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SBP2 in adipose tissue macrophages: a new target for Chinese Medicine treatment of insulin resistance

脂肪組織巨噬細胞的SBP2： 中藥治療胰島素抵抗的新靶點

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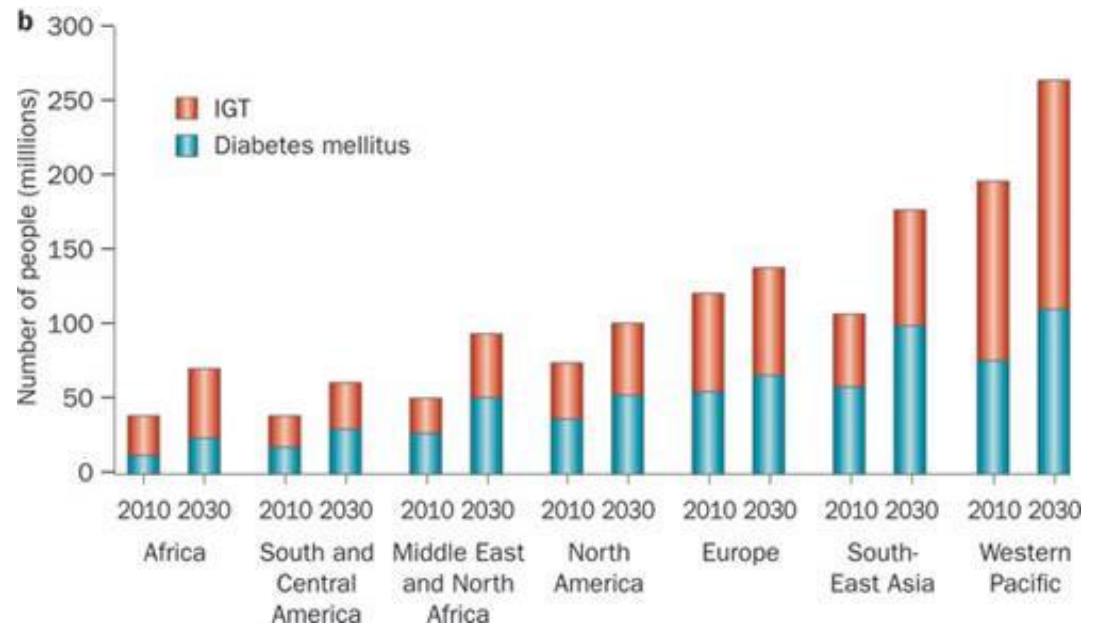
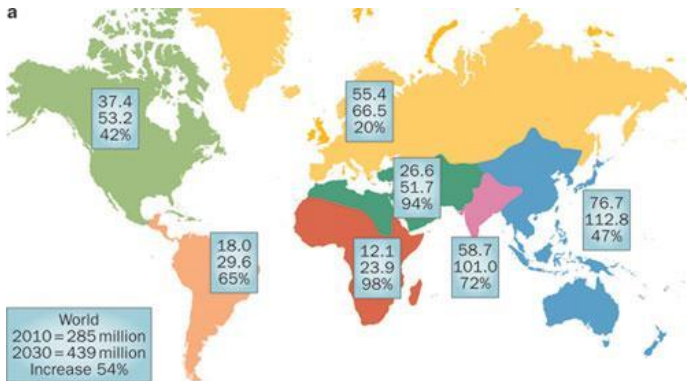
School of Chinese Medicine

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Diabetes: a global issue of healthcare

糖尿病：世界性的健康難題



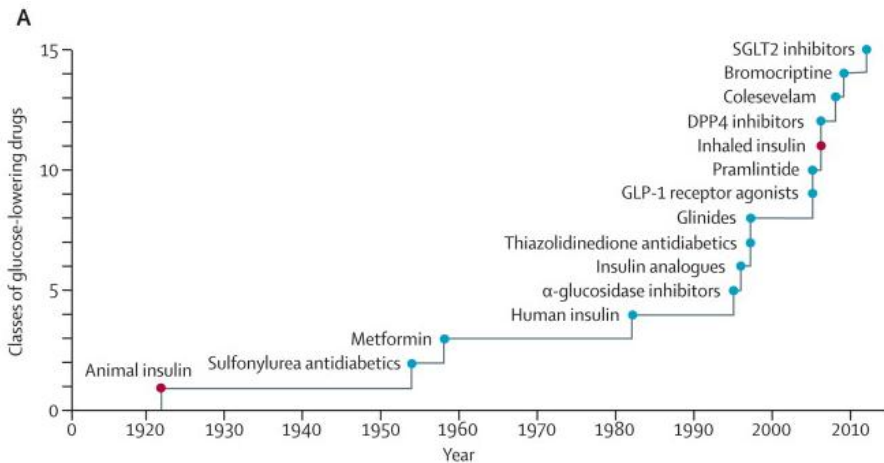
The number of people globally with diabetes mellitus is projected to rise from 285 million in 2010 to 439 million by 2030, a 54% increase.

Chen, L. et al. (2011) Nat. Rev. Endocrinol.

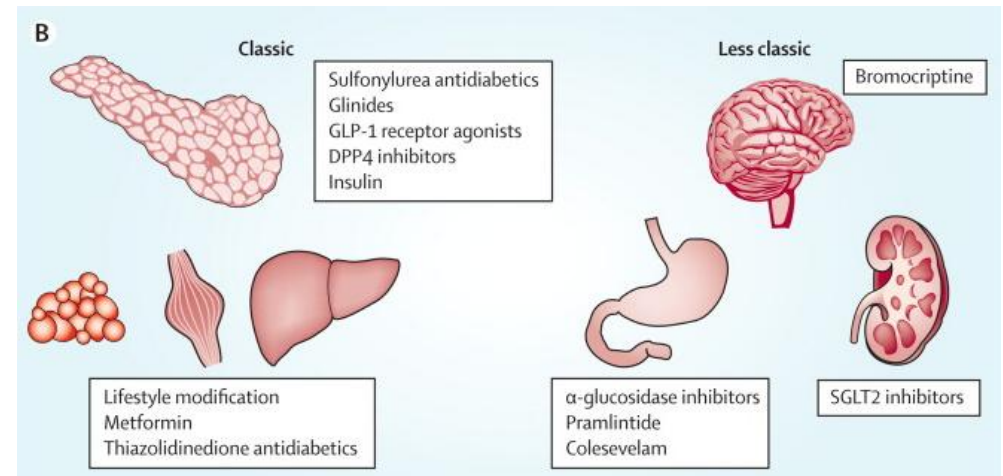


Current Treatment of Diabetes

目前的糖尿病治療策略



Development of antidiabetic treatment
糖尿病藥物的發展史

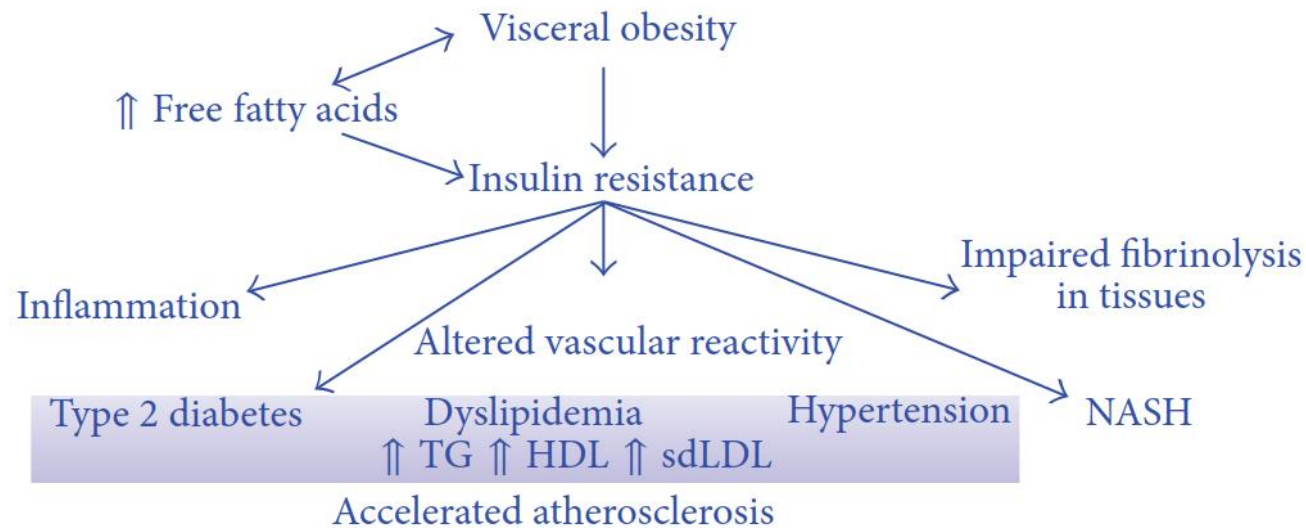


Targeted organ of antidiabetic treatment
糖尿病藥物的靶向器官



Insulin resistance: Important bridge between obesity and type II diabetes

胰島素抵抗：肥胖與II型糖尿病的重要橋樑



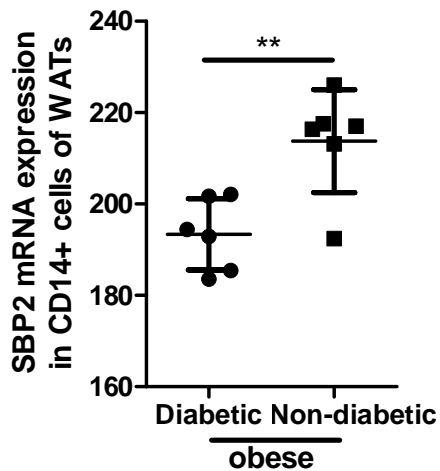
NASH = nonalcoholic steatohepatitis

TG = triglycerides; HDL = high density lipoprotein; sdLDL = small dense LDL



SBP2 is critically down-regulated during the development of obesity to diabetes

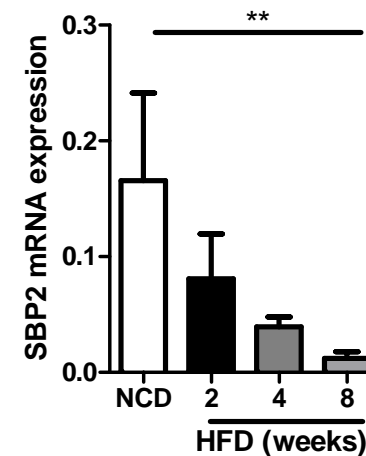
SBP2的表達在肥胖向糖尿病的進程中受到抑制



SBP2 expression in adipose tissue macrophages (ATMs) was suppressed in patients with diabetes compared with non-diabetic obese patients.

與非糖尿病肥胖病人相比，

糖尿病病人的脂肪組織巨噬細胞(ATMs)的SBP2表達降低。



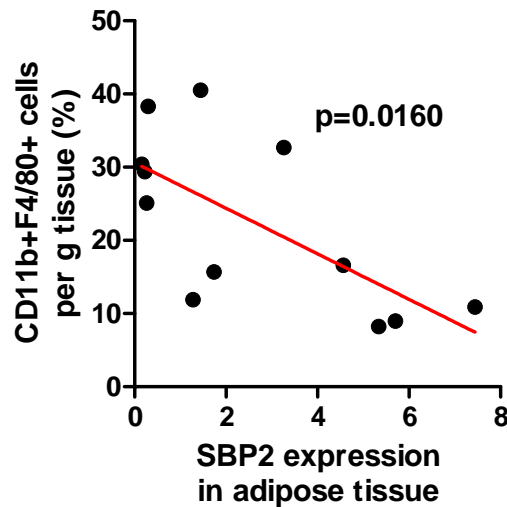
SBP2 expression in adipose tissue was suppressed during the development of insulin resistance of diet-induced obesity (DIO) in mice.

在高脂飲食誘導的肥胖小鼠模型中，
脂肪組織SBP2表達逐步降低。

Wang et al. (2019) *Sci. Adv.*

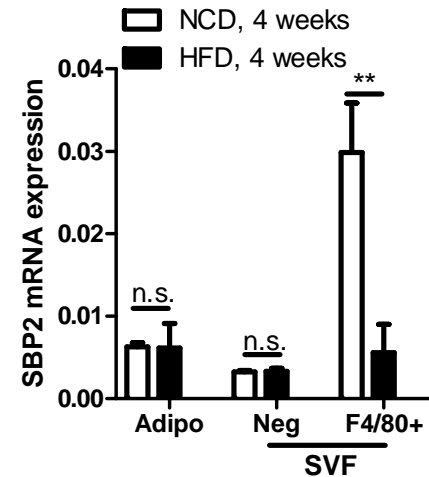
SBP2 is associated with ATMs during the development of insulin resistance

SBP2的表達與脂肪組織巨噬細胞相關



SBP2 expression was negatively associated with the infiltration of ATMs.

SBP2在脂肪組織的表達與ATMs的浸潤呈現負相關關係。



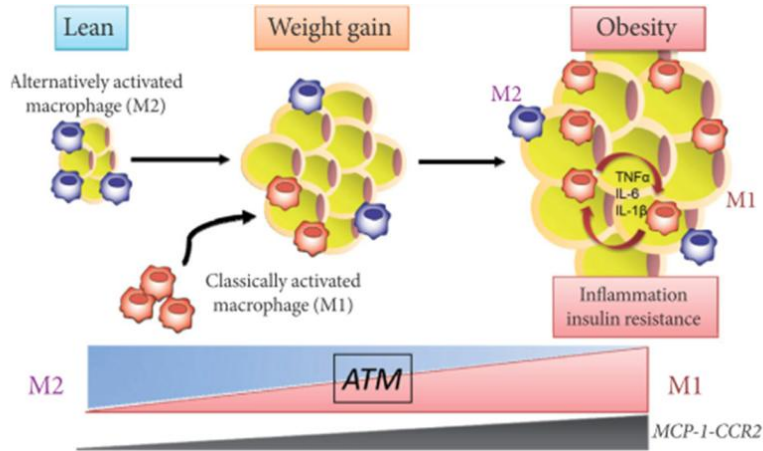
Suppression of SBP2 expression was associated with ATMs during development of insulin resistance

胰島素抵抗發展過程中，SBP2在脂肪組織中的表達被抑制主要與其ATMs中被抑制有關。



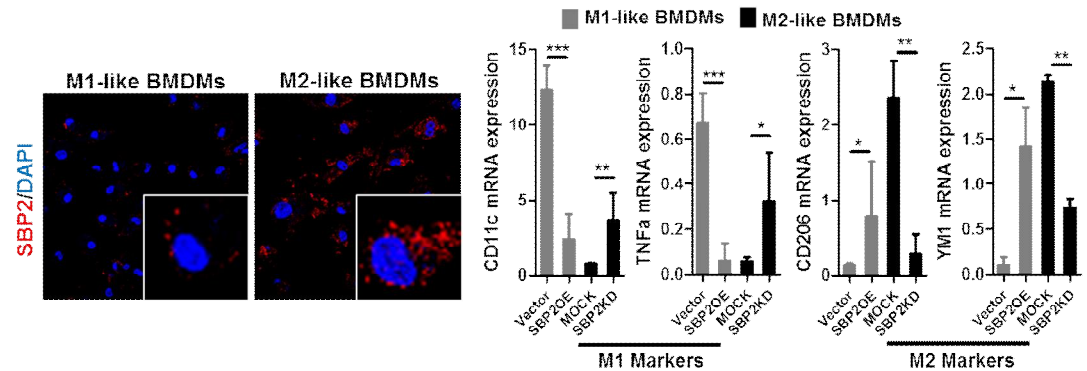
SBP2 regulates phenotypes of ATMs to suppress inflammation

SBP2通過調節ATMs抑制脂肪組織炎症



ATMs phenotype switches from M2 to M1 during development of insulin of resistance
在胰島素抵抗發展過程中，ATMs從M2亞型往M1亞型轉變。

Rehman et al. (2016) J. Biomed. Sci.

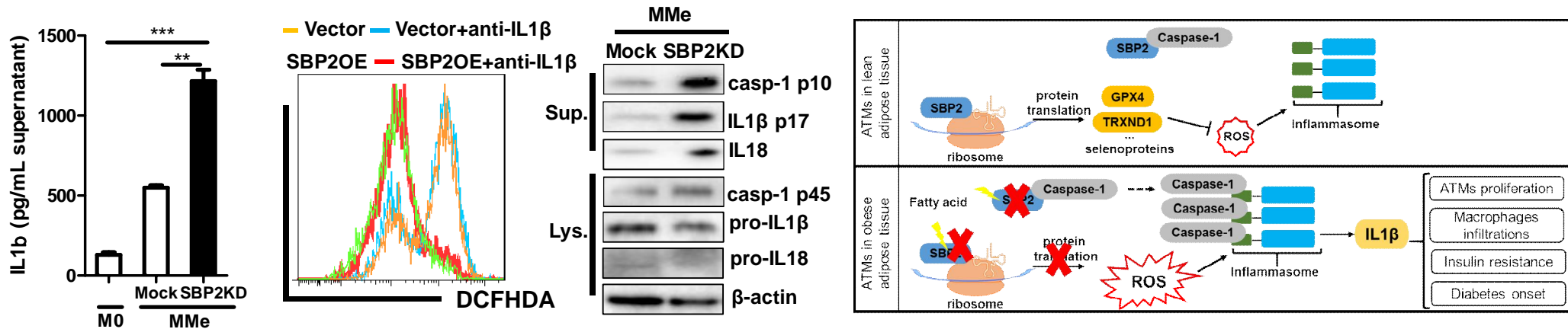


SBP2 switch ATMs from M1 phenotype to M2 one.
SBP2使脂肪組織巨噬細胞從M1亞型向M2亞型轉變。

Wang et al. (2019) Sci. Adv.

SBP2 regulates phenotypes of ATMs to suppress inflammation

SBP2通過調節ATMs抑制脂肪組織炎症

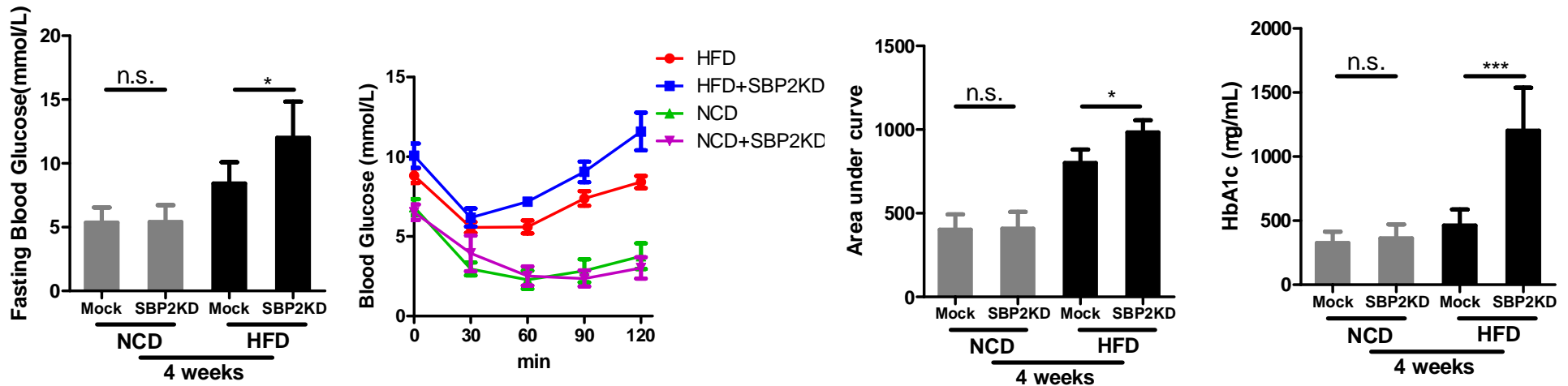


The mechanisms of SBP2 in inhibiting inflammation in ATMs: on one hand, SBP2 induces expression of anti-oxidative selenoproteins, leading to repression of intracellular ROS to suppress inflammasome activation; on the other hand, it could directly bind to caspase-1, inhibiting cleavage of pro-IL1β. Suppression of inflammasome reduces IL1β secretion and therefore inhibits inflammation.

SBP2的抗炎機制：一方面，SBP2誘導抗氧化的硒蛋白表達，抑制細胞內過氧化產物，從而抑制炎症小體；另一方面，SBP2直接與caspase-1結合，抑制IL1β前體活化。炎症小體的失活抑制了IL1β的釋放，從而降低了炎症。



Suppression of SBP2 in ATMs accelerates insulin resistance 抑制ATMs中的SBP2加速胰島素抵抗的產生



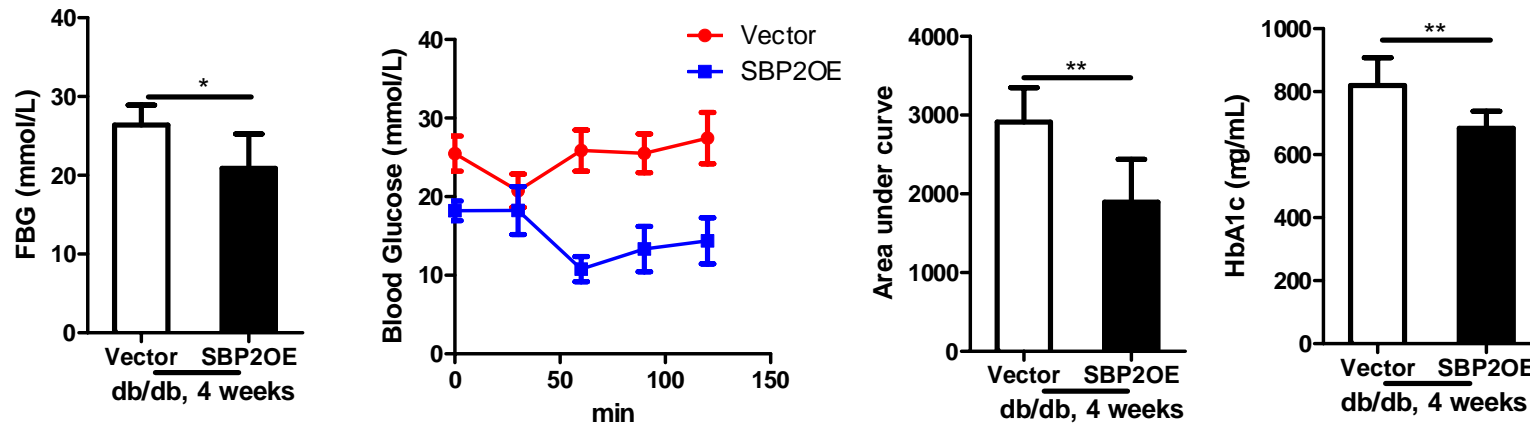
Knockdown of SBP2 in ATMs of mice increased fasting blood glucose, reduced insulin sensitivity and elevated serum Hb1Ac level in DIO mice, indicating accelerated development of insulin resistance

特異性地抑制ATMs中SBP2的表達使高脂飲食小鼠的空腹血糖升高，胰島素敏感性下降及血清糖化血紅蛋白水平升高，提示抑制ATMs的SBP2加速了胰島素抵抗的產生



Re-expression of SBP2 improves insulin sensitivity in diabetic mice

重表達SBP2提升糖尿病小鼠胰島素敏感性



Re-expression of SBP2 in diabetic mice suppresses fasting blood glucose, improves insulin sensitivity and reduces serum Hb1Ac, indicating improvement of insulin resistance.
重表達SBP2使高脂飲食小鼠的空腹血糖降低，胰島素敏感性提升及血清糖化血紅蛋白水平下降，提示胰島素抵抗的緩解。



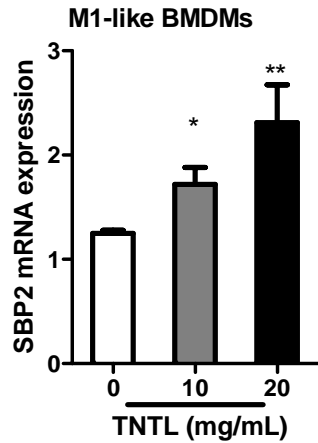
Can Chinese medicine formula treat diabetes? 中藥複方可以治療糖尿病或肥胖嗎？

- 我們的研究證明SBP2是一個在脂肪組織肥大細胞中調控肥胖和二型糖尿病的作用靶點，其升高可以恢復胰島素敏感性，提示SBP2可能為肥胖和二型糖尿病治療的新作用靶點。
- 目前尚未發現任何中西藥針對SBP2作用靶點。

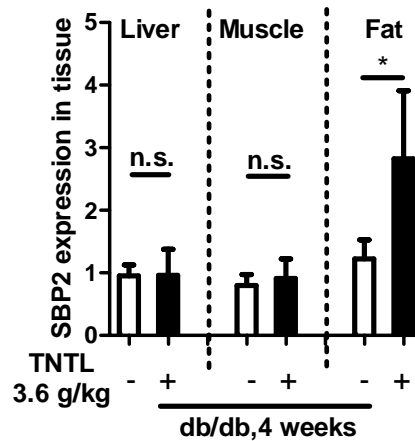


A Chinese Medicine formula, TNTL, could regulate SBP2 expression in ATMs

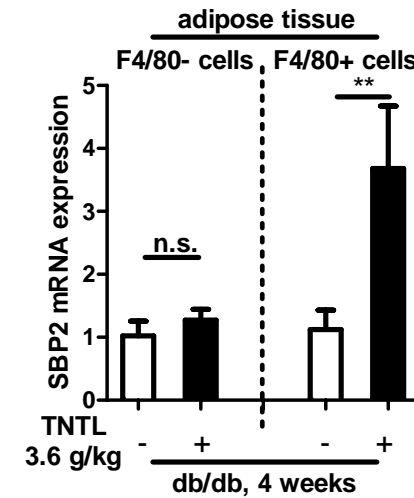
中藥複方TNTL能特異性地影響ATMs的SBP2



TNTL upregulates SBP2 expression in BMDMs
TNTL上調骨髓源巨噬細胞的SBP2表達



TNTL specifically upregulates SBP2 expression in adipose tissue of diabetic mice
TNTL特異性升高糖尿病小鼠脂肪組織SBP2表達



TNTL specifically upregulates SBP2 expression in ATMs
TNTL特異性升高糖尿病小鼠脂肪組織巨噬細胞SBP2表達



Chinese Medicine formula TNTL

中藥複方TNTL



Che-Qian-Cao
車前草



Shan-Yin-Hua
山銀花

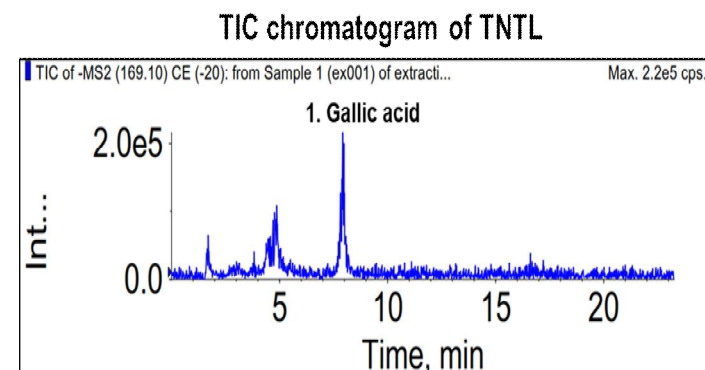


Xian-He-Cao
仙鶴草



Tian-Hua-Fen
(Fermented)
天花粉(發酵)

The herbal composition of TNTL
TNTL的組成中藥

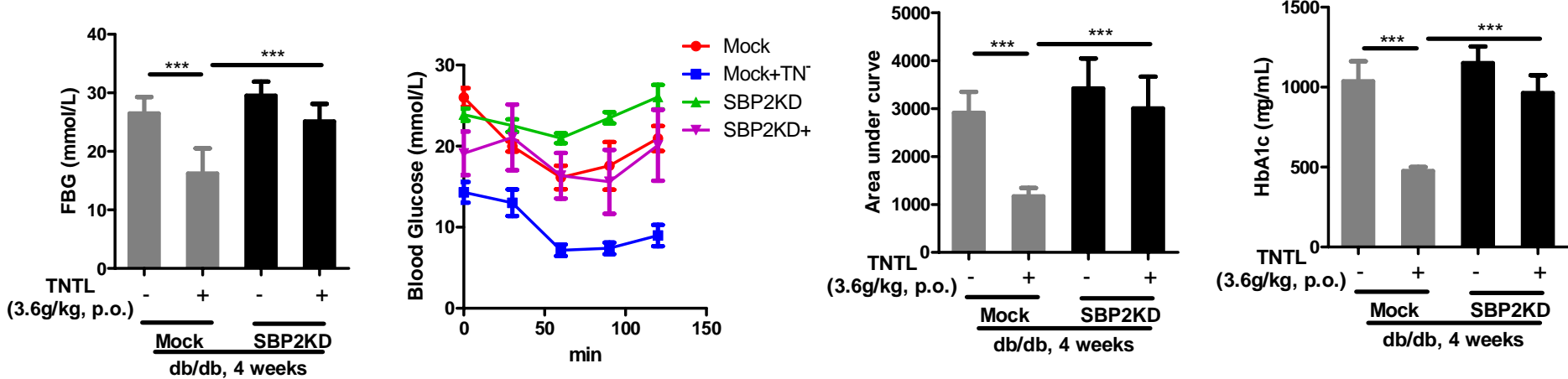


Chemical analysis of TNTL
TNTL的成分分析



TNTL improves insulin sensitivity in diabetic mice via SBP2

TNTL通過促進SBP2增強糖尿病小鼠的胰島素敏感性



Re-expression of SBP2 by TNTL in diabetic mice suppresses fasting blood glucose, improves insulin sensitivity and reduces serum Hb1Ac, which could be abolished by SBP2 knockdown

TNTL促使SBP2表達升高，從而使高脂飲食小鼠的空腹血糖降低，胰島素敏感性提升及血清糖化血紅蛋白水平下降。抑制TNTL引起的SBP2表達升高使其提高胰島素敏感性的作用減弱。

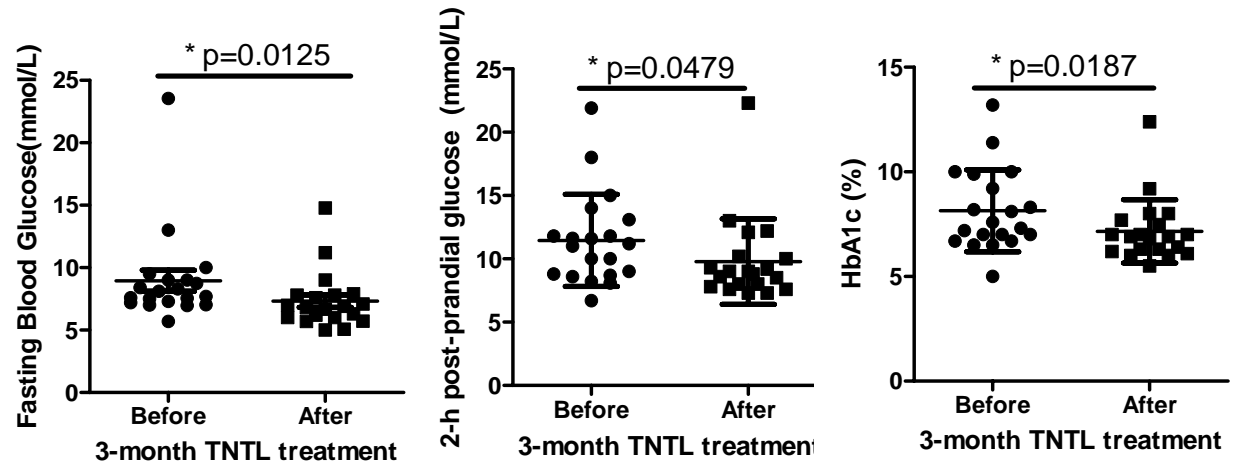


TNTL improves hyperglycemia in patients with diabetes

TNTL改善糖尿病病人血糖

Items	Characteristics (n=20)
Gender, male, n (%)	15(75%)
Age, Mean (SD), yrs	56.35(10.35)
Height, Mean (SD), cm	162.95(9.62)
Weight, Mean (SD), kg	66.75 (11.78)
Fasting blood glucose, Mean (SD), mmol/L	8.96(3.76)
Waist Circumference, Mean (SD), mmol/L	11.457(3.64)
HbA1c, Mean (SD), %	8.14%(1.95)
BMI, Mean (SD), kg/m ²	24.98(2.98)
Year since diagnosis, Mean(SD), yrs	4.70(4.45)
Antidiabetic treatment ever used	Metformin, Insulin, Gliclazide, Glimpiride, Acarbose, alone or in combination.

Patients information in clinical observation
臨床觀察病人基本情況



Patients with 3-month TNTL treatment (13.5 g/day, oral) showed improved fasting blood glucose, 2-h post-prandial glucose and Hb1Ac level
病人接受TNTL治療三個月後，空腹血糖、餐後血糖和糖化血紅蛋白水平得到改善。



Conclusion

結論

- 1. SBP2 is a novel target in the prevention and treatment of insulin resistance by improving adipose tissue inflammation.

SBP2作為一個新的靶點，可以抑制脂肪組織炎症的發生，從而預防和治療胰島素抵抗。

- 2. TNTL, a Chinese Miao formula, improves SBP2 expression and shows prominent effect in improving hyperglycemia in patients with diabetes.

作為一個苗藥傳統複方，TNTL能夠促進SBP2表達，並在臨床前的動物模型和糖尿病病人身上表現出顯著的降糖作用。



Conflict of Interest

Y.F. received research grants from Bailing Pharmaceutical Co., who provided a standardized extract of TNTL for the whole study. All other authors declare that they have no competing interests.

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Thank You