



UNIVERSITÀ DEGLI STUDI DI SALERNO



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***Determinazione del ruolo della proteina BAG3
nelle isole del Langerhans e suo coinvolgimento
nel meccanismo di secrezione dell'insulina***

settore scientifico disciplinare di afferenza: [BIO/11](#)

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Abstract

Diabetes is a metabolic alteration due to a decrease in activity of insulin. In particular, it may be a consequence of a reduced availability of this hormone, of an impediment to its normal action, or of a combination of these two factors. The secretion of insulin is a specialized activity of the β cells of the Langerhans islets that are functional endocrine pancreatic part. Diabetes is a widespread disease, particularly in so-called affluent countries, where some risk factors promote the onset. Actually, it should be considered a syndrome more complex than the simple hyperglycemia. In fact, it is associated to lipid metabolism abnormalities, and increased blood pressure, that, together with abdominal obesity and alterations in glucose homeostasis constitute the so-called 'metabolic syndrome': a multifactorial disease that increases the risk of cardiovascular disease. Given to the wide prevalence of this disease, it is therefore necessary a deeper understanding of the normal physiology of β cells and a complete characterization of the molecules involved in the mechanism of insulin secretion. Recently, there has been much progress in this direction, but much remains to be clarified.

BAG3 is a protein involved in some of the most important biological processes, such as apoptosis, autophagy, adhesion, migration, and cell invasion. The strong positivity of BAG3 protein in Langerhans islets, recently found in our laboratory, has prompted us to analyze the role of this protein in the β cells physiological functions. To this end, we analyzed BAG3 expression and subcellular localization in the murine insulinoma cell line β TC 6. BAG3 has an apparent mass of 74kDa and is localized in the cytoplasm, here has been shown the presence of a 60 kDa BAG3 form in the insulin-containing granules. The presence in this fraction can be explained by the fact that BAG3 appears to be associated with proteins constitutively expressed on the granules membranes involved in their exocytosis. Indeed, in this work, has been shown the physical interaction of BAG3 protein with t-SNARE SNAP-25 / Syntaxin, which mediate the fusion and exocytosis of insulin vesicles to the plasma membrane. In particular, BAG3 appears to regulate the assembly of the complex allowing a regulated secretion of insulin.

In addition, we have shown that BAG3 interacts with the focal adhesion complex FAK / Paxillin, involved in glucose induced F-actin remodeling. The interaction with FAK, induced by high glucose concentrations, appears to be essential for the phosphorylation of BAG3 by such kinases. BAG3 is also able to sustain ERK phosphorylation, contributing to the destruction of the actin cytoskeleton and increased secretion of insulin.

All together these findings disclose a role for BAG3 in regulating insulin release by islet β -cell.