Inhibition of Src with AZD0530 Reveals the Src-Focal Adhesion Kinase Complex as a Novel Therapeutic Target in Papillary and Anaplastic Thyroid Cancers

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ABSTRACT
Context: Focal adhesion kinase (FAK) and Src are overexpressed and activated in many cancers and have been associated with tumor progression. The role of the Src-FAK complex has not been characterized in papillary and anaplastic thyroid cancer (PTC and ATC).

Objective: The goal of this study was to determine the role of Src and FAK in the growth and invasion of PTC and ATC.

Design: PTC and ATC cells were treated with the oral Src inhibitor, AZD0530, to determine the consequences of Src inhibition using growth and invasion assays. FAK and phospho-FAK levels were analyzed in cell lines as well as in PTC tumor samples.

Results: AZD0530 treatment inhibited the growth and invasion in four of five thyroid cancer cell lines, and inhibition did not correlate with basal levels of phospho-Src. Instead, we show for the first time that FAK, a critical substrate and effector of Src, is phosphorylated at tyrosine residue 861 (pY861) in PTC and ATC cells, and high levels of phospho-FAK correlate with AZD0530 sensitivity. We further showed that pY861-FAK phosphorylation is Src-dependent. Sensitivity to AZD0530 was confirmed using a preclinical three-dimensional culture model. Phospho-ERK1/2 was not affected by AZD0530, indicating that Src signaling does not require MAPK. Finally, FAK and pY861-FAK were expressed in 10 of 10 and five of 10 PTC tumors, respectively.

Conclusions: Inhibition of the Src-FAK complex represents a promising therapeutic strategy for patients with advanced thyroid cancer, and phospho-FAK represents a potential biomarker for response.

Autoantibodies in Type 2 Diabetes Induce Stress Fiber Formation and Apoptosis in Endothelial Cells

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ABSTRACT
Context: Macular edema contributes to visual impairment, and albuminuria is associated with increased cardiovascular mortality in adults with type 2 diabetes mellitus. These microvascular complications result from increased capillary leakage of plasma proteins whose causation is not completely understood.

Objective: The objective of the present study was to test whether plasma from type 2 diabetes with maculopathy/albuminuria or control subjects contains autoantibodies that can induce apoptosis or activate Rho kinase (ROCK) in endothelial cells.

Design: A cohort of Veterans Affairs Diabetes Trial adults (~40 yr of age) was randomized to standard vs. intensive glycemic treatment lasting 5–7.5 yr.

Setting: The study was conducted in outpatient clinics.

Patients: Case and age-matched control subjects who differed for the baseline presence of significant diabetic maculopathy and/or progression to macro-albuminuria were included in the study.

Intervention: Pharmacological and lifestyle interventions in the Veterans Affairs Diabetes Trial generally resulted in substantially improved glycemic, blood pressure, and lipid levels.

Results: Autoantibodies from patients with macular edema or progression to albuminuria potently induced caspase-dependent apoptosis in endothelial cells (up to 60%), whereas IgG from age-matched normal plasma caused much less apoptosis (<10%; P < 0.0001). The active inhibitory autoantibodies triggered stress fiber formation in endothelial cells likely through the activation of Rho guanosine 5′-triphosphatase, which could be nearly completed inhibited by 10 nM Y27632, a specific ROCK inhibitor.

Conclusions: These results suggest that autoantibodies from a subset of advanced type 2 diabetes may contribute to diabetic vascular complications by activating ROCK, inducing stress fiber formation and apoptosis in endothelial cells.