### Potential roles of endoplasmic reticulum stress and cellular proteins implicated in diabesity

**Introduction**

- Diabetes is a condition associated with high amount of glucose in the blood.
- Obesity may co-exist with diabetes; a condition refers to as diabesity.
- Diabesity is associated with insulin resistance, hyperglycemia, hyperlipidemia, and ultimately endoplasmic reticulum (ER) stress.
- The aims of this paper is to critically review the roles of ER stress and its some cellular proteins implicated in diabesity

### Diabesity

- The word diabesity was coined in 1973 due to the co-occurrence of both diabetes and obesity.
- Diabesity or obese diabetes occurs in subjects with obesity, who then develops type II diabetes.
- ER stress triggers insulin signaling impairment via IRE1α phosphorylation with the resultant effect of systemic insulin dysfunction.

### ER Stress

- Cellular function, growth, and pathogenesis are critical for ER, the ER stress, and the resultant diseases such as diabetes, obesity, cancer, and diabesity.
- When the ER condition is unstable due to misfolded or unfolded proteins that exceed the handling ability of the ER, then ER stress sets in.
- ER stress affect the three-arm sensors i.e IRE1, PERK and ATF6.

### Cellular proteins & diabesity

- Cellular proteins implicated in the physiopathology of diabesity include endothelial nitric oxide synthase (eNOS), endothelium-derived endothelin-1 (ET-1), insulin receptor substrate (IRS-1), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and caveolin 1 (Cav-1).
- eNOS, as a cellular protein, plays an essential role in the production of nitric oxide (NO)
- ET-1 is a biomarker of diabetes, indicating micro- and macrovascular dysfunction.
- Chronic hyperglycemia will cause eNOS/NOS uncoupling leading to endothelial dysfunction via many unidentified pathways.
- IRS-1 plays an essential role in the insulin signaling pathways.
- NADPH oxidase is responsible for the production of reactive oxygen species that plays a role in the protein folding process.
- Cav-1 is the site for insulin signaling mechanisms, which could be interrupted possible due to ER stress.

### Conclusion

- ER homeostasis is critical in maintaining cellular survival and functions.
- ER homeostasis is disturbed due to chronic hyperglycemia and hyperlipidemia associated with diabesity and ER stress.
- It results in converging mechanisms related to lipid metabolism distress, oxidative stress, insulin resistance, as well as cell death leading to micro- and macrovascular complications.

---

Sagir Mustapha1,2, Mustapha Mohammed3,4, Ahmad Khusairi Azemi1, Ismaeel Yunusa2, Aishatu Shehu2, Lukman Mustapha6, Yusuf Wada4,5, Mubarak Hussaini Ahmad5, 6, Aida Hanum Ghulam Rosool1, Siti Safiah Mokhtar**

1Department of Pharmacology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kota Bharu, Malaysia
2Department of Pharmacology and Therapeutics, Ahmadu Bello University Zaria, Kaduna, Nigeria
3School of Pharmaceutical Sciences, Universiti Sains Malaysia, Health Campus, 11800 Penang, Pulau Pinang, Malaysia
4Department of Clinical Pharmacy and Pharmacy Practice, Ahmadu Bello University Zaria, Kaduna, Nigeria
5Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina, College of Pharmacy, Columbia, SC, USA
6Department of Pharmaceutical and Medicinal Chemistry, Kaduna State University, Nigeria
7Department of Medical Microbiology and Parasitology, School of Medical Sciences, Ahmadu Bello University Zaria, Kaduna, Nigeria
8School of Pharmacy Technician Training, Aminu Dabo College of Health Sciences and Technology, No. 9C Civic Center Road, Kano State, Nigeria

*Corresponding authors: safiahm@um.edu.my