticoids may offer a new opportunity for the use of anti-NOTCH1 therapies in human T-ALL.

Keywords

T-ALL; glucocorticoid resistance; gamma-secretase inhibitor; NOTCH1; gastrointestinal toxicity

Introduction

T-cell acute lymphoblastic leukemia (T-ALL) is a hematologic tumor resulting from the malignant transformation of immature T-cell progenitor cells and constitutes 15% of pediatric and 25% of adult ALL cases (1,2). Initially associated with a very poor prognosis, T-ALL can now be cured in about 80% of children and 50% of adults thanks to the use of highly intensive chemotherapy protocols (3–6, 7, Czuczman, 1999 #89, 8, 9). Despite this progress, leukemia relapse, generally associated with acquired chemotherapy resistance, still constitutes a significant clinical problem (9–11). In this context the development of new drugs and drug combinations effective against relapsed T-ALL has become a priority in the field.

Activating mutations in the *NOTCH1* gene are present in over 50% of human T-ALL cases making *NOTCH1* the most prominent oncogene specifically involved in the pathogenesis of this disease (12–16). Importantly, activation of NOTCH1 signaling requires its proteolytic processing by the presenilin-gamma secretase complex (17,18). Consequently, small molecule gamma-secretase inhibitors (GSIs) effectively block NOTCH1 activity in T-ALL cells and have been proposed as a molecularly targeted therapy for the treatment of this disease (12). However, animal studies have shown that systemic inhibition of NOTCH signaling results in gastrointestinal toxicity due to accumulation of secretory goblet cells in the intestine (19–22).

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In agreement with these results a phase I clinical trial analyzing the effects of a GSI in relapsed and refractory T-ALL showed significant gastrointestinal toxicity (23). Moreover, none of the patients enrolled in this study showed any significant clinical response, which correlates with the weak antileukemic effects of GSIs against human T-ALL cells in vitro (23). Despite these unsatisfactory results in the clinic, inhibition of NOTCH1 signaling has a profound effect on the homeostasis of T-ALL lymphoblasts, (24–26) suggesting that GSIs may sensitize T-ALL cells to chemotherapy. In this feature we summarize our results showing that GSIs may reverse glucocorticoid resistance in T-ALL and that glucocorticoid therapy may antagonize the effects of NOTCH inhibition in the intestinal epithelium and protect from GSI induced gut toxicity (27).

Inhibition of NOTCH1 signaling with GSIs reverses glucocorticoid resistance in T-ALL

Glucocorticoids play a fundamental role in the treatment of all lymphoid tumors due to their capacity to induce apoptosis in lymphoid progenitor cells (2,28,29). The importance of glucocorticoid therapy in leukemias and lymphomas is underscored by the strong association of glucocorticoid response with prognosis in childhood ALL. Thus, the initial response to 7 days of glucocorticoid therapy is a strong independent prognostic factor in this disease (6,30, 31). And resistance to glucocorticoids *in vitro* is associated with an unfavorable prognosis (32,33). Moreover, the majority of patients with ALL in relapse show increased resistance to glucocorticoid therapy, identifying glucocorticoid resistance as a major contributor to treatment failure (32,34).

NOTCH1 signaling plays a critical role in promoting cell growth, proliferation and survival in immature T-cells, which is somewhat opposed to glucocorticoid-induced cell death (35). Indeed, constitutive activation of NOTCH1 signaling may protect developing thymocytes against glucocorticoid-induced apoptosis (36). To address the relevance of this interaction in the context of oncogenic NOTCH1 signaling we tested the effects of GSIs and dexamethasone in T-ALL cells (27). These studies showed that inhibition of NOTCH1 with GSIs sensitized glucocorticoid-resistant T-ALL cell lines and primary samples to glucocorticoid induced apoptosis. This synergistic interaction was mediated by inhibition of NOTCH1 signaling and required activation of the glucocorticoid receptor (27). Interestingly, we did not observe a synergistic effect of GSIs and glucocorticoids in glucocorticoid-sensitive cells, suggesting that the increased antileukemic effects of GSIs plus glucocorticoids are specifically mediated by reversal of glucocorticoid resistance (27). Finally, these results did not extend to other chemotherapy drugs such as etoposide, methotrexate, vincristine and L-asparaginase (27).

Gene expression profiling analysis of the effects of GSI plus dexamethasone treatment in the CUTLL1 cell line showed increased expression of the glucocorticoid receptor (*NR3C1*) and glucocorticoid regulated genes (27). Notably, amplification of glucocorticoid receptor signaling via glucocorticoid receptor auto-upregulation is essential for glucocorticoid-induced apoptosis, and loss of glucocorticoid receptor auto-upregulation has been proposed as a prevalent mechanism of glucocorticoid resistance in ALL (37–42). In addition, retroviral expression of the glucocorticoid receptor was sufficient to restore glucocorticoid sensitivity in these cells (27). A mechanistic link between NOTCH1 signaling and glucocorticoid receptor autoupregulation was established by demonstrating that HES1, a transcriptional repressor controlled by NOTCH1, binds to each of three glucocorticoid receptor promoters involved in glucocorticoid receptor autoupregulation in T-ALL (27). Moreover, HES1 inactivation via shRNA knock down resulted in glucocorticoid receptor upregulation and restored glucocorticoid sensitivity (27). Consistent with this model, Bim, a critical apoptotic factor in glucocorticoid-induced cell death showed to be synergistically upregulated in cells treated with dexamethasone plus a GSI (27). *In vivo* validation of these results demonstrated the efficiency

of combined treatment of GSI and glucocorticoids in a xenograft model of glucocorticoid resistant T-ALL.

Glucocorticoid treatment protects from GSI-induced gut toxicity

An unexpected finding in these experiments was that glucocorticoid treatment seemed to have a protective effect against GSI-induced intestinal toxicity in mice (27). These surprising results were confirmed using an inducible model of Notch inactivation using *CSL/Rbpj* conditional knockout mice (27). Moreover dexamethasone treatment did not result in increased GSI metabolism ruling out that the decrease in GSI-induced gut toxicity by dexamethasone was mediated by a pharmacokinetic interaction (27).

The function of Klf4, a transcription factor inhibitor of cell cycle progression and a critical factor required for the generation of intestinal goblet cells (43,44), is related to the two main histological features associated with GSI-induced gut toxicity, namely, accumulation of secretory goblet cells and a prominent a block in cell proliferation. Importantly, we observed that Klf4 is markedly upregulated in the intestine of mice treated with a GSI and demonstrated that NOTCH1 negatively regulates *Klf4* via HES1-mediated control of the *Klf4* promoter (27). Overall these findings identify *Klf4* as an indirect target downregulated by NOTCH1 signaling and a critical mediator of GSI-induced gut toxicity. Now the open question is how does dexamethasone abrogate Klf4 upregulation? To address this question we first analyzed the effects of glucocorticoid treatment in the intestine. Detailed histological and gene expression profiling studies showed that dexamethasone treatment leads to accumulation of lysozyme positive Paneth cells in the bottom of the crypt and increased cell proliferation associated with increased expression of *Ccnd2* (27). Importantly, analysis of *Ccnd2* deficient animals showed that dexamethasone treatment failed to protect *Ccnd2* knock out mice from developing GSI-induced goblet cell metaplasia (27). Overall these results demonstrate a role of glucocorticoids in the control of cell homeostasis in the intestinal epithelium and identify *Ccnd2* as a critical mediator of the enteroprotective effects of glucocorticoids against GSI-induced gut toxicity.

Concluding remarks and future directions

Despite the central role of glucocorticoids in the treatment of lymphoid malignancies and the importance of glucocorticoid resistance in the clinic, the molecular mechanisms that mediate glucocorticoid resistance in ALL have not been resolved. Among other mechanisms, several groups have proposed alterations in the upregulation of glucocorticoid receptor expression in response to glucocorticoids as a possible mechanism mediating glucocorticoid resistance in ALL (37–42). The results of our studies demonstrate that oncogenic transcriptional networks and signaling pathways can modulate the activity of the glucocorticoid receptor and hence the therapeutic response to glucocorticoids in lymphoid tumors. Moreover the identification of a NOTCH1-HES1-glucocorticoid receptor regulatory axis highlights a critical role for glucocorticoid receptor autoupregulation in glucocorticoid induced apoptosis and glucocorticoid response. However, this is in contrast with recent studies showing effective glucocorticoid receptor upregulation in glucocorticoid resistant ALL cells (45). In addition, even though activating mutations in *NOTCH1* are highly prevalent most T-ALLs show adequate responses to glucocorticoid therapy and *NOTCH1* mutations do not seem to confer poor prognosis in T-ALL (16,46). An important factor that may account for these discrepant results is the difference between primary glucocorticoid resistance at diagnosis, in which the glucocorticoid receptor autoregulatory loop seems to be competent; and secondary glucocorticoid resistance at relapse, in which a fraction of ALL samples seem to have attenuated glucocorticoid receptor autoupregulation. Given that most *NOTCH1* mutated cases are sensitive to glucocorticoidsr, attenuation of glucocorticoid receptor autoupregulation by

NOTCH1-HES1 is most probably not sufficient to effectively block glucocorticoid induced apoptosis. However, release of this inhibitory effect by GSIs seems to be sufficient to trigger a more robust glucocorticoid response and glucocorticoid-induced apoptosis in otherwise glucocorticoid resistant T-ALL cells.

The interaction of glucocorticoids and GSIs in the intestine, which results in abrogation of GSI-induced gut toxicity, has uncovered a previously unrecognized effect of glucocorticoid therapy in the intestinal epithelium. Our results show that glucocorticoids promote Paneth cell differentiation and promote cell proliferation in part through upregulation of *Ccnd2* expression. Notably, downregulation of Klf4, a critical factor involved in GSI-induced gut toxicity by Ccnd2 seems to play a critical role n preventing GSI-induced goblet cell differentiation. However, several important questions regarding the mechanistic interaction between GSIs and glucocorticoids in the gut remain to be elucidated. How does dexamethasone affect Paneth cell differentiation? Is *Ccnd2* a direct transcriptional target of glucocorticoids in the gut? What is the specific mechanism that mediates *Klf4* downregulation by *Ccnd2*?

Overall, our data on the interaction between glucocorticoids and GSIs supports the development of clinical trials aiming to test the safety and efficacy of GSIs and glucocorticoids in T-ALL (27).

In addition, numerous recent reports have described a role for aberrant NOTCH signaling in the pathogenesis of solid tumors (47–52) and tumor angiogenesis, (53–58) suggesting a broader role for anti-NOTCH therapies in the treatment of human cancer. Moreover, the enteroprotective effects of glucocorticoids against GSI-induced gut toxicity may open new opportunities for the use of GSIs in the treatment of Alzheimer's disease. However, chronic glucocorticoid treatment is associated with significant toxicities and the combination of GSIs and glucocorticoids has a deleterious effect in the immune system. Scaling down the dose of glucocorticoids may reduce these undesired toxic effects while still protecting from the development of GSI-induced gut toxicity. In addition, improved understanding of the mechanisms mediating the enteroprotective effect of glucocorticoids should facilitate the identification of additional genes and pathways that can be targeted to prevent GSI-induced gut toxicity.

Acknowledgments

Supported by the NIH (grants R01CA120196 and R01CA129382), the Leukemia and Lymphoma Society (grants 1287-08 and 6237-08) (AF) and Fondo de Investigacion Sanitaria (grant CD07/00033) (PJR). Adolfo Ferrando is a Leukemia & Lymphoma Society Scholar.

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