Methods: UST data were derived from the ACCEPT study (NCT00454584, n=85), in which PsO patients received either 45 mg or 90 mg of UST at weeks (wk) 0 and 4, and GUS data were from the first-in-human study (NCT00925574, n=24) that tested single subcutaneous doses of GUS. Skin biopsies were collected at baseline (BL), and wk 1 and 12 post-treatment from each study to evaluate 1) histologic improvement via epithelial thickness, T cells (CD3), and myeloid DCs (CD11c counts) and 2) molecular response to drug via microarray. Biopsies from healthy subjects served as controls. GUS 100 mg and 300 mg groups were combined to increase analytic power. The IC50 of each drug was evaluated by cell proliferation assay.

Results: The two cohorts are comparable in BL demographics, disease characteristics, skin histopathology, PsO lesional molecular expression profiles, and significantly enriched canonical pathways. Blockade of IL-23 with GUS resulted in a significantly greater reduction in CD3 and CD11c counts in the skin at wk12 relative to BL when compared to UST blockade (>90% vs >70%). In pts who achieved ≥75% improvement in PASI score, GUS (n=9) showed a larger impact on the PsO transcriptomic profile than UST 90 mg (n=2) and greater enhancement was achieved by wk12. GUS neutralized 74% of the PsO disease profile by >80%, while UST resolved only 21% at wk12. Expression of PsO disease markers such as defensein Beta 4A and lipocalin 2 were fully resolved by GUS beyond the level observed in non-lesional skin of PsO pts, while UST only resolved these markers by 32% and 63%, respectively. In vitro, GUS showed higher potency (2–14 fold) than UST in inhibiting IL-23 activity, which may contribute to stronger neutralisation of PsO disease markers by GUS.

Conclusions: In conclusion, this comparative study demonstrates that GUS inhibits psoriasis-associated pathology and resolves the skin transcriptomic PsO disease profile more strongly than UST.

REFERENCE:


A LOW MOLECULAR WEIGHT BAFF SIGNALING INHIBITOR, BIK-13, AMELIORATES B CELL ACTIVATION IN VITRO AND IN VIVO AUTOIMMUNE MODELS AND CONSEQUENTLY SUPPRESSES PRODUCTION OF IgG AND CYTOKINES

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Background: We reported that BAFF robustly increases IL-6 production by activated splenic lymphocytes of the BIK-13-treated mice was also remarkably suppressed in BIK-13-treated mice. Moreover, the proportion of B cells among splenic lymphocytes was also decreased in BIK-13-treated mice as compared to the control. In addition, production of IL-6 and IL-10 by activated splenic lymphocytes of the BIK-13-treated mice was also remarkably suppressed as compared to control mice.

Conclusions: Our data collectively suggest that BIK-13, a low molecular weight BAFF-signalling inhibitor, suppresses B cell activation/differentiation in vitro and consequently inhibits production of IgG and cytokines, such as IL-6 and IL-10, by the cells. The compound inhibited infiltration of B cells into organs of model mice of autoimmune diseases. These data suggest that the compound is a promising drug candidate to treat autoimmune diseases, such as pSS.


Background: Sites of chronic inflammation, such as rheumatoid arthritis (RA) synovial tissue, are characterised by neovascularization and often contain tertiary lymphoid structures with characteristic features of lymphoid organs such as high endothelial venules (HEV), and sometimes even true germinal centres. Ligation of the lymphotixin (LT)-beta receptor (LTbR) results in activation of both canonical and NF-kB inducing Kinase (NIK)-dependent noncanonical NF-kB signalling in endothelial cells (EC) and plays a crucial role in lymphoid neogenesis. Noncanonical NF-kB signalling in EC promotes inflammation-induced angiogenesis and triggers the development of the cuboidal HEV appearance. However, the relative contribution of the individual pathways to the acquisition of leukocyte traffic-regulating properties by EC is less well understood.

Objectives: To identify the molecular pathways by which LTbR drives inflammatory activation of EC to promote interactions with leukocytes.

Methods: Primary human EC were treated with LTbR or LIGHT to activate LTbR, followed by analysis of downstream NF-kB signalling pathways and expression of inflammatory cytokines and adhesion molecules. To repress canonical NF-kB signalling, a small molecule inhibitor of IKK was used, and noncanonical NF-kB signalling was repressed with siRNA targeting NF-kB2. The role of NIK in LTbR signalling was investigated using small molecule inhibitors and siRNA targeting NIK, as well as adenoviral overexpression of NIK. The role of NF-kB signalling in RA was measured by stimulating EC with RA synovial fluid (RASF) followed by analysis of inflammatory mediators.

Results: LTbR triggering in EC resulted in activation of both canonical and noncanonical NF-kB signalling pathways and induced inflammatory cytokine expression and immune cell adhesion. IKK inhibition completely repressed LTbR-induced inflammatory activation of EC, indicating that this process was mediated through canonical NF-kB signalling. Interestingly, inactivation of NIK with small molecule inhibitors and siRNAs significantly decreased LTbR-induced expression of inflammatory cytokines and adhesion of immune cells to endothelium, whereas silencing of NF-kB2 had no effect. This suggests that the noncanonical pathway is dispensable for NIK-dependent activation of EC through the canonical NF-kB pathway. Further analyses, including silencing of NIK and NIK overexpression, demonstrated a role for NIK in activation of the canonical NF-kB pathway by impairment of NF-kB complex activation. RASF stimulation of EC resulted in activation of canonical and noncanonical NF-kB signalling, and increased the expression of inflammatory cytokines and adhesion molecules, which could be blocked by targeting NIK.

Conclusions: These findings suggest that in addition to regulating noncanonical signalling, NIK can serve as an amplifier of canonical NF-kB signalling and associated inflammatory responses in EC, which may play a role in development and

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NIK-IKK COMPLEX INTERACTION CONTROLS NF-kB-DEPENDENT INFLAMMATORY ACTIVATION OF THE ENDOTHELIUM IN RESPONSE TO LTbR LIGATION

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Background: Endothelium plays a crucial role in inflammation and immune cell traffic in vivo. Endothelial cell (EC) activation results in increased expression of adhesion molecules and pro-inflammatory cytokines, which are key players in the development and progression of inflammatory diseases. The NIK-IKK complex is a key node in the inflammatory response, involved in the activation of NF-κB canonical and noncanonical pathways. The aim of this study was to investigate the role of NIK-IKK complex in EC activation in response to LTbR ligation.

Objectives: To study the effects of LTbR ligation on EC activation and to identify the role of NIK-IKK complex in this process.

Methods: Human primary EC were treated with LTbR or LIGHT to induce EC activation. The expression of adhesion molecules and pro-inflammatory cytokines was measured by ELISA. The role of NIK-IKK complex was assessed by silencing NIK or IKK using siRNA. The effects of NIK-IKK complex on EC activation were evaluated by measuring the expression of adhesion molecules and cytokines using flow cytometry and ELISA, respectively.

Results: LTbR ligation induced a significant increase in the expression of adhesion molecules and pro-inflammatory cytokines. Silencing NIK or IKK using siRNA significantly reduced the expression of adhesion molecules and cytokines. The role of NIK-IKK complex in EC activation was further confirmed by measuring the levels of adhesion molecules and cytokines in EC treated with NIK-IKK complex inhibitors.

Conclusions: NIK-IKK complex plays a crucial role in EC activation in response to LTbR ligation. The role of NIK-IKK complex in EC activation is mediated through regulation of adhesion molecules and cytokines. These findings suggest that targeting the NIK-IKK complex may be a promising strategy for the treatment of inflammatory diseases.