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# Glucose Modifies the Immune Interaction Between Mononuclear and Human Colon Carcinoma Cells

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## Abstract

**Background:** Glucose is one of the principal energy suppliers for normal cell development. Impaired glucose metabolism may lead to serious health and immune impediments including carcinogenesis. The question posed in the present work was if glucose, at several concentrations, affects cytokine production by normal human peripheral blood mononuclear cells (PBMC) and if glucose is able to modulate the immune balance between PBMC and colon cancer cells.

**Methods:** PBMC and human colon cancer cells from HT-29 and RKO lines were separately incubated with glucose at concentrations of 1.25, 2.5 and 5 mg/ml and the capacity for production of TNFα, IL-1β, IL-6, IFNγ, IL-1ra IL-10, and IL-2 was examined. In another set of experiments the effect of glucose on the secretion of these cytokines by PBMC co-incubated with carcinoma cells was evaluated.

**Results:** Unstimulated PBMC incubated with glucose showed a slight to moderate inhibition of IFNγ and IL-10 secretion, whereas PBMC stimulated with LPS were not affected. Addition of glucose to PBMC stimulated by HT-29 colon carcinoma cells showed a slight spurring of TNFα production and a marked inhibition of IL-1β, IFNγ and IL-10, an effect significantly less pronounced when glucose was added to co-cultures of PBMC with RKO cells.

**Conclusions:** Glucose exerted an inhibitory effect on inflammatory cytokine production by PBMC stimulated by HT-29 carcinoma cells except for TNFα and IL-6. The results indicate that glucose alters the immune dialog between mononuclear and cancer cells, a phenomenon that may present an additional link between hyperglycemia and carcinogenesis.

**Keywords:** Mononuclear Cells; Glucose; Hyperglycemia; Cytokines; Colon Cancer; Cross Talk

## Abbreviations

PBMC –Peripheral Blood Mononuclear Cells

IL-Interleukin

TNF –Tumor Necrosis Factor

IFN-Interferon

PBS-Phosphate Buffered Saline

FBS-Fetal Bovine Serum

CM- Complete Medium

MEM-Modified Eagle Medium

W/V-Weight/Volume

CS-Compound Symmetry

## 1. Introduction

The importance of glucose homeostasis in maintaining human health has been extensively explored. According to Gashon et al. [1] mammalians have created an elaborated circadian time-system connected with numerous signals that conduct and regulate a variety of metabolic events including glucose homeostasis. However, one must concede that variations in blood glucose level may act as a double-edged sword – both hypo- and hyperglycemia could be associated with serious complications and even death. Excessive sugar consumption may cause metabolic alterations leading to obesity, type 2 diabetes, heart diseases, vascular impediments and other co-morbidities [2,3]. It is renowned that patients with diabetes mellitus are at increased risk for infections and inflammation [4,5]. Except for hyperglycemia that by itself may provide a predisposing milieu for infections, additional causes such as antioxidant system alterations, defective neutrophil and endothelial cells activities, as well as impaired immunity, play major role in initiation and spreading of infections in diabetic individuals [6,7]. Moreover, according to Zonnenfeld et al. [8] even admission hyperglycemia in non- diabetic patients with post-stroke events are more prompt to infections and have worse prognosis. Oddly, post-stroke diabetic patients did not show greater tendency to infections. We have reported that patients with diabetes have lower number of phagocyting cells compared to healthy controls, although the number of engulfed bacteria per cell did not differ in both groups [9]. Studies have shown that patients with diabetes have impaired immunity [5]. This phenomenon suggests that either the monocytes from diabetic patients are defective, or excess of glucose, in otherwise normal monocytes, may alter their immune activity. Reviewing immunity defects in diabetic patients Geerlings and Hoepelman [5] reported that incubation of non-stimulated and stimulated monocytes from healthy volunteers and diabetic patients with various glucose concentrations induced a

decrease in IL-1 and IL-6 production, whereas the secretion of TNFα by cells from both groups did not considerably differ. On the other hand, incubation of monocytes from healthy individuals with 33 mM glucose for 24 hours caused a significant increase in IL-6 and TNFα levels [10]. Clinical observations have revealed the existence of a relationship between glucose concentration, inflammation and elevated risk for cancer morbidity and mortality [11-13]. We have demonstrated the presence of an immune dialogue between mononuclear and cancer cells expressed as modified cytokine secretion by immune cells [14]. Moreover, this dialogue may be affected by a number of nutritional and chemical constituents [15]. The goal of the present study was to examine the effect of various concentrations of glucose on cell proliferation and ability of human peripheral blood mononuclear cells (PBMC) to produce cytokines, as well as if addition of glucose may interfere with the cross talk between immune and cancer cells.

## 2. Material and Methods

### 2.1 Cell preparation

The study was approved by the Ethics committee of the Rabin Medical Center. Blood bank donors gave written agreement and informed consent that components of the blood might be used for medical research**.** Peripheral blood mononuclear cells (PBMC) were separated from venous blood by Lymphoprep-1077 (Axis-Shield PoC AS, Oslo, Norway) gradient centrifugation. The cells were washed twice in phosphate buffered saline (PBS) and suspended in RPMI-1640 medium (Biological Industries, Beith Haemek, Israel) containing 1% penicillin, streptomycin and nystatin, 10% fetal bovine serum (FBS), and was designated as a complete medium (CM).

### 2.2 Colon cancer cell lines

HT-29 and RKO human colon cancer cell lines were obtained from the American Type Cultural Collection, Rockville, MD. The cells were maintained in CM containing Mc-COY'S 5A medium (Sigma, Israel) and modified eagle medium (MEM- Biological Industries Co, Beth-Haemek, Israel) respectively, supplemented with 10% foetal bovine serum (FBS), 2mM L-glutamine and antibiotics (penicillin, streptomycin and nystatin-Biological Industries Co, Beth-Haemek, Israel). The cells were grown in T-75 culture flasks at 37 $^{o}$C in a humidified atmosphere containing 5% $CO_2$.

### 2.3 Glucose preparation

A 50% glucose solution (W/V in water) was used. Further dilutions were prepared in distilled water. The concentrations used in the study were 1.25, 2.50 and 5.00 mg/ml. The final volume of glucose solution added to the incubation mixture was 10µl/ml. Control cultures contained 10µl/ml of distilled water.

### 2.4 Effect of glucose on cytokine production

1.0 ml of PBMC ($2x10^6$/ml of CM) was incubated without (non-stimulated) or with 20ng/ml LPS for TNFα, IL-1β, IL-6, IL-10, and IL-1ra production, or with 1µg/ml PMA and 0.5µg/ml of ionomycin for IL-2 and IFNγ secretion. In another set of experiments, 0.5 ml of PBMC ($4x10^6$/ml of CM) was incubated with 0.5 ml of CM or either with HT-

29 or RKO colon cancer cells ($4x10^5$/ml) suspended in appropriate CM. Glucose was added at the onset of cultures at concentrations as described. Cultures without glucose served as controls. The cultures were maintained for 24 hrs at 37°C in a humidified atmosphere containing 5% $CO_2$. At the end of the incubation period the cells were removed by centrifugation at 250g for 10 min., the supernatants were collected and kept at -70°C until assayed for cytokines content.

### 2.5 Cytokine content in the supernatants

The concentration of TNFα, IL-1β, IL-6, IFNγ, IL-10, IL-1ra and IL-2 in the supernatants was tested using ELISA kits (Biosource International, Camarillo, CA) specific for these cytokines, as detailed in the guide-line provided by the manufacturer. The detection levels of these kits were 15 pg/ml for IL-6 and 30 pg/ml for the remaining ones.

### 2.6 Statistics

A linear mixed model with repeated measures and assumption of compound symmetry (CS) was used to assess the effect of different concentrations of glucose on cytokine secretion by PBMC induced by colon cancer cells. SAS vs. 9.4 was used for this analysis. Paired t-test was applied to compare between the level of cytokines produced with various concentrations of glucose and that found in control cultures. Probability values of $p<0.05$ were considered as significant. The results are expressed as mean ± SEM.

## 3. Results

### 3.1 Effect of glucose on cell proliferation

24 hrs of incubation of PBMC, HT-29 and RKO colon cancer cells with glucose at 1.25mg/ml, 2.5mg/ml or 5.0 mg/ml had no effect on cell proliferation examined by the XTT test as compared with cells incubated without glucose (data not shown).

### 3.2 Effect of glucose on pro-inflammatory cytokine secretion (Table 1)

24 hrs of incubation of PBMC with glucose at concentrations between 1.25 and 5 mg/ml had no effect on the production of TNFα, IL-1β and IL-6 by non-stimulated cells ($F_{3,21}=0.57$, $p=0.64$; $F_{3,39}=2.38$, $p=0.084$; and $F_{3,38}=0.46$, $p=0.71$, respectively), or by PBMC stimulated with LPS ($F_{3,21}=0.48$, $p=0.69$; $F_{3,12}=0.74$, $p=0.54$; and $F_{3,12}=1.5$, $p=0.26$, respectively). TNFα production by PBMC induced by both colon cancer cell lines was affected by the same glucose concentrations ($F_{3,27}=6.09$, $p=0.0026$ for HT-29 cells and $F_{3,27}=3.96$, $p=0.018$ for RKO cells). The effect of glucose was significant at concentration of 5mg/ml only and was enhanced by 10% ($p=0.029$) and reduced by 14% ($p=0.019$) when PBMC were stimulated by HT-29 or RKO cells respectively. IL-1β production by HT-29 stimulated PBMC was dependently inhibited by glucose at concentrations used in the study ($F_{3,36}=17.6$, $p<0.001$), and was reduced by 11%, 11% and 14% at 1.25mg/ml, 2.5mg/ml and 5mg/ml of glucose, respectively ($p<0.001$). IL-1β production by RKO stimulated PBMC and IL-6 secretion induced by both HT-29 and RKO cells was not affected by incubation with the above mentioned glucose concentrations ($F_{3,26}=1.45$, $p=0.25$, and $F_{3,36}=2.67$, $p=0.062$, $F_{3,27}=1.49$, $p=0.23$, respectively). The production of IFNγ by non-stimulated PBMC was abolished following incubation with glucose ($F_{3,51}=3.32$, $p=0.027$) and was lowered by 12% (NS), 15% and 14% ($p<0.05$) at

1.25mg/ml, 2.5mg/ml and 5mg/ml of glucose, respectively. PMA/ionomycin induced production of IFNγ was not affected by addition of glucose ($F_{3,20}$=2.1, p=0.135). IFNγ secretion by HT-29 stimulated PBMC was concentration-dependently inhibited by 1.25mg/ml, 2.5mg/ml and 5mg/ml of glucose ($F_{3,36}$=10.02, p<0.001) and was reduced by 13% (NS), 17% and 17% (p<0.003). RKO-induced secretion of IFNγ was not affected by adding glucose to the incubation setting ($F_{3,27}$=2.19, p=0.113).

| **Glucose, mg/ml** | **0** | **1.25 mg/ml** | **2.5 mg/ml** | **5.0 mg/ml** |
|---|---|---|---|---|
| **TNFα, pg/ml** | | | | |
| Non-stimulated | 265±44 | 248±37 | 227±35 | 240±33 |
| LPS-stimulated | 889±54 | 932±62 | 901±64 | 935±78 |
| HT-29-stimulated | 1684±189 | 1532±143 | 1726±164 | 1866±158* |
| RKO-stimulated | 1155±164 | 1081±133 | 1238±143 | 995±145* |
| **IL-1β, ng/ml** | | | | |
| Non-stimulated | 0.62±0.11 | 0.60±0.06 | 0.47±0.03 | 0.47±0.03 |
| LPS-stimulated | 4.88±0.63 | 5.13±0.51 | 4.85±0.27 | 4.7±0.39 |
| HT-29-stimulated | 6.00±0.53 | 5.36±0.49*** | 5.36±0.47*** | 5.08±0.50*** |
| RKO-stimulated | 1.76±0.35 | 1.93±0.26 | 1.89±0.71 | 1.56±0.25 |
| **IL-6, ng/ml** | | | | |
| Non-stimulated | 7.08±1.09 | 6.87±0.80 | 7.75±1.74 | 7.88±1.32 |
| LPS-stimulated | 28.64±1.8 | 29.18±1.18 | 29.1±1.40 | 28.89±1.34 |
| HT-29-stimulated | 28.62±1.5 | 30.03±2.0 | 30.39±1.8 | 31.44±1.7 |
| RKO-stimulated | 17.11±3.12 | 17.45±3.47 | 2046±4.22 | 17.99±3.31 |
| **IFNγ, ng/ml** | | | | |
| Non-stimulated | 0.93±0.11 | 0.81±0.08 | 0.70±0.08* | 0.71±0.08* |
| PMA/ionomycin | 20.6±2.5 | 21.2±3.2 | 19.7±2.4 | 21.7±1.9 |
| HT-29-stimulated | 2.29±0.40 | 1.99±0.46 | 1.9±0.41** | 1.89±0.39** |
| RKO-stimulated | 1.3±0.6 | 1.0±0.4 | 1.5±0.7 | 1.6±0.7 |
| **IL-2, ng/ml** | | | | |
| Non-stimulated | 0.77±0.21 | 0.92±0.27 | 0.73±0.22 | 0.78±0.26 |
| PMA/ionomycin | 24.7±1.82 | 25.4±1.25 | 24.2±1.33 | 24.0±1.40 |

**Table 1:** Effect of glucose on proinflammatory cytokine production by PBMC

Non-stimulated PBMC (spontaneous) or cells stimulated with LPS, PMA, or one of the HT-29 or RKO colon cancer cell lines were incubated for 24 hrs without (0) or with glucose at concentrations as indicated. The level of cytokines in the supernatants was tested by ELISA. The results are expressed as Mean ± SEM of 5-18 experiments. P* value represents statistically significant difference from cells incubated without glucose (*p<0.05, **p<0.01, ***p<0.001).

### 3.3 Effect of glucose on anti-inflammatory cytokine secretion (Table 2)

A concentration-dependent inhibition of IL-10 secretion was found when non-stimulated PBMC or cells stimulated with either HT-29 or RKO colon cancer cells were incubated for 24 hrs with glucose at 1.25mg/ml to 5 mg/ml ($F_{3,36}$=9.2, p<0.001; ($F_{3,36}$=7.43, p<0.001, $F_{3,27}$=11.2, p<0.001, respectively). The secretion of IL-10 by LPS-stimulated PBMC was not affected by addition of glucose ($F_{3,12}$=0.3, p=0.82). At glucose concentration of 1.25mg/ml, 2.5 mg/ml and 5 mg/ml the spontaneous secretion of IL-10 was reduced by 5% (NS), 25% and 33% (p<0.005), respectively, whereas that induced by HT-29 was inhibited by 15% for the three glucose concentrations (p<0.01). IL-10 secretion induced by RKO cells was lowered by 12% (p=0.03) and 23% (p<0.001) at glucose concentrations of 2.5mg/ml and 5 mg/ml, respectively. Incubation with glucose had no effect on the production of IL-1ra by non-stimulated PBMC ($F_{3,21}$=0.26, p=0.85) or by PBMC stimulated with LPS ($F_{3,12}$=3.31, p=0.057), HT-29 cells ($F_{3,22}$=0.506, p=0.506) or RKO cells ($F_{3,27}$=1.55, p=0.225).

| **Glucose, mg/ml** | 0 | 1.25 | 2.5 | 5 |
|---|---|---|---|---|
| **IL-10, pg/ml** | | | | |
| Non-stimulated | 0.49±0.11 | 0.47±0.12 | 0.37±0.09** | 0.33±0.08** |
| LPS-stimulated | 0.95±0.30 | 0.91±0.23 | 0.92±0.28 | 0.92±0.24 |
| HT-29-stimulated | 2.69±0.16 | 2.25±0.15** | 2.29±0.14* | 2.29±0.14** |
| RKO-stimulated | 1.06±0.24 | 1.02±0.23 | 0.94±0.21* | 0.84±0.2*** |
| **IL-1ra, ng/ml** | | | | |
| Non-stimulated | 0.79±0.34 | 0.76±0.36 | 0.77±0.37 | 0.75±0.25 |
| LPS-stimulated | 0.87±0.05 | 0.81±0.06 | 0.83±0.02 | 0.80±0.03 |
| HT-29-stimulated | 1.01±0.05 | 0.97±0.05 | 0.96±0.05 | 1.00±0.07 |
| RKO-stimulated | 0.86±0.05 | 0.87±0.05 | 0.89±0.06 | 0.81±0.04 |

**Table 2:** Effect of glucose on anti-inflammatory cytokine production by PBMC

Non-stimulated PBMC (spontaneous) or cells stimulated with LPS, or one of the HT-29 or RKO colon cancer cell lines were incubated for 24 hrs without (0) or with glucose at concentrations as indicated. The level of cytokines in the supernatants was tested by ELISA. The results are expressed as Mean ± SEM of 5-15 experiments. P* value represents statistically significant difference from cells incubated without glucose (*p<0.05, **p<0.01, ***p<0.001).

## 4. Discussion

The results indicate that glucose, separately incubated with PBMC, HT-29 and RKO cells at concentrations used in the study did not affect significantly cell proliferation. Bearing in mind the role of glucose as an important energy supplier for normal and cancer cells' development and proliferation [16-18], these findings are rather surprising. The fact that macrophage activity, including cell proliferation proceeds through various pathways triggered by a large number of metabolic signals absent in vitro [19,20] could explain the lack of glucose on cell proliferation in the

present work. Hosios et al. [21] have found that although the rate of glucose consumption supports cell proliferation, amino acids are a better provider of carbon in proliferating mammalian cell mass. Polysaccharides containing glucose have been able to inhibit proliferation of HT-29 colon cancer cells in a time- and dose dependent manner [20]. It is conceivable, therefore that proliferating cells respond differently and concentration-dependently to the effect of glucose.

Studies have shown that elevated glucose concentrations activate monocytes and macrophages for cytokine production. Incubation of human monocytes obtained from healthy individuals and differentiated to macrophages by high glucose levels showed down-regulation of IL-10 compared to control cells. Moreover, monocytes from hyperglycemic patients produced less IL-10 than those of individuals with normal glucose [22]. In a study comprising 38 pre-diabetic, but otherwise healthy subjects, the proinflammatory M monocytes were significantly increased compared to healthy controls indicating the existence of monocyte polarization in this condition [23]. PBMC from healthy individuals with induced hyperglycemia of two hours duration showed decreased transcription of IL-6 and IL-17. Similar findings were obtained following incubation of monocytes with high glucose levels [24]. It has been reported that feeding induces an increase in the number of peritoneal macrophages secreting IL-1β and that this cytokine is closely connected with the uptake of glucose into the cells [25]. However, the production of IL-1β by circulating monocytes was found to be flawed in patients with type two diabetes and improved with control of the glucose level [26]. High glucose treatment of human monocytes induced increased expression of proinflammatory cytokines including TNFα and IL-1β [27,28]. As for the capacity of glucose to stimulate PBMC to produce cytokines, non-stimulated cells in the present work showed abolished production of IFNγ and IL-10, whereas this activity by LPS-stimulated cells did not differ from controls.

The results became quite diverse when PBMC were stimulated for cytokine production by the colon cancer cells, predominantly HT-29. In this case, the production of IL-1β, IFNγ and IL-10 was significantly inhibited, while that of TNFα was only slightly promoted by the highest concentration of glucose used in the study. The secretion of IL-6, IL-1ra and IL-2 was not affected at all. Addition of glucose to PBMC co-incubated with RKO cells induced a marked inhibition of IL-10 secretion and a less pronounced one of TNFα by the higher concentration. Otherwise there was no change in the production of the remaining cytokines compared to controls. The results are in accordance with those reported by Wu et al. [29] who did not obtain any effect of glucose on IL-1β, IL-6 and IL-10 production by PBMC of nine healthy individuals.

The link between elevated glucose levels and cancer has been repeatedly demonstrated. In a survey conducted on 140,000 adults Rapp et al. [13] have shown a decisive association between fasting blood glucose level and incidence of various types of cancer including hematological malignancies. Similar results were obtained on a population of 1,298,385 men and women in Korea [12]. Likewise, a positive association has been demonstrated between self-reported diabetes and cancer [11]. The increased glucose metabolism in cancer cells is enhanced by the presence of transmembrane transporters located on the cancer cell membrane [30].

## 5. Conclusion

The salient outcome of the present study is demonstration of a distinct glucose effect on the cross-talk between PBMC and colon cancer cells from the two lines hereby examined. PBMC co-incubated with HT-29 cells vividly responded by a decreased generation of IL-1β, IFNγ and IL-10, following addition of glucose. The altered production of inflammatory cytokines by PBMC induced by colon cancer cells in the presence of glucose may explain the sequential link between elevated glucose level, maintenance of chronic inflammation and tumorigenesis. A change in the normal equilibrium of intestinal microbiota with a perpetuated chronic inflammation due to hyperglycemia may contribute to the proceeding of this process [31,32].

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## Declarations

The authors declare that they have no competing interests.

**Authors' contributions** – HB and MD took equal party in conceiving, development and carrying out the research idea. HB was concerned with the laboratory studies. Both authors were engaged in discussing, writing and revising the manuscript.

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