Human Anti-CD38 Autoantibodies Raise Intracellular Calcium and Stimulate Insulin Release in Human Pancreatic Islets

Alessandro Antonelli,1 Germano Baj,2,3 Piero Marchetti,4 Poupak Fallahi,1 Nicola Surico,3 Cinzia Pupilli,5 Fabio Malavasi,2 and Ele Ferrannini1

CD38 is involved in transmembrane signaling in many cell types; anti-CD38 autoantibodies have been described in diabetic patients. We tested whether human anti-CD38 antibodies possess signaling properties by measuring their ability to raise intracellular calcium ([Ca2+]i) using the fluo-3-acetoxymethyl ester method in a human-derived T-cell line (Jurkat T-cells, expressing high levels of surface CD38) and in dispersed human islet cells from normal donors. In Jurkat T-cells, 11 of 19 anti-CD38-positive sera raised [Ca2+]i, (by ≥20% of baseline), whereas no [Ca2+]i-mobilizing activity was found in 27 anti-CD38-negative sera (χ² = 20.5, P < 0.0001). In dispersed human islet cells, 5 of 11 anti-CD38-positive sera (and none of three anti-CD38-negative sera) raised [Ca2+]i significantly. When preincubated with Staphylococcus aureus protein A to remove IgG, anti-CD38-positive sera showed a 70 ± 5% reduction in [Ca2+]i-mobilizing activity. Preincubation with CD38-transfected NIH-3T3 fibroblasts, but not with mock-transfected NIH-3T3 cells, abolished [Ca2+]i mobilization. In blocking experiments, preincubation with nonagonistic anti–CD38 monoclonal antibodies also prevented [Ca2+]i mobilization. In cultured human islets, anti-CD38-positive sera exhibiting [Ca2+]i-mobilizing activity in Jurkat T-cells (n = 6) significantly stimulated insulin release at 3.3 mmol/l glucose (median [interquartile range] 738 μU/ml [234], P = 0.0001 vs. 320 [52] μU/ml of control), whereas 6 anti-CD38-positive sera without [Ca2+]i-mobilizing activity and 10 anti–CD38-negative did not. In further incubations, the five anti-CD38-positive sera displaying [Ca2+]i-mobilizing activity in dispersed islet cells significantly stimulated insulin release at both 3.3 mmol/l glucose (2.2 ± 0.3% of insulin islet content, P < 0.002 vs. 1.2 ± 0.1% of control) and 16.7 mmol/l glucose (3.7 ± 0.3 vs. 2.3 ± 0.3%, P < 0.002). We conclude that human anti-CD38 autoantibodies with agonistic properties on the CD38 effector system occur in nature; in human islets, their [Ca2+]i-mobilizing activity is coupled with the ability to stimulate insulin release. Diabetes 50:985-991, 2001

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uman CD38 is a surface and cytosolic glycoprotein endowed with pleiotropic functions (1). One is that of a bifunctional enzyme with both ADP-ribosyl cyclase and hydrolase activity. CD38 is also a surface receptor involved in transmembrane signaling in different cell types (2,3). CD38 is expressed on the surface of monocytes, platelets, NK cells, T- and B-cells, myeloid cells, vascular endothelium, and in tissues such as brain, cardiac and skeletal muscle, spleen, heart, liver, prostate, and kidney (4). Recent studies suggest that CD38 is also expressed in rat (3) and human pancreatic islets (4). According to a model originally proposed by Okamoto et al. (5), in β-cells glucose-induced ATP synthesis inhibits cyclic ADP-ribose (cADPR) degradation by CD38, thereby leading to a preponderance of the cyclase activity and an accumulation of cADPR. This second messenger binds to ryanodine receptors, thereby triggering a cytoplasmic Ca2+ wave that depolarizes the membrane and favors further Ca2+ influx from the extracellular fluid. The resulting increase in intracellular Ca2+ concentration ([Ca2+]i) leads to insulin release.

Autoantibodies reacting with CD38 have been found in ~12% of Japanese patients with type 2 diabetes (6). In rat pancreatic islets, these anti-CD38 antibodies inhibit the cyclase activity of CD38, thereby diminishing cADPR synthesis and, consequently, insulin release (6). Recently, we have reported the presence of anti–CD38 antibodies in ~10% of Caucasian patients with type 2 or type 1 diabetes (7). In cultured human islets, these autoantibodies exert a stimulatory effect on insulin release both at low and high glucose concentrations, thus mimicking the action of anti–CD38 monoclonal antibodies (mAbs) (7).

The aim of the present study was to test whether human anti–CD38-positive sera influence [Ca2+]i. To do this, we used both a human-derived T-cell line expressing high levels of surface CD38 molecule (Jurkat T-cells) and dispersed human islet cells. To evaluate the association between the [Ca2+]i-modulating activity and the biological effect of anti–CD38 antibodies, sera were simultaneously
tested on human pancreatic islets for their ability to stimulate insulin release.

**RESEARCH DESIGN AND METHODS**

**Detection of anti-CD38 antibodies.** The clinical characteristics of the population screened for anti-CD38 autoimmunity and the methods for the detection of anti-CD38 antibodies have been reported previously (7). Briefly, recombinant CD38–maltose binding protein (MBP) fusion protein (rCD38-MBP) (68 kDa) was obtained from a human CD38 cDNA encoding amino acids 45–300 (8). Then, 10 µg of rCD38-MBP was separated on a 10% SDS polyacrylamide gel and transferred to a polyvinylidene fluoride membrane. The membranes were subsequently blocked with a solution of phosphate-buffered saline (PBS) containing 5% nonfat dry milk and 0.15% Tween-20 and incubated for 60 min. Sera from diabetic patients and control subjects were diluted (1:10,000) in the same buffer. After rinsing with PBS containing 0.15% Tween-20, the membranes were incubated for 60 min with a purified rabbit Ig specific for human Ig (G+M) labeled with horseradish-peroxidase. The signals were revealed by using an enhanced chemiluminescence detection system; the intensity of the bands was measured by densitometry (7). For the present study, 46 sera were used: 34 from type 2 diabetic patients (13 men and 21 women, mean age 60 ± 9 years) and 12 from healthy controls (5 men and 7 women, mean age 58 ± 10 years).

**mAbs and polyclonal antibodies.** B4 (an agonistic anti-CD38 mAb, IgG2a), used as the intact molecule or the F(ab')2 fragment, was used as the reference agonistic mAb. IB6 (anti-CD38 mAb, IgG2a) and OKT10 (anti-CD38 mAb, IgG1), both nonagonistic mAbs, were used to compete with CD38 binding by autoantibodies in blocking experiments. CB-45 (anti-CD38 mAb, IgG1) and CB-ICAM-1 (anti-CD54, IgG2a) were used as isotype controls. All mAbs used in the [Ca^{2+}]i mobilization experiments were purified by affinity chromatography and high-performance liquid chromatography on hydroxylapatite and prepared pyrogen-free in the laboratory (9).

**T-cell line.** Jurkat T-cells, a human T-cell acute lymphocytic leukemia line closed by limiting dilution or positively selected by MACS (Miltenyi Biotech GmbH, Bergisch-Gladbach, Germany) to obtain a population displaying a homogeneous CD3 CD38 CD31 phenotype, were cultured in RPMI-1640 medium supplemented with penicillin, streptomycin, glutamine, and 10% fetal calf serum (FCS) (Seromed; Biochrom KG, Berlin), herein referred to as complete medium. Murine NIH-3T3 fibroblasts stably transfected with human CD38 gene and mock-transfected controls were obtained as described (10) and maintained in complete medium.

**Human islets.** Isolation and culture of pancreatic islets from human donors were performed as previously described (7,11,12). Briefly, islets were prepared by collagenase digestion and density-gradient purification from the pancreas of human cadaver donors referred to the local organ-procurement organization (with the permission of the Institutional Ethics Committee of the University of Pisa School of Medicine). At the end of the isolation procedure, islets were resuspended in M199 tissue culture medium supplemented with 10% serum and antibiotics and kept at 37°C in a 5% CO2 atmosphere.

**Dispersed human islet cells.** Islets were dissociated into single cells according to previously reported procedures (13). Briefly, islets were gently resuspended in a calcium-free Krebs-Ringer-HEPES buffer with 1 mMol/l EGTA at 30°C. After 5 min, trypsin (16.5 µg/ml) and DNAase (2 µg/ml) were added, and a further 8- to 10-min incubation at 30°C was allowed. Islet cell dissociation was monitored by observing aliquots of the suspension under an inverted light microscope. When most cells were single or in small groups of two to three, the procedure was stopped by adding Krebs-Ringer bicarbonate (KRB) buffer containing 1.67 mMol/l calcium and 1% calf serum. At the end of the procedure, islets were washed with PBS, resuspended in M199 culture medium, and eventually placed at 37°C in a CO2 incubator.

**[Ca^{2+}]i mobilization experiments.**

**Jurkat T-cells.** Changes in [Ca^{2+}]i levels in Jurkat T-cells were monitored by flow cytometry after loading cells with fluo-3-acetoxymethyl ester (fluo-3-AM), a [Ca^{2+}]-sensitive fluorescent dye, and 4-bromo A23187 ionophore. Fluo-3-AM, 10 µmol/l of Jurkat cells (10 7 cells/ml in complete medium). Murine NIH-3T3 fibroblasts stably transfected with human CD38 gene and mock-transfected controls were obtained as described (10) and maintained in complete medium.

**CD38 blocking experiments.** CD38 blocking experiments were performed in an attempt to identify the serum component(s) responsible for [Ca^{2+}]i mobilization. Jurkat T-cells were loaded with fluo-3-AM and incubated (10 min at room temperature) with a mixture of IB6 and OKT10 (nonagonistic anti-CD38 mAbs)—both at 10 µg/ml—used as a blocking tool. A mixture of BI-ICAM-1 and CB-gp120 (17)—both used at the same concentrations as above—was used as control. Sera were then assayed on these cells for their ability to mobilize [Ca^{2+}]i.

**Assay of insulin secretion.** Within 7–12 days of isolation, the insulin secretory function of the islets in response to 3.3 mMol/l glucose was assessed by the batch incubation method, as previously reported (13,18). Groups of islets of comparable size (~500tube) were preincubated at 37°C for 45 min in KRB solution and supplemented with 5.5 mMol/l glucose and 0.5% BSA. The islets were then washed and incubated at 37°C in 1 ml of medium containing 3.3 mMol/l glucose, either with or without the addition of 10% anti-CD38-positive or anti-CD38-negative serum. For each test serum, two to four groups of islets were incubated separately. At the end of the incubation period, aliquots of the medium were collected for the measurement of insulin concentration.

To control for the inherent effect of serum islet exposure to high glucose (16), in additional islet preparations, 14 of the 22 sera tested as above were reassayed by measuring insulin islet content using acid alcohol extraction (13,18); the insulin secretory response to 3.3 or 16.7 mMol/l glucose was expressed as percentage of total islet hormone content. At 3.3 mMol/l glucose, there was a positive relationship between insulin release expressed as insulin concentration in the medium and as percentage of total islet content (r = 0.59, P < 0.04).

**Data analysis.** Sera were considered to be positive for anti-CD38 autoantibody (anti-Sigma), and a threshold for positive response was defined as the optical density with undefined serum components or contaminants, sera were considered to be negative. To differentiate agonistic activity mediated by CD38 signaling after autoantibody ligation from artifacts related to the presence of undefined serum components or contaminants, sera were considered to be negative for anti-CD38 autoantibodies if the optical density on the Western blot was equal to 3 SD above the mean of the previously reported control group (i.e., ≥1.9 units) (7).

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Data are given as means ± SE. Because of their nonnormal distribution, insulin concentrations are given as median and interquartile range and were log-transformed for use in parametric statistical analyses. Comparison of median group values was performed by analysis of variance (ANOVA); simultaneous testing for group and treatment was performed by two-way ANOVA, with Bonferroni-Dunn post hoc testing for individual group comparisons. The χ2 test was used as a measure of association between categorical variables.
RESULTS

Detection of anti–CD38 autoantibodies. On the Western blot, a band of ~68 kDa was observed in the sera of some diabetic patients and normal subjects. The signals were abolished by preincubating anti–CD38-positive sera with human recombinant CD38, whereas preincubation with LacZ(β-galactosidase)-MBP did not affect reactivity with the CD38 target. T16, an anti–human CD38 mAb, yielded a pattern similar to that obtained with anti–CD38-positive human sera. While we were immunoblotting sera containing putative anti–CD38 autoantibodies against recombinant CD38 from *Pichia pastoris*, a band of apparent molecular mass of ~30 kDa (corresponding to the soluble CD38) was revealed; also evident was a second band of higher molecular weight, as previously reported (19). No signals were produced by sera lacking anti–CD38 activity.

When preincubated with *S. aureus* protein A to remove IgG, anti–CD38-positive sera with [Ca^{2+}]_i-mobilizing activity showed a 70 ± 5% reduction in activity (4 of 4 sera) (Fig. 3), indicating that the native [Ca^{2+}]_i-mobilizing activity was likely due to IgG. In contrast, no change was observed when the same treatment was applied to sera without [Ca^{2+}]_i-mobilizing activity, whether they were positive or negative for anti–CD38 autoantibodies.

To rule out unknown effects of serum IgGs other than those reacting with CD38, sera were incubated with CD38-transfected NIH-3T3 fibroblasts (CD38/NIH-3T3). Preincubation of anti–CD38-positive sera with CD38/NIH-3T3 fibroblasts abolished [Ca^{2+}]_i mobilization (Fig. 3C), whereas no effect was observed with the preincubation with mock-transfected (CD38-negative) NIH-3T3 cells, indicating specific absorption of the anti–CD38 autoantibodies.

To verify that blocking CD38 counteracted native [Ca^{2+}]_i-mobilizing activity, Jurkat T-cells were first preincubated with saturating concentrations (50 mg/ml) of IB6 and OKT10 (two nonagonist anti–CD38 mAbs) then used in [Ca^{2+}]_i mobilization in Jurkat T-cells. We first tested the ability of sera (*n = 46*) to induce changes in [Ca^{2+}]_i in Jurkat T-cells. The results of the experiments are summarized in Table 1. Of 19 anti–CD38-positive sera, 11 (58%) showed significant (>20% of basal) increases in [Ca^{2+}]_i (Fig. 2), whereas no [Ca^{2+}]_i-mobilizing activity was found in 27 anti–CD38-negative sera ($\chi^2 = 20.5, P < 0.0001$ for the association between CD38 positivity and [Ca^{2+}]_i-mobilizing activity).

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![FIG. 1. Western blot of a human serum with activity against recombinant CD38 from *P. pastoris* without preincubation (lanes A and D) or with preincubation with recombinant CD38 (lane B) or with *S. aureus* protein A (lane C); preabsorption with recombinant CD38 or removal of IgG cancels the band at ~30 kDa (soluble CD38).](image)

![FIG. 2. [Ca^{2+}]_i-mobilizing effects induced by sera from two anti–CD38-positive (D WB*) diabetic patients, two anti–CD38-negative diabetic patients (D WB*), and two anti–CD38-negative normal individuals (NI WB*) on Jurkat T-cells. Data are presented as color density plots of the shift in fluo-3-AM fluorescence over a 540-s time course. Colors represent intervals of event numbers and have a linear spacing (10%) between them. The representative experiments show that [Ca^{2+}]_i mobilization is elicited by sera from WB* diabetic patients.](image)

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*CD38* and CD38*: positive or negative for anti–CD38 activity; CaM*+* and CaM*−* = positive or negative for [Ca^{2+}]_i-mobilizing activity.

TABLE 1

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*CD38* and CD38*: positive or negative for anti–CD38 activity; CaM*+* and CaM*−* = positive or negative for [Ca^{2+}]_i-mobilizing activity.
mobilization assays. In these experiments, anti-CD38-positive sera eliciting a $[\text{Ca}^{2+}]_i$ response in untreated cells lost their $[\text{Ca}^{2+}]_i$-mobilizing activity after preincubation with either IB6 or OKT10, suggesting transmembrane signaling mediated by the CD38 molecule (Fig. 3D). In fact, CB-gp120 and CB-ICAM-1 mAbs, used as controls, were ineffective in blocking serum-induced $[\text{Ca}^{2+}]_i$-mobilization.

**Mobilization of $[\text{Ca}^{2+}]_i$ in dispersed human islet cells.** Incubation of dispersed islet cells with 16 mmol/l glucose caused a prompt and sustained threefold increase in $[\text{Ca}^{2+}]_i$ (Fig. 4), demonstrating that the cell preparation protocol yielded functional β-cells. Incubation of a separate sample from the same cell preparation with an anti-CD38-positive serum gave a less intense (approximately twofold) but clearly detectable increase in $[\text{Ca}^{2+}]_i$ (Fig. 4). This signal disappeared when cells were preincubated with a mixture of IB6 and OKT10 (nonagonistic anti-CD38 mAbs). An anti-CD38-negative serum gave no signal.

A total of 14 sera, 11 of which were positive for anti-CD38 autoantibodies, were tested in islet cells; 5 sera positive for anti-CD38 displayed significant $[\text{Ca}^{2+}]_i$-mobilizing activity (Table 1).

**Insulin release from human islets.** We first tested whether CD38 positivity or $[\text{Ca}^{2+}]_i$-mobilizing activity in Jurkat T-cells was associated with stimulation of insulin release in isolated human islets. In islets cultured with 3.3 mmol/l glucose, 22 sera were tested, of which 6 were anti-CD38-positive and had $[\text{Ca}^{2+}]_i$-mobilizing activity, 6 were anti-CD38-positive but devoid of $[\text{Ca}^{2+}]_i$-mobilizing activity, and 10 had neither CD38 positivity nor $[\text{Ca}^{2+}]_i$-mobilizing activity (no anti-CD38-negative sera were found to have detectable $[\text{Ca}^{2+}]_i$-mobilizing activity). The
results show that the six anti–CD38-positive sera with 
[Ca^{2+}]_i-mobilizing activity induced significantly (P = 0.002) greater insulin release than control incubations, whereas sera without [Ca^{2+}]_i-mobilizing activity, whether CD38 positive or negative, did not (Fig. 5).

Finally, we tested whether sera exhibiting [Ca^{2+}]_i-mobilizing activity in dispersed human islet cells were also capable of stimulating insulin release in cultured human islets. In nine control incubations with 3.3 mmol/l glucose and five control incubations with 16.7 mmol/l glucose, insulin in the medium averaged 1.17 ± 0.07 and 2.30 ± 0.35%, respectively, of total islet insulin content. When incubated with sera positive for anti–CD38 and [Ca^{2+}]_i-mobilizing activity (n = 5), cultured islets showed an increase in insulin release at both 3.3 and 16.7 mmol/l glucose, whereas sera positive for anti–CD38 but not [Ca^{2+}]_i-mobilizing activity (n = 6) and sera negative for both anti–CD38 and [Ca^{2+}]_i-mobilizing activity (n = 6) did not stimulate insulin release at either glucose concentration (P < 0.0001 for the effect of glucose and P < 0.002 for the effect of group by two-way ANOVA) (Fig. 6).

In a total of 14 sera, [Ca^{2+}]_i-mobilizing activity in dispersed human islet cells was well correlated both with [Ca^{2+}]_i-mobilizing activity in Jurkat T-cells and with insulin release at 3.3 mmol/l glucose in cultured islets (Fig. 7).

DISCUSSION
The present work confirms that human sera reacting with recombinant CD38 during immunoblotting contain IgG autoantibodies that recognize recombinant CD38 from P. pastoris (i.e., the soluble CD38). The new finding is that sera containing anti–CD38 reactive autoantibodies consistently stimulate [Ca^{2+}]_i in Jurkat T-cells, a human T-cell clone displaying a homogeneous CD3^+CD38^-CD31^- phenotype. In the 46 human sera tested, the association between anti–CD38 reactivity and [Ca^{2+}]_i-mobilizing activity, though incomplete (~50%), was highly significant statistically. The [Ca^{2+}]_i-mobilizing activity was largely lost when anti–CD38-positive sera were either depleted of their IgG or preincubated with murine fibroblasts transfected with human CD38 or when CD38 was specifically blocked by nonagonist anti–CD38 mAbs. Thus, the native anti–CD38 IgG autoantibodies not only bind to the soluble protein but also deliver an intracellular signal. To our knowledge, these results provide the first evidence that autoantibodies with agonist properties on the CD38 effector system—i.e., [Ca^{2+}]_i—occur in nature. These findings also support the receptor nature of the CD38 molecule and its ability to activate outside/inside signaling (20). Furthermore, they indirectly confirm the existence of one or more ligands (14), whose interaction with functional domains of the CD38 molecule is mimicked by the natural autoantibodies. Recent work in the MC3T3.E1 cell line (21) has demonstrated the presence of CD38 on the inner nuclear membrane, where it triggers nucleoplasmic Ca^{2+} release through the intranuclear cyclization of NAD to cADPR. Taken together, these observations support the notion that CD38 modulates Ca^{2+} homeostasis in both cytosolic and nucleoplasmic cellular compartments. The biological effects of CD38 activation depend on the cell type as well as the intracel-

FIG. 4. [Ca^{2+}]_i-mobilizing in dispersed human islet cells exposed to an anti–CD38-positive serum before (WB^+) and after pretreatment with a mixture of nonagonistic mAbs (IB6/OKT10+WB^+), to an anti–CD38-negative serum (WB^-), and to 16 mmol/l glucose.

FIG. 5. Insulin release by cultured human islets exposed to 3.3 mmol/l glucose after incubation without (control) or with (serum) sera previously tested for their anti–CD38 activity (CD38^+/-) and [Ca^{2+}]_i-mobilizing activity in Jurkat T-cells (Ca^{2+/-}). *P = 0.002 for the comparison between control and serum.
lular localization of the Ca\(^{2+}\) transients evoked by cADPR binding. Thus, through nucleoplasmic Ca\(^{2+}\) waves, CD38 may transduce metabolic stress (signaled by the amount of NAD generated by metabolic activity) to highly Ca\(^{2+}\)-sensitive nuclear processes, such as gene transcription and apoptosis, as seen in T-cells (15).

The relevance of CD38 agonism to the modulation of [Ca\(^{2+}\)]\(_i\) in \(\beta\)-cells has been debated (22). For example, it has been difficult to reproduce both cADPR increases by glucose in rat pancreatic islets (23) and Ca\(^{2+}\) release by cADPR in rat islets, \(ob/ob\) mouse \(\beta\)-cells, and RINm5F or INS-1 cell lines (24–26). On the other hand, Okamoto et al. (5) have produced in vitro and experimental evidence that stimulation of CD38 activity is involved in insulin stimulus-secretion coupling. According to their results, cADPR accumulates in response to glucose stimulation in rat islets (27) and cADPR releases Ca\(^{2+}\) in rat islet microsomes (28).

To address this issue directly, we measured [Ca\(^{2+}\)]\(_i\) in human islet cells. In our study, half of the anti–CD38-positive sera (and none of the anti–CD38-negative sera) produced a clear-cut increment in [Ca\(^{2+}\)]\(_i\). This response, which was approximately one-third the magnitude of that elicited by high glucose, was specific, because it could be blocked by nonagonistic mAbs. Moreover, in the 14 human sera that could be tested in both cell systems, there was a very good correspondence between the ability of sera to generate a Ca\(^{2+}\) signal in Jurkat T-cells and in human islet cells. The only precedent for our finding that we are aware of is the study by Juntti-Berggren et al. (29), in which sera from four patients with type 1 diabetes (two of whom had the disease diagnosed after the age of 40 years) were found to increase the activity of \(\alpha\)-type Ca\(^{2+}\) channels in mouse \(\beta\)-cells, RINm5F cells, and in a cell line (GH 3) derived from a pituitary tumor. Interestingly, the [Ca\(^{2+}\)]\(_i\)-mobilizing activity of these sera was lost after depletion of immunoglobulins and could not be identified with anti-

GAD autoantibodies. In that study, the insulin secretory response was not measured, but prolonged (48-h) incubation of RINm5F cells with these sera was associated with enhanced DNA fragmentation.

With regard to the physiological consequences of raising [Ca\(^{2+}\)]\(_i\) by CD38 agonism in \(\beta\)-cells, our previous work in cultured human islets (7) demonstrated that human anti-CD38-positive sera generally stimulate insulin release. We now report that the insulin-stimulating activity of anti-CD38-positive sera is largely restricted to those displaying [Ca\(^{2+}\)]\(_i\)-mobilizing activity in Jurkat T-cells (Fig. 5) or human islet cells (Fig. 6). In fact, the observed stimulation of insulin release was roughly proportional to the [Ca\(^{2+}\)]\(_i\)-mobilizing activity (Fig. 7). Therefore, our findings are a strong indication that the ability of antibodies raised against CD38 to stimulate insulin release is mediated by intracellular Ca\(^{2+}\) mobilization.

The overall role that native CD38 autoimmunity may play in the \(\beta\)-cell dysfunction of human diabetes remains...
to be defined. It is possible that chronic stimulation of insulin release may lead to β-cell exhaustion, a phenomenon long suspected to underlie the progression of normal glucose tolerance to clinical hyperglycemia in obese subjects (30). Alternatively, stimulating anti-CD38 antibodies may sustain insulin release by β-cells that are failing under the pressure of genetic programming or environmental insults. Finally, the biologically relevant consequences of autoimmune CD38 activation may be the longer-term effects mediated by nucleoplasmic [Ca2+]i mobilization—i.e., gene expression and apoptosis (21,29)—rather than effects mediated by nucleoplasmic [Ca2+]i transient. To complicate the matter, in animal models of diabetes, CD38 expression is reduced and cADPR generation is downregulated (5). Consequently, the impact of CD38 autoimmunity may be different in islets of diabetic and nondiabetic subjects.

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REFERENCES


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