CELL CYCLE
2017, VOL. 16, NO. 15, 1387–1388
https://doi.org/10.1080/15384101.2017.1345229

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EDITORIALS: CELL CYCLE FEATURES

Inappropriate movement of Rac1 contributes to glucotoxicity of the islet β-cell

Anjaneyulu Kowluru

β-Cell Biochemistry Laboratory, John D. Dingell VA Medical Center, Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI, USA

ARTICLE HISTORY Received 1 June 2017; Accepted 5 June 2017

Glucose-stimulated insulin secretion [GSIS] from pancreatic β-cells is mediated largely *via* the generation of soluble second messengers, including cyclic nucleotides, hydrolytic products of phospholipases and adenine nucleotides. In addition to regulation of GSIS by adenine nucleotides, published evidence affirms the contributory roles for guanine nucleotides [GTP] in physiological insulin secretion. Although the precise mechanisms underlying the regulatory role[s] of GTP remain elusive, available evidence indicates that they might involve activation of one [or more] GTP-binding proteins [G proteins]. At least 2 major groups of G proteins, namely the heterotrimeric [G_i, G_s, G_z] and small G proteins [Arf6, Cdc42, Rap1 and Rac1] have been identified in β-cells. Over the years, several regulatory factors/proteins have been identified in the islet β-cell that precisely regulate small G proteins, which cycle between their inactive [GDP-bound] and active [GTP-bound] conformations.[1] These regulatory proteins/factors include: [i] guanine nucleotide exchange factors [Tiam1, Vav2, Cool-1/βPIX], which facilitate the exchange of GDP/GTP exchange; [ii] GDP-dissociation inhibitors [GDIα, caveolin-1], which prevent dissociation of GDP from G proteins; and [iii] GTPase-activating proteins; they facilitate the conversion of active G proteins to their respective inactive conformations. To further the complexities involved in regulation of these G proteins, it is well established that both small G proteins and the γ-subunits of trimeric G proteins have been shown to undergo post-translational modifications [farnesylation and geranylgeranylation; commonly referred to as prenylation] at their C-terminal cysteine residues; these signaling steps have been shown to be essential for trafficking/targeting of these G proteins to appropriate cellular compartments [plasma membrane and secretory granules] for optimal interaction with their effector proteins culminating in GSIS.[1]

In an attempt to identify potential alterations in these signaling pathways in islet β-cell dysregulation and demise under conditions of chronic exposure to hyperglycemic conditions [referred to as glucotoxicity], we observed paradoxical activation of Rac1, a small G protein, which appears to play critical regulatory roles in the induction of islet dysfunction by promoting oxidative and stress kinase pathways.[1,2] Using a variety of experimental approaches, we have reported obligatory roles for Rac1 in the regulation of phagocyte-like NADPH oxidase, JNK1/2, p38MAPK, p53 and ATM kinases in clonal INS-1 832/13 cells, rodent islets and human islets. Some of these findings were confirmed in islets derived from animal models of type 2 diabetes [ZDF rat].[1,2] These findings led us to propose novel negative modulatory roles for Rac1 in the pathogenesis of islet dysfunction in diabetes. Based on these observations highlighted below in pancreatic β-cells and supporting evidence in other cell types, we propose a Working Model [Fig. 1] that suggests that aberrant prenylation could contribute to the "inappropriate" localization of unprenylated, and yet constitutively active Rac1, promotes β-cell dysfunction and demise *via* accelerated stress kinase signaling pathway.

First, studies by Veluthakal et al[3] have demonstrated significant inhibition of prenyltransferase activities in pancreatic β-cells exposed to glucotoxic conditions, leading to accumulation of unprenylated proteins. A paradoxical stimulation of Rac1 activity was also seen under these conditions.[1] Second, studies from multiple laboratories demonstrated that pharmacological inhibition of protein prenylation [e.g., statins] results in non-canonical activation of small G-protein [e.g., Cdc42, Rho, Rac].[4,5] Third, exposure of HEL[4] or HCT116[5] cells to statins results in decreased association of GTP-bound, active Rho with GDI. Fourth, these *in vitro* findings were recapitulated in prenyltransferase deficient cells which exhibited increased abundance of active G proteins [Rac1, Cdc42 and Rho].[6] Fifth, while targeting defects [nuclear association] of unprenylated G proteins [Rac1] under glucotoxic conditions remains to be demonstrated in the islet β-cell, studies by Roberts et al in NIH3T3 cells have demonstrated cytosolic as well as nuclear localization of unprenylated Rho G proteins following pharmacological inhibition of prenylation.[7] Lastly, Sidarala et al have recently demonstrated significant Rac1-dependent acceleration of stress kinase pathways [p38MAPK, p53, ATM kinase and JNK1/2] in pancreatic β-cells under the duress of glucotoxicity.[2] These observations were replicated in islets derived from the ZDF rat, a model for T2DM.

Together, the above discussed findings affirm support for our original hypothesis that aberrant prenylation of specific

CONTACT Anjaneyulu Kowluru akowluru@med.wayne.edu β-Cell Biochemistry Laboratory, John D. Dingell VA Medical Center, 4646 John R, Detroit, MI 48201, USA.

Feature to: Veluthakal R, Arora DK, Goalstone ML, Kowluru RA, Kowluru A. Metabolic stress induces Caspase-3 mediated degradation and inactivation of farnesyl and geranylgeranyl transferase activities in pancreatic β-cells. Cell Physiol Biochem 2016; 39:2110-2120; PMID:27802439; https://doi.org/10.1159/000447907; and Sidarala V, Kowluru A. Exposure to chronic hyperglycemic conditions results in Ras-related C3 botulinum toxin substrate 1 (Rac1)-mediated activation of p53 and ATM kinase in pancreatic β-cells. Apoptosis 2017; 22:597-607; PMID:28220272; https://doi.org/10.1007/s10495-017-1354-6

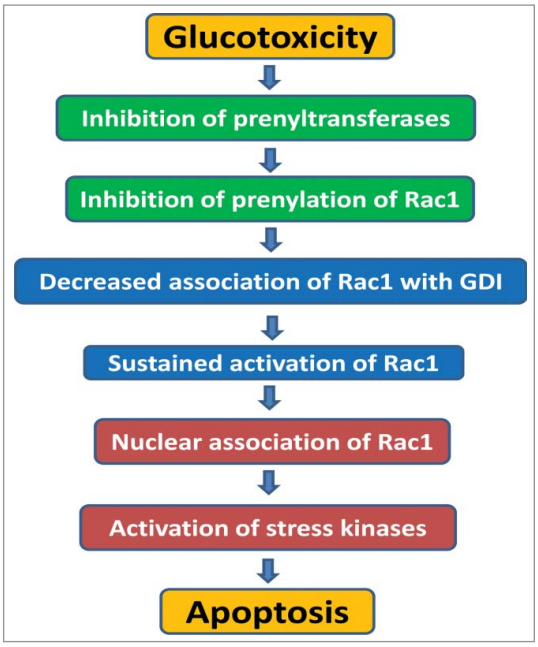

Figure 1. Glucotoxic conditions promote inactivation of protein prenyltransferases leading to inhibition of prenylation of Rac1. Unprenylated Rac1 undergoes sustained activation, which may, in part, be due to its weak association with GDI as well as activation by at least 2 GEFs [Tiam1 and Vav2]. Unprenylated, but active Rac1, translocates to the nucleus and promotes activation of proapototic stress kinases/factors leading to β-cell dysfunction and apoptosis.

G-proteins leads to metabolic dysfunction of the pancreatic β-cell under conditions of glucolipotoxicity. We propose that alterations in the metabolic fate of Rac1 [i.e., inhibition of prenylation, non-canonical activation and "inappropriate" localization in non-relevant cellular compartments [nucleus] could play a significant role in the induction of metabolic defects in the islet β-cell. It may be likely that other pathological stimuli [e.g., exposure to saturated fatty acids and endoplasmic reticulum stress inducers] could elicit similar abnormalities in prenylation signaling pathway leading to cell dysfunction. Indeed, recent demonstration of reduced prenyltransferase activities by these stimuli in the pancreatic β-cell[3] provides clues for future investigations in this area of islet biology.

Disclosure of potential conflicts of interest

The author declares no potential conflicts of interest

ORCID

Anjaneyulu Kowluru http://orcid.org/0000-0003-1700-0077

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