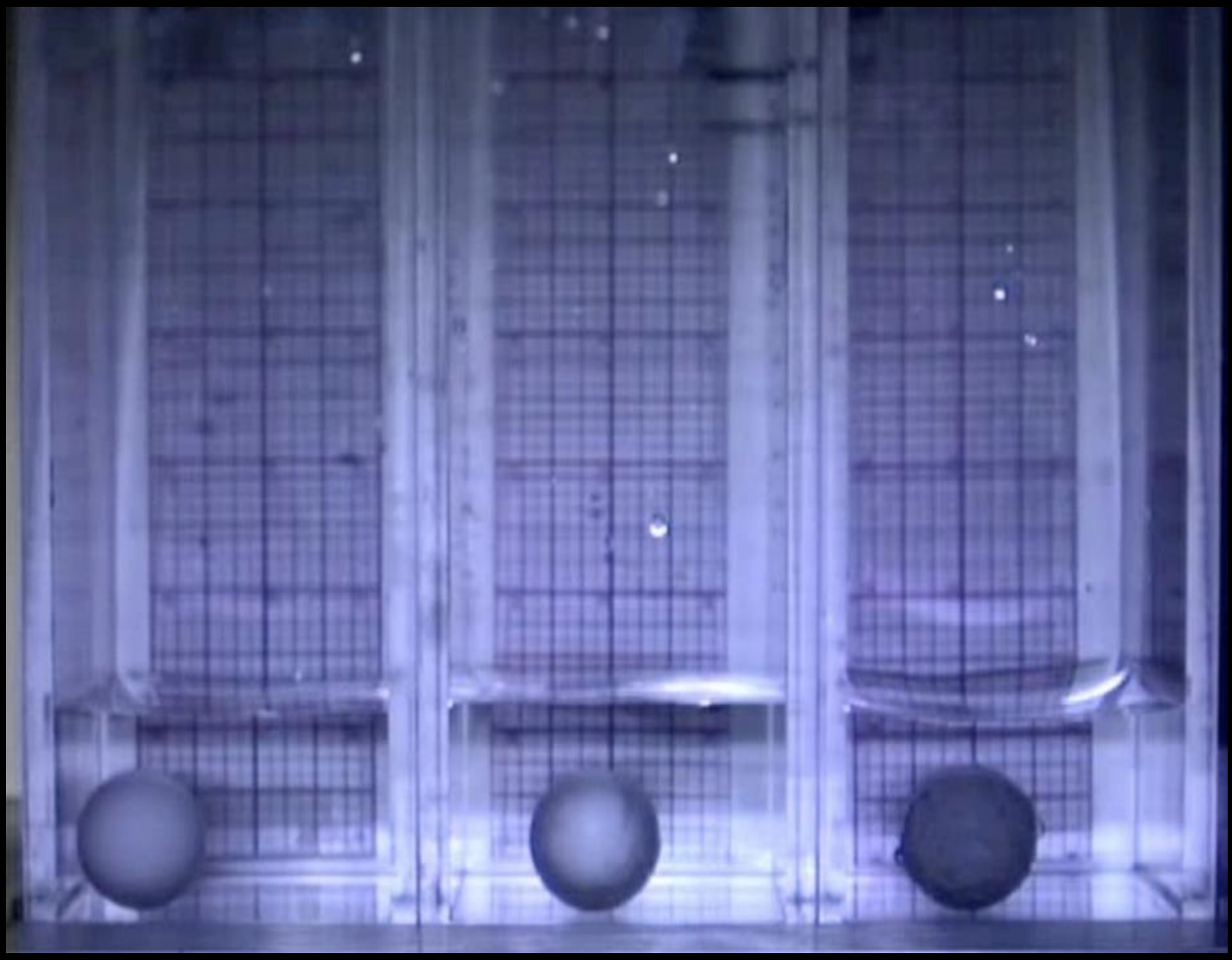
Volume 01, Issue 02
January 2019

Print: ISSN 2574-1721
Online: ISSN 2573-1882

Science Documents®



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Undergraduate Envision

Glucose as a DAMP, Danger Associated Molecular Pattern: A New Proposition of Glucose Molecule in Inflammation-Associated Diabetes

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Context

Inflammation is the human body's defense mechanism to protect from foreign invaders- yet is also the causal agent of an array of diseases that immensely burden our society today. The innate immune response is a nonspecific mechanism through which inflammatory cells (e.g. neutrophils, macrophages, etc.), destroy pathogens such as bacteria, fungi, and viruses, and also respond to internal tissue injury. The death of local tissues through necrosis can lead to the introduction of molecular sequences normally found on the inside of the cell – to the extracellular environment. These sequences are termed damage associated molecular patterns (DAMPs), and can bind to toll like receptors (TLRs) on inflammatory cells to propagate a pro-inflammatory response through the release of cytokines and chemoattractants. It is established that intracellular molecules such as DNA, histones, and ATP act as DAMPs upon extracellular release. [1] However, the potential of glucose as a DAMP is a research target than requires further investigation.

Vision

Glucose is a monosaccharide essential for cellular metabolism. Though glucose circulates in physiological conditions at low levels, it has the potential to trigger the inflammatory response at high local concentrations when a cell lyses through necrosis. Additionally, glucose contains a reactive aldehyde group in hemiacetal form, acting as reducing agent inducing oxidative stress, which furthers the pro-inflammatory environment at local tissue destruction and through the systemic circulation.[2] Through these mechanisms, a high glucose environment is proposed to induce an inflammatory response at the site of tissue injury directly by acting as a damage associated molecular pattern.

Analysis

The ability of a high glucose environment to induce an inflammatory response can be studied by treating cells that contain TLRs (neutrophils, macrophages, and endothelial cells) with increasing concentrations of glucose solution. [3] A treatment with saline would be a positive control, and a

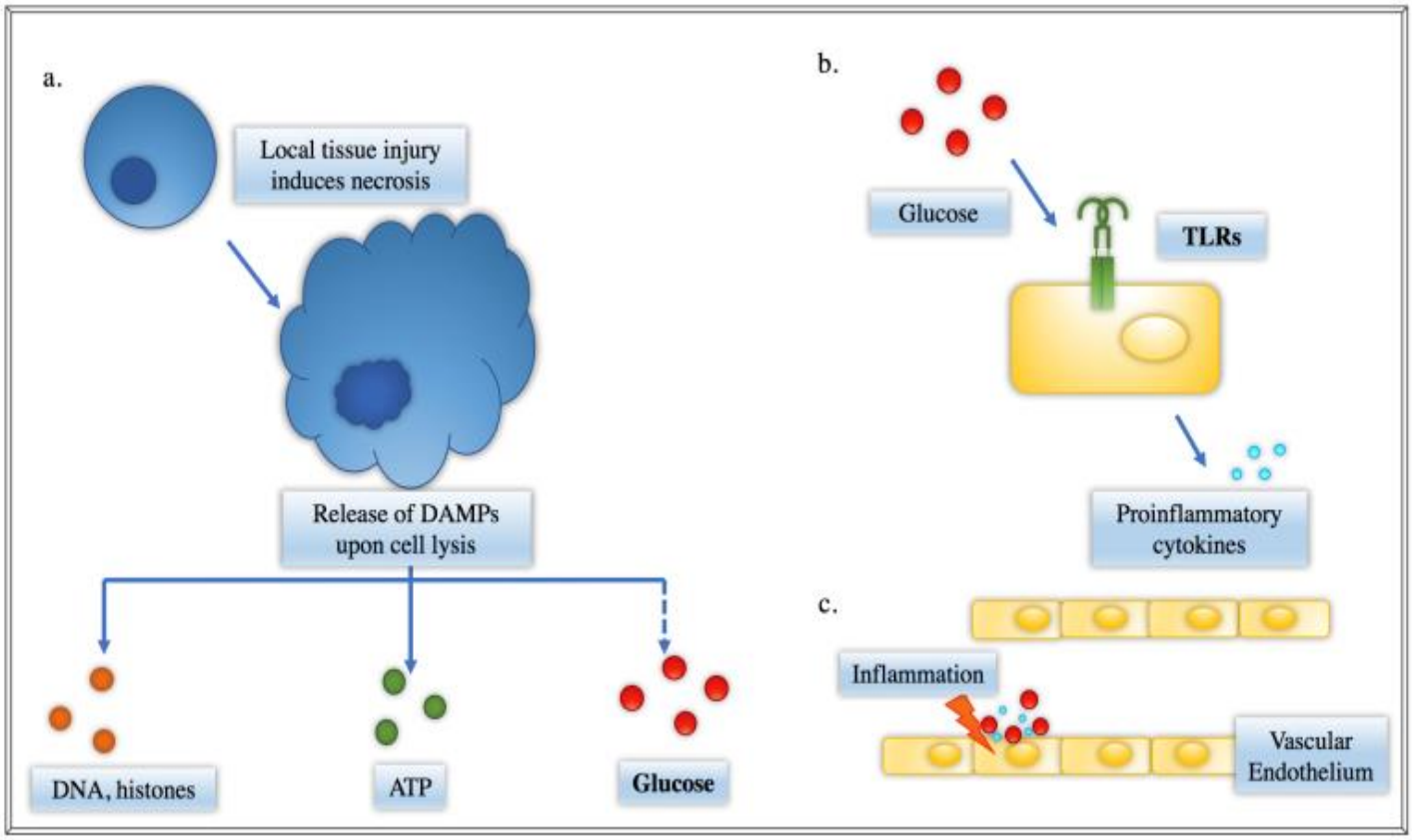

Fig. 1. (a) Intracellular contents (DAMPs) released after necrosis. (b) Glucose binding TLRs release pro-inflammatory cytokines. (c) Pro-inflammatory environment leads to vascular injury.

Science Documents doi: 10.32954/synsdocs.2019.001.06 Volume 01, Issue. 02, January 2019

solution containing histones, a known DAMP, would be used as a negative control. The resultant inflammatory response would be quantified through a measurement of proinflammatory cytokines released by the treated cells though a cytokine antibody array. A physiological measurement of an inflammatory response would be performed through immunofluorescence studies visualizing intracellular calcium release, which would induce vesicular release of proinflammatory cytokines. This would be further confirmed with a mutant line of these inflammatory cells – namely macrophages- with a TLR knockout. It is hypothesized that a high glucose treatment would not induce an inflammatory response in TLR deficient cell lines, but would illicit a pro-inflammatory response in wild type cell lines. If this hypothesis is supported in vitro, the research question can be further implemented in rodent models to study the proinflammatory effects of high glucose in wild type as well as TLR knockout mice lines.

Implementation

Establishing glucose as a direct modulator of the immune response by acting as a DAMP would elucidate the how the pro-inflammatory environment of the hyperglycemic state in the diabetic model induces neuropathy, inhibits wound healing, and ultimately furthers tissue necrosis. Limiting extracellular glucose levels could thus attenuate inflammation and control its adverse effects.

Conflicts of Interest

No conflict of interest.

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