LETTER TO THE EDITOR

Tyrosine 397 phosphorylation is critical for FAK-promoted Rac1 activation and invasive properties in oral squamous cell carcinoma cells

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Sir,

In a recent issue of *Laboratory Investigation*, Chiu *et al*[1] describe that inhibition of FAK and Rac1 reduce invasive properties of cancer cell lines. Through an elegant series of experiments, they show that FAK and its pY397 is essential in regulating Rac1 and invasive properties in OSCC cells. They thus propose FAK and Rac1 inhibitors as a potential therapeutic to be used to combat oral squamous cell carcinoma in humans. Undiscussed are the translational insights these findings offer into potential negative side effects of inhibiting Rac1 on glucose homeostasis on a whole body level.

Rac1 is expressed in significant amounts in pancreas and muscle. The interplay between these two tissues has an essential role in the regulation of whole body glucose homeostasis.[2] Following a meal, insulin is released into the circulation where it stimulates glucose uptake by peripheral tissues, including muscle, resulting in lowering of blood glucose. The pancreatic beta cells and peripheral tissues thus act together to reduce blood glucose following a meal, and dysregulation can result in Type 2 diabetes.

Insulin release by the pancreas is regulated by Rac1, and its activation is essential for normal regulation of insulin secretion and islet survival.[3] In skeletal muscle, Rac1 is activated by insulin, and knockout of Rac1 results in insulin resistance and reduced insulin-stimulated glucose uptake.[4,5] Given that muscle makes up 40% of the body's volume, muscle has an essential role in post-prandial lowering of blood glucose.

Pharmacological long-term administration of FAK and Rac1 inhibitors could potentially result in a hazardous cocktail of reduced insulin secretion in combination with insulin resistance in skeletal muscle. This cocktail is well described in the metabolic disease Type 2 diabetes in which patients cannot secrete enough insulin to overcome peripheral insulin resistance, resulting in hyperglycemia and the complications that follow.

In conclusion, Chiu *et al*[1] present new data that clarify the role of FAK and Rac1 in the invasive properties of oral squamous cell carcinoma. These findings are promising as FAK and Rac1 inhibition could potentially be used to block tumor spreading. However, global whole body inhibition of Rac1 could disturb glucose homeostasis and thereby increase the risk of developing Type 2 diabetes. Cancer drugs that aim to inhibit FAK and Rac1 should thus also be evaluated regarding potential long-term metabolic effects.

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DISCLOSURE/CONFLICT OF INTEREST

The author declares no conflict of interest.

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