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Dysregulated pathways in type 2 diabetes mellitus.

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Abstract

Objective: Type 2 Diabetes Mellitus (T2DM) is a leading health problem worldwide. In this study, we aimed to identify the pathways significantly relevant to T2DM, and a brief review based on these pathways was made.
Materials and methods: The genes associated with T2DM were extracted by text mining tool from literature database. Then we employed the Fisher's exact test based on the cumulative hypergeometric distribution to evaluate the pathways relevant to T2DM.
Result: A total of 135 genes associated with T2DM were confirmed and 76 pathways significantly relevant to T2DM were identified from 880 cellular pathways. These 76 pathways could be classified mainly in five classes: adipocytokine, inflame, PPAR, insulin and T2DM pathway. Adipocytokine pathway from KEGG database was the most relevant pathway.
Conclusion: Disregulation of adipocytokine and inflammatory pathway is the hallmark of T2DM originated from the organism in the status of excess energy over long time span.

Keywords: Type 2 diabetes mellitus, Pathways, Dysregulation, Adipocytokine, Insulin.

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Introduction

Type 2 Diabetes (T2DM) has become a leading health problem worldwide. According to the International Diabetes Federation, the total number of the patients with diabetes is predicted to rise to 552 million by the year of 2030 [1]. Furthermore, the patients with T2DM tended to develop cardiovascular disease and other vascular complications such as peripheral vascular disease, diabetic nephropathy, and diabetic retinopathy and so on. It is widely accepted that T2DM is a complex disease as a joint action of genetic background and environmental factor. Therefore, great efforts have been made to identify the genes associated with T2DM, and a number of genes have been identified. The genes always performed biological function in cooperation way rather than alone, particularly in complex diseases. In the development of T2DM, the signaling pathway of pathological mechanism was more important than individual genes. Admittedly, there were a great number of signaling pathways related to T2DM, which were discussed in the medicine literature database.

In this study, we reviewed signaling pathways related to T2DM, which was identified as dysregulated pathway associated with disease [2-5]. As refer to system review, meta-analysis was also employed to evaluate the parameters from different studies. The genes associated with T2DM by text mining tool were extracted from literature database. Then we employed the Fisher's exact test based on the cumulative hypergeometric distribution to evaluate the pathways relevant to T2DM.

Method

Construction of cellular pathways database

All of the pathways with the gene members were downloaded from an integrated pathway database Molecular Signatures Database (MSigDB) [6], which is a large collection of annotated functional gene sets. There are 880 canonical pathways with 6804 genes members in the database, including the metabolic and signaling pathways collected from Biocarta (www.Biocarta.com), KEGG [7], and Reactome [8].

Extraction of genes related to T2DM from the literature

We searched candidate genes associated with T2DM by PolySearch text mining system, which can produce a list of concepts relevant to the user's query by analyzing multiple information sources including PubMed, OMIM, DrugBank and Swiss-Prot. It covers many types of biomedical concepts

including diseases, genes/proteins, drugs, metabolites, SNPs, pathways and tissues [9]. The query type is 'Disease-Gene/ Protein Association' and the query keyword is 'type 2 diabetes'. PolySearch system returns 1325 literatures. To check the accuracy, we manually confirmed whether these genes were associated with the T2DM. Finally a total of 135 candidate genes were obtained (Table 1).

Table 1. Top 10 statistically relevant pathways with T2DM ranked by P-value

SN	Pathway Name	Class	p-value
1	KEGG adipocytokine signaling pathway	Adipocytokine	3.17E-07
2	KEGG type ii diabetes mellitus	T2DM	4.88E-07
3	BIOCARTA PPARA pathway	PPAR	6.56E-07
4	BIOCARTA cytokine pathway	Inflammation	1.91E-06
5	BIOCARTA INFLAM pathway	Inflammation	1.68085E-05
6	Reactome regulation of lipid metabolism by peroxisome proliferator activated receptor alpha	PPAR	2.28286E-05
7	BIOCARTA IL5 pathway	Inflammation	2.74777E-05
8	Reactome signal attenuation	Insulin	4.28557E-05
9	BIOCARTA DC pathway	Inflammation	5.60284E-05
10	KEGG PPAR signaling pathway	PPAR	5.65648E-05

Identification of dysregulated pathways associated with T2DM

To examine the association of the pathway with T2DM, Fisher's exact test based on the cumulative hypergeometric distribution was employed. The P-value was calculated to evaluate statistical significance of a given pathway by the formula as follow.

$$p = 1 - \sum_{i=0}^{k-1} \frac{\binom{m}{i}\binom{N-m}{n-i}}{\binom{N}{n}}$$

In this formula, N represents the total number of genes in the background population; n represents the number of genes related to T2DM extracted from literatures; m denotes the number of genes within the given pathways. The number of genes that overlapped with both T2DM related genes and this pathway are denoted as k. In this study, the pathway is considered association with T2DM if its P-value is less than 0.05.

Result

Pathways associated with T2DM

Of eight hundreds and eighty pathways, three hundreds and seventy four pathways contain at least one gene of the one hundred and thirty five genes related to T2DM (Table 2). Seventy six pathways statistically associated with T2DM were identified ($p<0.05$, Table 2).

Table 2. 374 pathways which contain at least one gene related to T2DM and their P-value.

SN	Pathway name	P-value	Number of genes in the pathway	Number of overlapped genes
1	KEGG adipocytokine signaling pathway	3.17E-07	67	12
2	KEGG type ii diabetes mellitus	4.88E-07	47	9
3	BIOCARTA PPARA pathway	6.56E-07	58	9
4	BIOCARTA cytokine pathway	1.91E-06	21	6
5	BIOCARTA INFLAM Pathway	1.68085E-05	29	6
6	Reactome regulation of lipid metabolism by peroxisome proliferator activated receptor alpha	2.28286E-05	61	8
7	BIOCARTA IL5 pathway	2.74777E-05	10	4

8	Reactome signal attenuation	4.28557E-05	11	4
9	BIOCARTA DC pathway	5.60284E-05	22	5
10	KEGG PPAR signaling pathway	5.65648E-05	69	8
11	KEGG leishmania infection	7.72476E-05	72	8
12	Reactome PI3K cascade	8.67844E-05	38	6
13	KEGG maturity onset diabetes of the young	0.00010699	25	5
14	Reactome IRS related events	0.000150919	79	8
15	Reactome downstream signaling of activated FGFR	0.000177383	43	6
16	BIOCARTA GH pathway	0.000190377	28	5
17	KEGG JAK STAT signaling pathway	0.000228524	155	11
18	BIOCARTA IL10 pathway	0.000283718	17	4
19	Reactome chylomicron mediated lipid transport	0.000283718	17	4
20	KEGG cytokine cytokine receptor interaction	0.000754833	267	14
21	BIOCARTA insulin pathway	0.000808775	22	4
22	BIOCARTA leptin pathway	0.00110817	11	3
23	BIOCARTA NTHI pathway	0.001138568	24	4
24	KEGG aldosterone regulated sodium reabsorption	0.001321971	42	5
25	KEGG hematopoietic cell lineage	0.001688182	88	7
26	Reactome lipoprotein metabolism	0.001797438	27	4
27	BIOCARTA granulocytes pathway	0.002341151	14	3
28	SIG insulin receptor pathway in cardiac myocytes	0.002654552	49	5
29	BIOCARTA stem pathway	0.002884567	15	3
30	KEGG toll like receptor signaling pathway	0.003910244	102	7
31	BIOCARTA PML pathway	0.00418812	17	3
32	Reactome regulation of insulin like growth factor activity by insulin like growth factor binding proteins	0.00418812	17	3
33	KEGG cytosolic DNA sensing pathway	0.004764438	56	5
34	Reactome metabolism of lipids and lipoproteins	0.005288124	228	11
35	KEGG insulin signaling pathway	0.005574524	137	8
36	KEGG allograft rejection	0.006395459	38	4
37	SIG PIP3 signaling in cardiac myoctes	0.007857084	63	5
38	BIOCARTA HER2 pathway	0.00882709	22	3
39	KEGG graft versus host disease	0.009127855	42	4
40	Reactome GPCR ligand binding	0.010184646	392	15
41	KEGG type I diabetes mellitus	0.010740936	44	4
42	KEGG intestinal immune network for IGA production	0.014493763	48	4
43	KEGG adherens junction	0.016001105	75	5
44	Reactome nuclear receptor transcription pathway	0.016645491	50	4
45	BIOCARTA NKT pathway	0.017231882	28	3

46	ST STAT3 pathway	0.018967271	11	2
47	KEGG T cell receptor signaling pathway	0.01971209	108	6
48	KEGG asthma	0.020755172	30	3
49	BIOCARTA NFAT pathway	0.021524131	54	4
50	BIOCARTA ASBCELL pathway	0.022469461	12	2
51	BIOCARTA ACE2 pathway	0.026215434	13	2
52	BIOCARTA TCRA pathway	0.026215434	13	2
53	Reactome SOS mediated signalling	0.026215434	13	2
54	BIOCARTA IL1R pathway	0.026726425	33	3
55	Reactome platelet adhesion to exposed collagen	0.03019464	14	2
56	Reactome SHC related events	0.03019464	14	2
57	BIOCARTA carm ER pathway	0.031163931	35	3
58	KEGG prion diseases	0.031163931	35	3
59	Reactome regulation of insulin secretion by glucagon like peptide 1	0.031983614	61	4
60	KEGG nod like receptor signaling pathway	0.033682644	62	4
61	BIOCARTA longevity pathway	0.034396291	15	2
62	BIOCARTA nuclearrs pathway	0.034396291	15	2
63	Reactome class C3 metabotropic glutamate pheromone receptors	0.034396291	15	2
64	SA MMP cytokine connection	0.034396291	15	2
65	BIOCARTA toll pathway	0.035963655	37	3
66	Reactome PI3K akt signalling	0.035963655	37	3
67	Reactome G alpha S signalling events	0.038177788	126	6
68	Reactome glucose transport	0.038497865	38	3
69	BIOCARTA rela pathway	0.038809538	16	2
70	Reactome diabetes pathways	0.038839459	383	13
71	BIOCARTA IL17 pathway	0.043426096	17	2
72	BIOCARTA IL7 pathway	0.043426096	17	2
73	BIOCARTA lair pathway	0.043426096	17	2
74	BIOCARTA NO2IL12 pathway	0.043426096	17	2
75	KEGG renin angiotensin system	0.043426096	17	2
76	Reactome regulation of gene expression in beta cells	0.049148321	101	5
77	BIOCARTA biopeptides pathway	0.052485943	43	3
78	BIOCARTA TH1TH2 pathway	0.053227544	19	2
79	BIOCARTA TID pathway	0.053227544	19	2
80	Reactome CD28 dependent PI3K AKT signaling	0.053227544	19	2
81	Reactome MYD88 cascade	0.053227544	19	2
82	Reactome downstream events in GPCR signaling	0.058232248	448	14
83	Reactome regulation of insulin secretion by free fatty acids	0.05839479	20	2

84	Reactome G alpha I signalling events	0.060669959	177	7
85	Reactome class A1 rhodopsin like receptors	0.062787056	292	10
86	BIOCARTA IL6 pathway	0.069217801	22	2
87	Reactome regulation of beta cell development	0.074677825	114	5
88	BIOCARTA IL12 pathway	0.074856758	23	2
89	BIOCARTA NFKB pathway	0.074856758	23	2
90	Reactome phospholipase cmediated cascade	0.074856758	23	2
91	Reactome toll like receptor 9 cascade	0.074856758	23	2
92	BIOCARTA CSK pathway	0.080636382	24	2
93	BIOCARTA PGC1A pathway	0.080636382	24	2
94	KEGG nicotinate and nicotinamide metabolism	0.080636382	24	2
95	Reactome activated TLR4 signalling	0.080636382	24	2
96	KEGG hypertrophic cardiomyopathy HCM	0.086981297	85	4
97	KEGG neuroactive ligand receptor interaction	0.088943124	272	9
98	KEGG TGF beta signaling pathway	0.0898965	86	4
99	Reactome platelet degranulation	0.0898965	86	4
100	Reactome hemostasis	0.092072368	274	9
101	Reactome FGFR ligand binding and activation	0.098749518	27	2
102	Reactome FRS2mediated cascade	0.098749518	27	2
103	SIG IL4receptor in B lyphocytes	0.098749518	27	2
104	Reactome the role of NEF in HIV1 replication and disease pathogenesis	0.105020165	28	2
105	Reactome toll like receptor 4 cascade	0.105020165	28	2
106	KEGG thyroid cancer	0.111395597	29	2
107	Reactome CD28 co stimulation	0.111395597	29	2
108	Reactome regulation of glucokinase by glucokinase regulatory protein	0.111395597	29	2
109	ST PAC1 receptor pathway	0.112893641	6	1
110	Reactome cell surface interactions at the vascular wall	0.114852428	94	4
111	BIOCARTA HDAC pathway	0.117870092	30	2
112	Reactome peptide ligand binding receptors	0.127151728	173	6
113	KEGG alanine aspartate and glutamate metabolism	0.131089449	32	2
114	Reactome glucagon type ligand receptors	0.137822509	33	2
115	ST G alpha I pathway	0.144630194	34	2
116	Reactome TRKA signalling from the plasma membrane	0.146132767	103	4
117	KEGG regulation of autophagy	0.15150708	35	2
118	Reactome costimulation by the CD28 family	0.160167933	70	3
119	Reactome formation of platelet plug	0.161866188	186	6
120	ST interferon gamma pathway	0.164501309	9	1
121	KEGG RIG I like receptor signaling pathway	0.164970398	71	3

122	BIOCARTA barrestin pathway	0.181032002	10	1
123	BIOCARTA EPHA4 pathway	0.181032002	10	1
124	BIOCARTA FREE pathway	0.181032002	10	1
125	BIOCARTA SARS pathway	0.181032002	10	1
126	BIOCARTA SODD pathway	0.181032002	10	1
127	KEGG limonene and pinene degradation	0.181032002	10	1
128	Reactome calcitonin like ligand receptors	0.181032002	10	1
129	Reactome ethanol oxidation	0.181032002	10	1
130	Reactome regulation of RHEB GTPASE activity by AMPK	0.181032002	10	1
131	Reactome removal of the flap intermediate from the C strand	0.181032002	10	1
132	KEGG tryptophan metabolism	0.186746657	40	2
133	BIOCARTA EPONFKB pathway	0.197238684	11	1
134	BIOCARTA IL4 pathway	0.197238684	11	1
135	BIOCARTA monocyte pathway	0.197238684	11	1
136	BIOCARTA SET pathway	0.197238684	11	1
137	BIOCARTA TCAPOPTOSIS pathway	0.197238684	11	1
138	Reactome CD28 dependent VAV1 pathway	0.197238684	11	1
139	Reactome HDL mediated lipid transport	0.197238684	11	1
140	Reactome recycling of bile acids and salts	0.197238684	11	1
141	Reactome signaling by VEGF	0.197238684	11	1
142	Reactome G ALPHA Q signalling events	0.198766887	157	5
143	KEGG pathways in cancer	0.199838877	328	9
144	Reactome metabolism of vitamins and cofactors	0.201152563	42	2
145	ST differentiation pathway in PC12 cells	0.201152563	42	2
146	KEGG FC EPSILON RI signaling pathway	0.204794347	79	3
147	Reactome metabolism of carbohydrates	0.208609462	119	4
148	BIOCARTA VDR pathway	0.213126719	12	1
149	Reactome amino acid synthesis and interconversion	0.213126719	12	1
150	Reactome facilitative NA independent glucose transporters	0.213126719	12	1
151	Reactome hormone sensitive lipase HSL mediated triacylglycerol hydrolysis	0.213126719	12	1
152	Reactome PECAM1 interactions	0.213126719	12	1
153	BIOCARTA CHREBP2 pathway	0.215684056	44	2
154	KEGG amino sugar and nucleotide sugar metabolism	0.215684056	44	2
155	BIOCARTA CARM1 pathway	0.228702605	13	1
156	Reactome death receptor signalling	0.228702605	13	1
157	Reactome early phase of HIV life cycle	0.228702605	13	1
158	Reactome notch HLH transcription pathway	0.228702605	13	1
159	Reactome platelet activation	0.234452963	167	5

160	Reactome class B2 secretin family receptors	0.235974908	85	3
161	Reactome toll receptor cascades	0.241254985	86	3
162	Reactome regulation of insulin secretion	0.24157095	212	6
163	BIOCARTA PS1 pathway	0.243972659	14	1
164	BIOCARTA THELPER pathway	0.243972659	14	1
165	Reactome polymerase switching	0.243972659	14	1
166	Reactome regulation of AMPK activity via LKB1	0.243972659	14	1
167	Reactome removal of the flap intermediate	0.243972659	14	1
168	Reactome SEMA3A plexin repulsion signaling by inhibiting integrin adhesion	0.243972659	14	1
169	KEGG glycerolipid metabolism	0.252357662	49	2
170	KEGG prostate cancer	0.257208586	89	3
171	BIOCARTA ERYTH pathway	0.258942366	15	1
172	BIOCARTA HIF pathway	0.258942366	15	1
173	BIOCARTA HSP27 pathway	0.258942366	15	1
174	BIOCARTA PITX2 pathway	0.258942366	15	1
175	Reactome repair synthesis of patch 27 30 bases long by dna polymerase	0.258942366	15	1
176	Reactome SEMA3A PAK dependent axon repulsion	0.258942366	15	1
177	BIOCARTA CDMAC pathway	0.273617327	16	1
178	BIOCARTA GATA3 pathway	0.273617327	16	1
179	BIOCARTA IL22BP pathway	0.273617327	16	1
180	BIOCARTA P53 pathway	0.273617327	16	1
181	KEGG pantothenate and COA biosynthesis	0.273617327	16	1
182	KEGG riboflavin metabolism	0.273617327	16	1
183	Reactome CRMPS in SEMA3A signaling	0.273617327	16	1
184	Reactome trafficking OF GLUR2 containing AMPA receptors	0.273617327	16	1
185	KEGG MTOR signaling pathway	0.274461925	52	2
186	KEGG starch and sucrose metabolism	0.274461925	52	2
187	KEGG amyotrophic lateral sclerosis als	0.281827569	53	2
188	KEGG autoimmune thyroid disease	0.281827569	53	2
189	BIOCARTA 41BB pathway	0.288004756	17	1
190	Reactome activated AMPK stimulates fatty acid oxidation in muscle	0.288004756	17	1
191	Reactome energy dependent regulation of MTOR by LKB1 AMPK	0.288004756	17	1
192	Reactome chemokine receptors bind chemokines	0.29654026	55	2
193	Reactome signaling in immune system	0.297591031	366	9
194	BIOCARTA CARDIACEGF PATHWAY	0.302108705	18	1
195	BIOCARTA CCR5 pathway	0.302108705	18	1
196	Reactome synthesis and interconversion of nucleotide DI and triphosphates	0.302108705	18	1
197	Reactome TIE2 signaling	0.302108705	18	1

198	BIOCARTA MAL pathway	0.315935373	19	1
199	BIOCARTA TGFB pathway	0.315935373	19	1
200	Reactome unfolded protein response	0.315935373	19	1
201	ST WNT CA2 CYCLIC GMP pathway	0.315935373	19	1
202	KEGG pathogenic Escherichia coli infection	0.325816274	59	2
203	BIOCARTA NKCELLS pathway	0.329490364	20	1
204	Reactome lagging strand synthesis	0.329490364	20	1
205	KEGG acute myeloid leukemia	0.333091259	60	2
206	BIOCARTA IGF1 pathway	0.342778444	21	1
207	BIOCARTA TOB1 pathway	0.342778444	21	1
208	Reactome CTLA4 inhibitory signaling	0.342778444	21	1
209	Reactome NEF mediates down modulation of cell surface receptors by recruiting them to clathrin adapters	0.342778444	21	1
210	KEGG colorectal cancer	0.347572803	62	2
211	KEGG glycolysis gluconeogenesis	0.347572803	62	2
212	KEGG beta alanine metabolism	0.355805397	22	1
213	Reactome E2F transcriptional targets AT G1 S	0.355805397	22	1
214	Reactome regulation of insulin secretion by acetylcholine	0.355805397	22	1
215	BIOCARTA IGF1R pathway	0.368575513	23	1
216	KEGG mismatch repair	0.368575513	23	1
217	Reactome collagen mediated activation cascade	0.368575513	23	1
218	Reactome cytosolic TRNA aminoacylation	0.368575513	23	1
219	Reactome integrin ALPHAIIBBETA3 signaling	0.368575513	23	1
220	ST MYOCYTE AD pathway	0.368575513	23	1
221	BIOCARTA CXCR4 pathway	0.381093919	24	1
222	BIOCARTA ECM pathway	0.381093919	24	1
223	BIOCARTA EIF4 pathway	0.381093919	24	1
224	BIOCARTA TPO pathway	0.381093919	24	1
225	Reactome further platelet releasate	0.381093919	24	1
226	Reactome translocation of ZAP70 to immunological synapse	0.381093919	24	1
227	BIOCARTA stress pathway	0.393366933	25	1
228	KEGG ascorbate and aldarate metabolism	0.393366933	25	1
229	ST granule cell survival pathway	0.393366933	25	1
230	KEGG pancreatic cancer	0.404331386	70	2
231	KEGG renal cell carcinoma	0.404331386	70	2
232	BIOCARTA WNT pathway	0.40539825	26	1
233	KEGG galactose metabolism	0.40539825	26	1
234	KEGG glycosaminoglycan biosynthesis heparan sulfate	0.40539825	26	1
235	Reactome phosphorylation of CD3 and TCR zeta chains	0.40539825	26	1

236	Reactome platelet aggregation plug formation	0.40539825	26	1
237	KEGG melanoma	0.411269367	71	2
238	KEGG leukocyte transendothelial migration	0.4139359	118	3
239	BIOCARTA GSK3 pathway	0.417192519	27	1
240	Reactome GS alpha mediated events in glucagon signalling	0.417192519	27	1
241	Reactome metabolism of bile acids and bile salts	0.417192519	27	1
242	Reactome mtor signalling	0.417192519	27	1
243	ST GAQ pathway	0.417192519	27	1
244	KEGG viral myocarditis	0.425026476	73	2
245	BIOCARTA ERK pathway	0.428754508	28	1
246	Reactome extension of telomeres	0.428754508	28	1
247	ST tumor necrosis factor pathway	0.428754508	28	1
248	Reactome transmembrane transport of small molecules	0.43253684	218	5
249	BIOCARTA TNFR1 pathway	0.440088451	29	1
250	BIOCARTA VEGF pathway	0.440088451	29	1
251	KEGG histidine metabolism	0.440088451	29	1
252	Reactome PD1 signaling	0.440088451	29	1
253	KEGG arrhythmogenic right ventricular cardiomyopathy arvc	0.445347369	76	2
254	KEGG O glycan biosynthesis	0.45119977	30	1
255	Reactome inhibition of insulin secretion by adrenaline noradrenaline	0.45119977	30	1
256	Reactome trafficking of AMPA receptors	0.45119977	30	1
257	KEGG neurotrophin signaling pathway	0.455945611	126	3
258	KEGG peroxisome	0.458673954	78	2
259	BIOCARTA EGF pathway	0.462091982	31	1
260	BIOCARTA NO1 pathway	0.462091982	31	1
261	Reactome dna strand elongation	0.462091982	31	1
262	BIOCARTA PDGF pathway	0.472768962	32	1
263	Reactome integration of energy metabolism	0.475275159	229	5
264	Reactome integrin cell surface interactions	0.478314638	81	2
265	KEGG propanoate metabolism	0.483236372	33	1
266	Reactome E2F Mediated Regulation OF dna replication	0.483236372	33	1
267	Reactome global genomic NER	0.483236372	33	1
268	ST phosphoinositide 3 kinase pathway	0.483236372	33	1
269	Reactome glucose and other sugar SLC transporters	0.484766066	82	2
270	BIOCARTA AT1R pathway	0.493496954	34	1
271	BIOCARTA MPR pathway	0.493496954	34	1
272	KEGG butanoate metabolism	0.493496954	34	1
273	Reactome glucagon signaling in metabolic regulation	0.493496954	34	1

274	ST adrenergic	0.493496954	34	1
275	KEGG ECM receptor interaction	0.497520685	84	2
276	KEGG huntingtons disease	0.499771774	185	4
277	KEGG base excision repair	0.503555775	35	1
278	KEGG primary immunodeficiency	0.503555775	35	1
279	Reactome downstream signal transduction	0.503555775	35	1
280	Reactome generic transcription pathway	0.503555775	35	1
281	Reactome innate immunity signaling	0.506625831	136	3
282	KEGG progesterone mediated oocyte maturation	0.510074735	86	2
283	KEGG natural killer cell mediated cytotoxicity	0.511562943	137	3
284	BIOCARTA AGR pathway	0.513415813	36	1
285	KEGG dna replication	0.513415813	36	1
286	KEGG apoptosis	0.522423923	88	2
287	BIOCARTA ALK pathway	0.52308166	37	1
288	BIOCARTA MET pathway	0.52308166	37	1
289	Reactome generation of second messenger molecules	0.52308166	37	1
290	KEGG systemic lupus erythematosus	0.526218712	140	3
291	BIOCARTA IL2RB pathway	0.532556772	38	1
292	BIOCARTA integrin pathway	0.532556772	38	1
293	ST JNK MAPK pathway	0.532556772	38	1
294	ST B cell antigen receptor	0.541845322	39	1
295	KEGG dilated cardiomyopathy	0.546496153	92	2
296	KEGG pyruvate metabolism	0.550950289	40	1
297	Reactome tRNA aminoacylation	0.550950289	40	1
298	KEGG bladder cancer	0.568625212	42	1
299	KEGG fatty acid metabolism	0.568625212	42	1
300	Reactome amine ligand binding receptors	0.568625212	42	1
301	KEGG ABC transporters	0.585609257	44	1
302	KEGG lysine degradation	0.585609257	44	1
303	KEGG nucleotide excision repair	0.585609257	44	1
304	KEGG valine leucine and isoleucine degradation	0.585609257	44	1
305	KEGG vasopressin regulated water reabsorption	0.585609257	44	1
306	Reactome transcription coupled NER	0.585609257	44	1
307	ST T cell signal transduction	0.585609257	44	1
308	BIOCARTA keratinocyte pathway	0.601929247	46	1
309	SIG BCR signaling pathway	0.601929247	46	1
310	KEGG melanogenesis	0.602930248	102	2
311	BIOCARTA TCR pathway	0.60984844	47	1

312	KEGG NOTCH signaling pathway	0.60984844	47	1
313	Reactome downstream TCR signaling	0.60984844	47	1
314	KEGG MAPK signaling pathway	0.612801313	267	5
315	KEGG proteasome	0.61761117	48	1
316	Reactome signalling by NGF	0.619395375	215	4
317	Reactome glucose regulation of insulin secretion	0.621608973	161	3
318	KEGG regulation of actin cytoskeleton	0.623069227	216	4
319	Reactome nucleotide excision repair	0.625220656	49	1
320	KEGG endometrial cancer	0.64715898	52	1
321	KEGG taste transduction	0.64715898	52	1
322	Reactome hormone biosynthesis	0.64715898	52	1
323	KEGG alzheimers disease	0.654370368	169	3
324	KEGG arginine and proline metabolism	0.661071062	54	1
325	KEGG oocyte meiosis	0.663511038	114	2
326	KEGG basal cell carcinoma	0.667821884	55	1
327	KEGG steroid hormone biosynthesis	0.667821884	55	1
328	KEGG vibrio cholerae infection	0.674438596	56	1
329	BIOCARTA HIVNEF pathway	0.687282801	58	1
330	Reactome host interactions of HIV factors	0.690930426	120	2
331	Reactome platelet activation triggers	0.693515301	59	1
332	Reactome toll like receptor 3 cascade	0.693515301	59	1
333	Reactome steroid metabolism	0.711481452	62	1
334	Reactome signaling by PDGF	0.722874284	64	1
335	Reactome TCR signaling	0.722874284	64	1
336	KEGG cell cycle	0.724623084	128	2
337	KEGG axon guidance	0.728611171	129	2
338	Reactome insulin synthesis and secretion	0.728611171	129	2
339	KEGG chemokine signaling pathway	0.730600953	190	3
340	Reactome transmission across chemical synapses	0.732550442	130	2
341	Reactome semaphorin interactions	0.73382026	66	1
342	Reactome phase 1 functionalization of compounds	0.739131451	67	1
343	KEGG epithelial cell signaling in helicobacter pylori infection	0.744336963	68	1
344	KEGG cell adhesion molecules CAMS	0.747829139	134	2
345	Reactome NCAM signaling for neurite out growth	0.749439776	69	1
346	KEGG long term potentiation	0.754441381	70	1
347	KEGG metabolism of xenobiotics by cytochrome P450	0.754441381	70	1
348	Reactome metablism of nucleotides	0.759343803	71	1
349	KEGG VEGF signaling pathway	0.782436311	76	1

350	Reactome telomere maintenance	0.786783814	77	1
351	ST integrin signaling pathway	0.79104501	78	1
352	KEGG WNT signaling pathway	0.804703653	151	2
353	Reactome neuroransmitter receptor binding and downstream transmission in the postsynaptic cell	0.814893723	84	1
354	KEGG ERBB signaling pathway	0.825784147	87	1
355	KEGG antigen processing and presentation	0.832688689	89	1
356	Reactome synthesis of DNA	0.832688689	89	1
357	Reactome SLC mediated transmembrane transport	0.852308095	169	2
358	Reactome gene expression	0.853637636	425	6
359	KEGG GNRH signaling pathway	0.868767738	101	1
360	Reactome G1 S transition	0.87139976	102	1
361	KEGG calcium signaling pathway	0.871946394	178	2
362	Reactome HIV life cycle	0.87397939	103	1
363	Reactome S phase	0.87397939	103	1
364	Reactome DNA repair	0.876507699	104	1
365	Reactome HIV infection	0.881798148	183	2
366	KEGG focal adhesion	0.911776602	201	2
367	KEGG lysosome	0.912539721	121	1
368	Reactome biological oxidations	0.922582686	127	1
369	Reactome apoptosis	0.925669074	129	1
370	KEGG purine metabolism	0.959681332	159	1
371	Reactome axon guidance	0.96129626	161	1
372	Reactome metabolism of amino acids	0.962079525	162	1
373	KEGG endocytosis	0.975333571	183	1
374	Reactome cell cycle mitotic	0.998067737	306	1

Table 3. *The categorical frequency of other 66 pathways associated with T2DM.*

Class Name of Pathway	Frequency
Adipocytokine pathway	1
inflammatory pathway	21
Insulin and its up-downstream pathway	17
PPAR and Lipid metabolism pathway	3
T2DM pathway	1
Other pathway	23

Description of top 10 pathways ranked by p-value

These ten pathways could be attributed to five classes signaling pathways including adipocytokine, inflammatory, Peroxisome Proliferators Activated Receptor (PPAR), insulin and T2DM pathway (Table 1). Of the other 66 pathways associated with T2DM, there were only 23 pathways that could not be attributed to the five classes signaling pathways mentioned previously (Tables 3 and 4).

Adipocytokine pathway

Adipose tissue is a heterogeneous mix of adipocytes, pre-adipocytes, immune cells, and endothelium [10]. Adipocytokine refer to the cytokines secreted from adipose tissue. There are three kinds of adipocytokines (Leptin, Adiponectin and TNFα) in the adipocytokine pathways from KEGG database. Increased adiposity is associated with decreased adiponectin secretion and positively correlated with leptin production. Leptin and its receptor play roles in food intake and energy balance [11]. The binding of leptin to its receptor initiates a phosphorylation cascade that results in transcriptional activation of target genes of STAT5 and STAT3 and activation of the PI3K pathway, the MAPK/ERK pathway, and mTOR/S6K pathway. Leptin regulates energy intake and

metabolic rate primarily by its effect on hypothalamic nuclei and exerts its anorectic effects by modulating the levels of neuropeptides such as NPY, AGRP, and alpha-MSH. Adiponectin has beneficial effects on insulin sensitivity to lower plasma glucose and Free Fat Acids (FFAs) improvement. These effects are partly induced by adiponectin-induced AMPK activation, which in turn stimulates skeletal muscle fatty acid oxidation and glucose uptake. The proinflammatory cytokine TNF-α has been implicated as a link between obesity and insulin resistance. TNF-α may inhibit IRS1 tyrosine phosphorylation by promoting its serine phosphorylation.

Table 4. *Class of other 66 pathways associated with T2D.*

SN	Pathway name	Class ID *
1	KEGG leishmania infection	4
2	Reactome PI3K cascade	5
3	KEGG maturity onset diabetes of the young	5
4	Reactome IRS related events	5
5	Reactome downstream signaling of activated FGFR	5
6	BIOCARTA GH pathway	5
7	KEGG JAK STAT signaling pathway	0
8	BIOCARTA IL10 pathway	4
9	Reactome chylomicron mediated lipid transport	3
10	KEGG cytokine cytokine receptor interaction	4
11	BIOCARTA insulin pathway	5
12	BIOCARTA leptin pathway	1
13	BIOCARTA NTHI pathway	4
14	KEGG aldosterone regulated sodium reabsorption	0
15	KEGG hematopoietic cell lineage	0
16	Reactome lipoprotein metabolism	3
17	BIOCARTA granulocytes pathway	4
18	SIG insulin receptor pathway in cardiac myocytes	5
19	BIOCARTA stem pathway	0
20	KEGG toll like receptor signaling pathway	4
21	BIOCARTA PML pathway	0
22	Reactome regulation of insulin like growth factor activity by insulin like growth factor binding proteins	5
23	KEGG cytosolic DNA sensing pathway	0
24	Reactome metabolism of lipids and lipoproteins	3
25	KEGG insulin signaling pathway	5
26	KEGG allograft rejection	4
27	SIG PIP3 signaling in cardiac myoctes	5
28	BIOCARTA HER2 pathway	0
29	KEGG graft versus host disease	4
30	Reactome GPCR ligand binding	0
31	KEGG TYPE I diabetes mellitus	5
32	KEGG intestinal immune network for IGA production	4

33	KEGG adherens junction	0
34	Reactome nuclear receptor transcription pathway	0
35	BIOCARTA NKT pathway	4
36	ST STAT3 pathway	0
37	KEGG T cell receptor signaling pathway	4
38	KEGG asthma	4
39	BIOCARTA NFAT pathway	0
40	BIOCARTA ASBCELL pathway	4
41	BIOCARTA ACE2 pathway	0
42	BIOCARTA TCRA pathway	0
43	Reactome SOS mediated signalling	5
44	BIOCARTA IL1R pathway	4
45	Reactome platelet adhesion to exposed collagen	0
46	Reactome SHC related events	5
47	BIOCARTA carm ER pathway	0
48	KEGG prion diseases	0
49	Reactome regulation of insulin secretion by glucagon like peptide 1	5
50	KEGG NOD like receptor signaling pathway	0
51	BIOCARTA longevity pathway	0
52	BIOCARTA nuclearrs pathway	0
53	Reactome class C3 metabotropic glutamate pheromone receptors	0
54	SA MMP cytokine connection	4
55	BIOCARTA toll pathway	4
56	Reactome PI3K akt signalling	5
57	Reactome G ALPHA S signalling events	0
58	Reactome glucose transport	5
59	BIOCARTA RELA pathway	4
60	Reactome diabetes pathways	2
61	BIOCARTA IL17 pathway	4
62	BIOCARTA IL7 pathway	4
63	BIOCARTA LAIR pathway	4
64	BIOCARTA NO2IL12 pathway	4
65	KEGG renin angiotensin system	0
66	Reactome regulation of gene expression in beta cells	5

*:1: Adipocytokine pathway; 2:T2D pathway; 3: PPAR and Lipid metabolism pathway; 4: Flammation pathway; 5: Insulin and its up-downstream pathway; 0: Other pathway.

Inflammatory pathways

Inflammation is a protective response to infection or injury by immune system that requires communication between different classes of immune cells to coordinate their actions. Each of these cell types communicates with other immune cells using secreted factors called cytokines, including interleukins, TNF, and the interferons. Inflammation can be classified as acute or chronic, local or systemic. Chronic low-grade inflammation,

which is characterized by the production of abnormal adipocytokine such as TNF-α, IL-1, IL-6, leptin and adiponectin, is frequently observed in obese individuals. These factors inhibit insulin signaling and are involved in the development of insulin resistance, which increases the risk of T2DM. MCP-1 is one of the chemo attractants secreted from adipocytes, which plays an important role in the recruitment of macrophages to the adipose tissues. Moreover, obesity is associated with increased plasma levels of MCP-1 and overexpression in adipose tissue [12,13]. The macrophages which reside in adipose tissue are responsible for the expression of most tissue's TNF-α and IL-6. The expression of macrophage markers in human adipose tissue is high in the subjects with obesity and insulin resistance, and is correlated with the expression of TNF-α and IL-6 [12,14].

PPAR pathways

PPARs are ligand activated nuclear hormone receptors that are activated by fatty acids and their derivatives. There are three kinds of identified PPARs, PPAR-α, PPAR-β and PPAR-γ. They work as the master regulators of glucose, lipids metabolism, energy balance and inflammation [15-17]. PPAR-α is highly expressed in tissues such as liver and skeletal muscle, where activation of PPAR-α results in the clearance of circulating or cellular lipids via the regulation of gene expression involved in lipid uptake, catabolism and homeostasis [18]. The primary effects of PPAR-β are involved in lipid oxidation and cell proliferation. PPAR-γ is highly expressed in adipocytes, skeletal muscle, liver and kidney. PPAR-γ enhances blood glucose and fatty acid uptake by regulating expression of genes that mediate adipocyte differentiation, energy metabolism and insulin action [19,20]. Accordingly, PPAR-γ activation results in an increase in insulin sensitivity and anti-inflammatory effects [21-23]. Dysregulation of PPARs contributes to the development of T2DM and Metabolic syndrome (Mets). Therefore, PPARs are important therapeutic targets in the clinical management of T2DM, obesity and Mets. PPARα agonists, such as fenofibrate, clofibrate and gemfibrozil, act as hypolipidemic agents and are clinically used for the treatment of hyperlipidemia, particularly hypertriglyceridemia associated with MetS, diabetes and diabetes-linked disease [24,25]. Likewise, Thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, which are specific ligands for PPARγ, act as insulin sensitizers and are currently marketed for the treatment of hyperglycemia in patients with T2DM [23,26].

Interplay of adipocytokine, inflammatory, PPAR and insulin pathway

T2DM pathway is the interplay of adipocytokine, inflammatory, PPAR and insulin pathway. T2DM pathway from KEGG database consists from 47 proteins, of which there are 20 members overlapped with these pathways (Figure 1 and Table 5). The significant overlap members, in another word, the nodes of these pathways are TNF (from 4 pathways: adipocytokine, inflammatory, PPAR and T2DM), ADIPOQ (from 3 pathways: adipocytokine, PPAR and T2DM) and IRSs (from 3 pathways: adipocytokine, insulin and T2DM) (Figure 1). FFA and TNF-α induce insulin resistance through inhibition of IRS1 functions by various kinases including ERK, JNK, IKK-β, PKC and mTOR. Adiponectin has beneficial effects on improving insulin sensitivity. Increased adiposity is associated with decreased adiponectin secretion and leads to insulin resistance. Insulin resistance leads to chronic hyperglycemia. The combined effects of excess nutrient load, hyperglycemia and cytokines induce multiple defects in beta-cells [27].

Table 5. *Members in the top 10 pathways.*

Pathway ID*	Members of the pathway
1	PRKAG3,PPARA,PRKAG1,LEPR,PRK,AG2,NFKB1,CAMKK1,CAMKK2,AKT1,SLC2A4,SLC2A1,CHUK,AKT3,AKT2,IRS4,IRS2,SOCS3,RXRB,RXRA,RELA,PRKAB2,RXRG,ADIPOR2,PRKAB1,ADIPOR1,IRS1,PPARGC1A,PRKCQ,G6PC,CD36,MAPK9,MAPK8,TRAF2,TNF,NFKBIE,STK11,NFKBIB,NFKBIA,POMC,G6PC2,TNFRSF1A,TNFRSF1B,ACSL1,PRKAA1,PRKAA2,ACSL4,ACSL3,AGRP,ACSL6,ACSL5,CPT1C,CPT1B,MAPK10,ACACB,PCK2,ADIPOQ,STAT3,CPT1A,TRADD,PTPN11,PCK1,LEP,NPY,IKBKG,JAK2,MTOR,IKBKB
2	PRKCZ,TNF,HK2,HK1,PDX1,KCNJ11,SLC2A4,INS,SLC2A2,HK3,PIK3CA,PIK3R5,PIK3R3,INSR,PIK3R1,PIK3R2,IRS4,PIK3CG,IRS2,SOCS2,PIK3CB,SOCS3,PIK3CD,SOCS1,SOCS4,MAPK10,PRKCE,IRS1,ADIPOQ,PRKCD,MAPK1,GCK,PKM2,PKLR,MAPK3,CACNA1G,MAPK9,MAPK8,CACNA1E,MTOR,MAFA,IKBKB,CACNA1C,ABCC8,CACNA1D,CACNA1A,CACNA1B
3	ACOX1,PPARA,PTGS2,PDGFA,STAT5A,EHHADH,STAT5B,CITED2,PRKACG,PRKAR2B,PRKAR2A,APOA2,APOA1,PIK3CA,NOS2,PRKACB,MYC,NR2F1,PIK3CG,PRKCA,HSP90AA1,RXRA,RELA,NR0B2,RB1,PPARGC1A,PRKCB,NRIP1,MAPK1,NCOA1,CD36,EP300,JUN,MAPK3,MED1,ME1,TNF,FRA8B,NFKBIA,HSPA1A,MRPL11,INS,FAT1,HSD17B4,PIK3R1,NR1H3,CPT1B,LPL,CREBBP,SRA1,DUSP1,SP1,PRKAR1B,PRKAR1A,FABP1,NCOR1,NCOR2,DUT
4	IL4,IL3,IL6,IL5,TNF,IL8,IL16,IL18,IL9,IL13,IL15,IL10,IFNA1,IL17A,IFNB1,IFNG,IL12A,IL12B,LTA,IL1A,IL2
5	CSF3,CSF2,TNF,HLA-DRB1,PDGFA,CSF1,TGFB3,IL13,IL15,TGFB1,IL10,IL11,TGFB2,IFNA1,IFNG,CD4,LTA,IL1A,IL4,IL3,IL6,IL5,IL8,IL7,IFNB1,IL12A,IL12B,HLA-DRA,IL2
6	ACOX1,SLC27A1,PPARA,CPT2,EHHADH,APOA2,SIN3B,APOA1,SIN3A,SMARCD3,SLC2A2,CYP7A1,APOA5,TGS1,TBL1XR1,ACADM,SULT2A1,RXRA,NCOA1,NCOA2,CD36,DGAT1,NCOA3,NCOA6,PRIC285,CARM1,MED1,ME1,ABCA1,CHD9,UGT1A9,ACSL1,CYP4A22,PLIN2,PLIN1,AGT,FASN,PLTP,NR1H3,ANGPTL4,SREBF1LPL,SCD,FADS1,CREBBP,ACACA,FADS2,UCP1,SLC10A2,CPT1A,MTTPABCB4,PEX11A,CYP4A11,HDAC3,UGT2B4,FABP4,TBL1X,NCOR1,SCP2,NCOR2
7	IL4,CCL11,IL6,IL5,HLA-DRB1,CCR3,IL1B,CD4,IL5RA,HLA-DRA

8	DOK1,IRS2,GRB10,INS,GRB2,SOS1,MAPK3,SHC1,INSR,IRS1,CRK
9	IL4,CSF2,IL3,IL5,TLR2,IL13,TLR4,ANPEP,CD40,TLR7,IL10,TLR9,IFNA1,ITGAX,IFNB1,CD33,IFNG,IL12A,CD2,IL12B,CD5,CD7
10	ACOX2,ACOX1,SLC27A1,PPARA,PPARD,CPT2,EHHADH,PPARG,AQP7,MMP1,ACOX3,APOA2,PDPK1,APOA1,CYP7A1,APOA5,ILK,SCD5,ACADM,RXRB,RXRA,RXRG,ACADL,CD36,CYP27A1,UBC,SLC27A6,SLC27A2,SLC27A5,SLC27A4,ACAA1,ME1,GK2,ACSL1,CYP4A22,SORBS1,PLIN1,APOC3,ACSL4,ACSL3,ACSL6,PLTP,ACSL5,NR1H3,ANGPTL4,CPT1C,CPT1B,LPL,OLR1,SCD,FADS2,UCP1,PCK2,ADIPOQ,DBI,CPT1A,PCK1,CYP4A11,HMGCS2,FABP3,FABP4,FABP1,GK,FABP2,FABP7,CYP8B1,SCP2,FABP5,FABP6

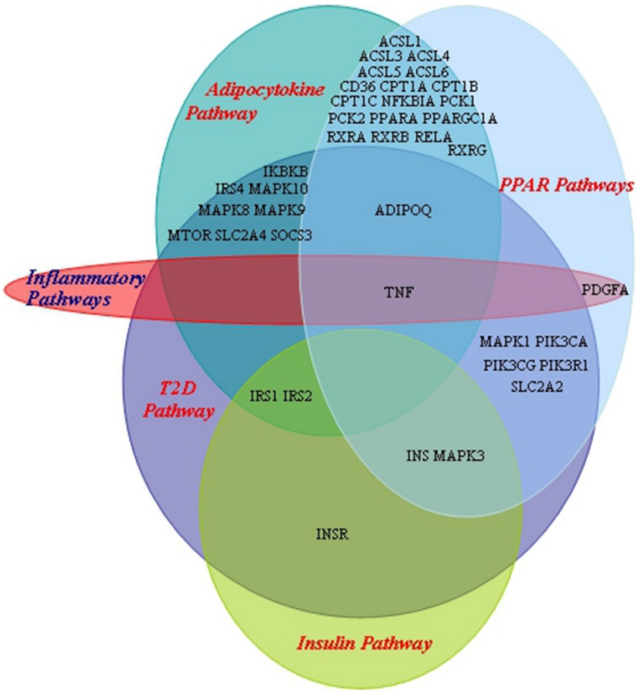

Figure 1. *T2DM pathway is the interplay of adipocytokine, inflammatory, PPAR and insulin pathway. This figure is stemmed from the top 10 statistically relevant pathways with T2DM ranked by P-value. Inflammatory pathways contain 4 pathways (See Table 1).*

Discussion

Energy metabolism exists in all organisms. Mammals obtain energy from nutriment. The supply of nutriment and the energy demand for animal is variety. Thus, a delicate mechanism for energy metabolism to regulate energy balance has been developed in the long journey of biological evolution. For most wild animal and even human in the ancient times, scarcity of food and obtaining food by arduous physical activity are their theme. How did they survive from the short period of food scarcity? Adipose tissue acted as an optimum pattern to store energy occurred. In fed states, high levels of nutrients and growth factors drive lipid uptake in adipose tissue, while in fasting state, adipose tissue release fatty acids into the circulation. These fatty acids are generated by the breaking down of triacylglycerols, which contain more energy per unit mass than carbohydrates and can essentially be stored anhydrously. Triacylglycerols are stored as energy material in adipose tissue, which is very efficient. Phenotype of obesity is a result of enough triacylglycerols stored in adipose tissue. It is a beneficial trait as a result of nature selection for organism's survival under rigorous condition [28,29].

Glucose is a common energy material and can be utilized by almost all organs. To maintain a security level of blood glucose is important. Glucose homeostasis in mammals is primarily maintained through a tight regulation of glucose uptake in peripheral tissues and the glucose production in liver. This complicate process is under the control of hormones and energy sensors. We guess that insulin resistance is a compromise strategy for mammals to keep a security level of blood glucose. As referrer to insulin resistance associated with T2DM, it is often defined as status of a decreased uptake and utilization of glucose in liver, muscles and adipose tissue by reduction of insulin sensitivity. As mentioned before, insulin resistance often happens in the status of obesity and inflammation. Two main molecules, fat acid and TNF-α induce insulin resistance through inhibition of IRS1's functions by various pathways [30]. Fat acid is used as fuel when glucose is limiting, which happen in the condition of food scarcity. Therefore, we consider that insulin resistance is a compromise strategy for mammals to keep a security level of blood glucose to cope with the condition of food scarcity and maintain enough energy sources to cope with the other unexpected biological event such as inflammation, a protective response to infection or injury [31].

Phenotype of obesity considered as a beneficial trait and insulin resistance considered as a beneficial mechanism are the results of nature selection in the long journey of biological evolution [32]. However, they became arch-criminal of T2DM and Mets currently. The reason should be that the mammals adapt to the rigorous condition of food scarcity and obtain food by arduous physical activity. All molecular mechanisms have been tailored in this condition. Suddenly, this scenario changed. People nowadays enjoy the redundant food with sedentary life style. Organism cannot adapt to the status of excess energy over a long time span. It coincides with our result in this study. Obesity leads to dysregulation of adipocytokine pathway, moreover, it leads to insulin resistance by impaired insulin signaling pathway. Insulin resistance leads to chronic hyperglycemia. The combined effects of excess nutrient load, hyperglycemia and cytokines induce multiple defects in beta-cells [27]. Insulin resistance is a major factor in the pathogenesis of T2DM.

Conclusion

Our result suggests that analysis of pathway is a helpful way to facilitate us to understand the mechanism of T2DM. T2DM is the result of dysregulated energy metabolism originated from the status of excess energy over a long time span. Dysregulation of the adipocytokine and inflammatory pathway

is the hallmark of this status, which lead to insulin resistance by impaired insulin signaling pathway. Chronic hyperglycemia induces defects in beta-cells and T2DM.

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