Soluble interleukin-6 receptor determines exercise responsiveness in term of insulin sensitivity and glycemic control

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Introduction

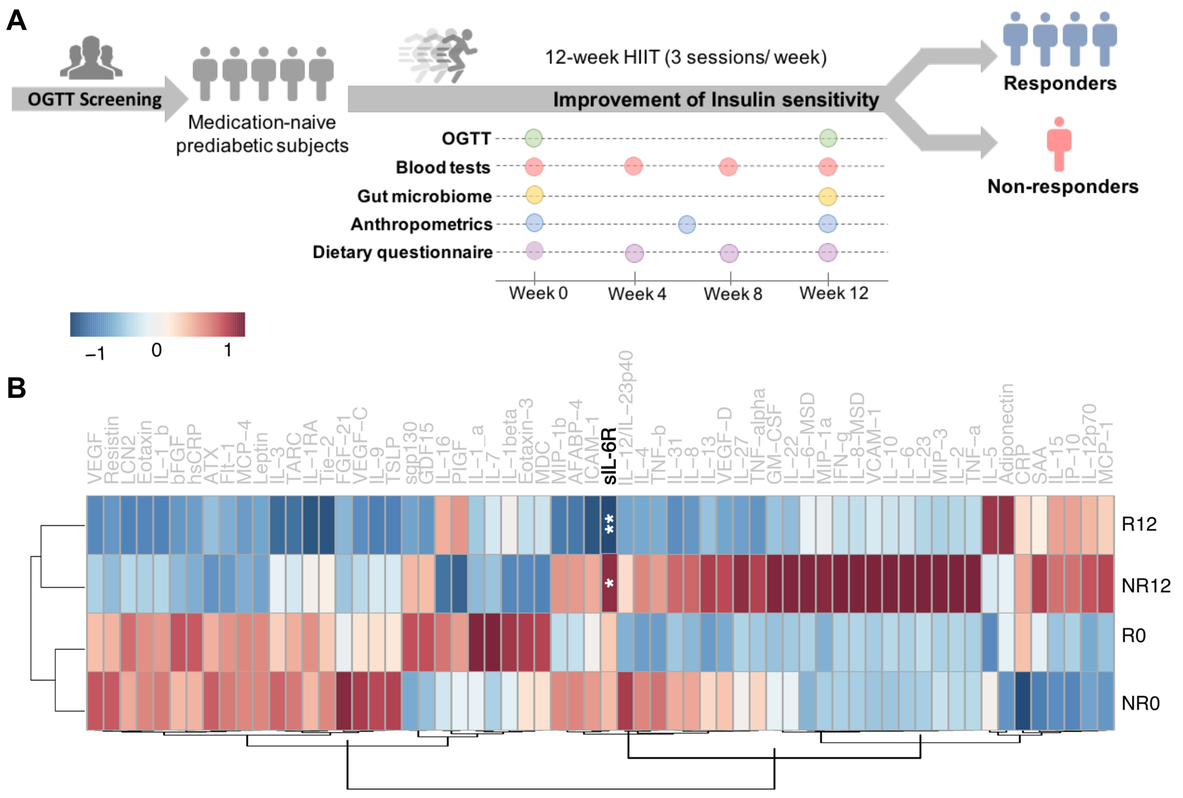
- Exercise is an effective non-pharmacological approach for diabetes management. However, highly interpersonal responsiveness in exercise and the lack of predictive biomarkers for exercise response restrain its current clinical implementation.
- Our previous clinical study demonstrated about 30% participants failed to improve insulin sensitivity and glycaemic control after exercise training.[1]
- Soluble interleukin-6 receptor (sIL6R) is a soluble form of the IL-6R, which is cleaved by the metalloproteinases ADAM17 from cellular membrane. [2]
- The sIL-6R is a major chemotactic cytokine playing vital roles in white adipose tissue macrophage recruitment and inflammation.[3]
- Serum sIL-6R levels correlate with the development of obesity and type 2 diabetes in humans.[3]

Objective

- To monitor the dynamic changes of serum cytokines and hormones levels in obese pre-diabetic subjects after 12-week exercise intervention;
- To screen blood-based exercise responsive biomarkers;
- To interrogate whether sIL-6R is a novel exercise responsive factor determining outcomes of exercise in term of insulin sensitivity and glucose metabolism

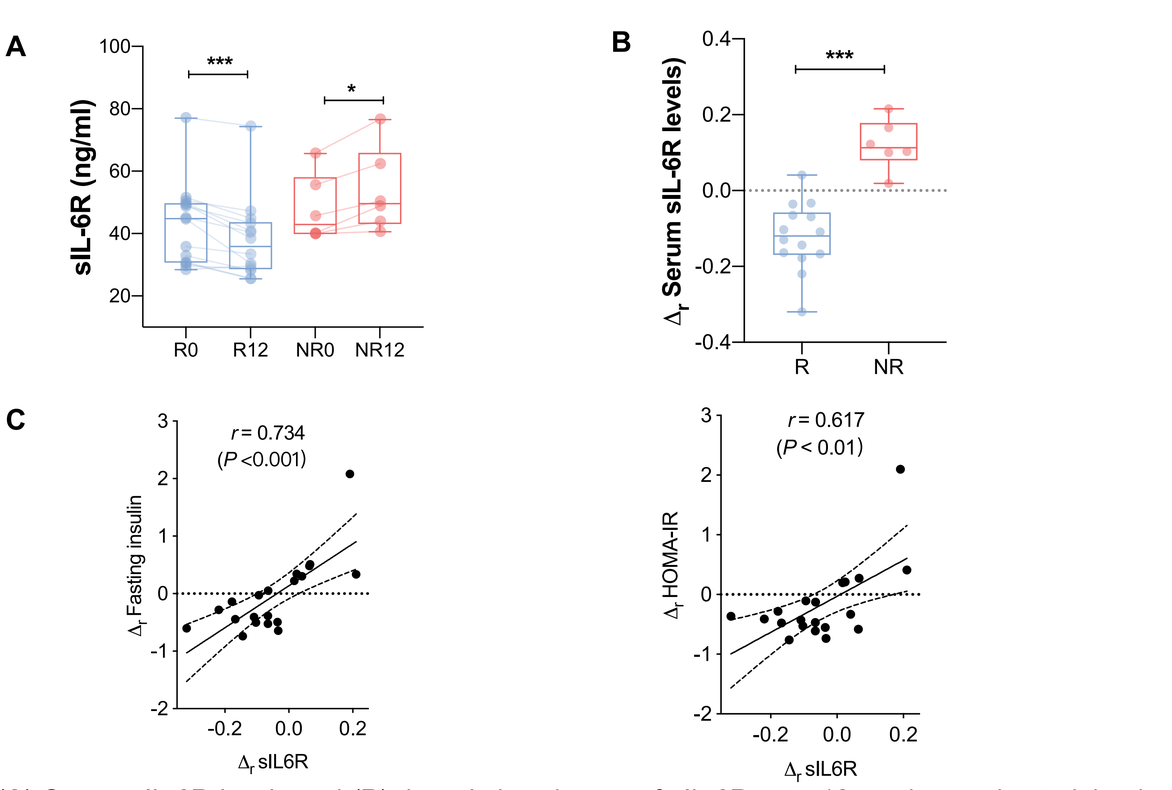
Results

Dynamic change of serum cytokines profiles in exercise responders and non-responders over 12-week exercise intervention program



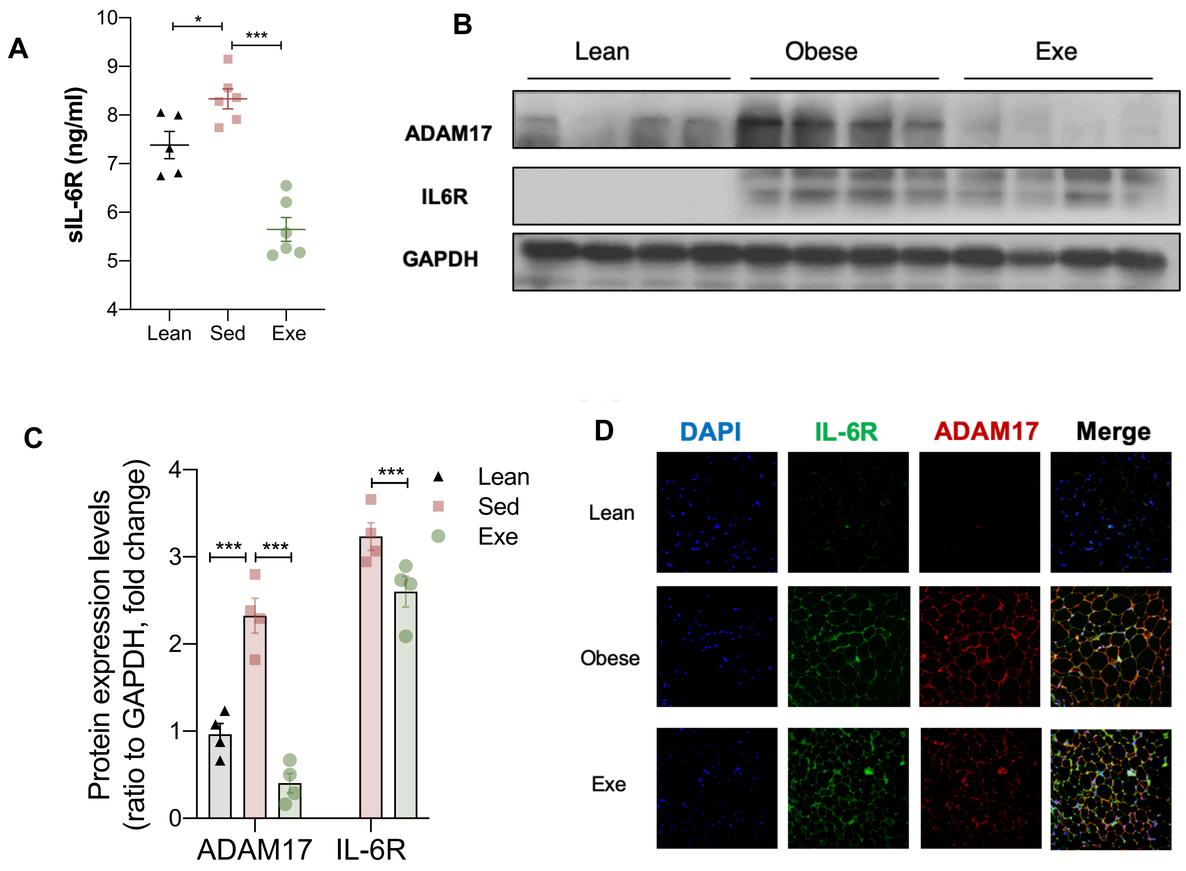
(**A**) Schematic diagram of the study design. (**B**) Heatmap showing the cytokines level assayed by MESO Scale Discovery electrochemiluminescence technology (MSD) or ELISA in serum from R and NR before (R/NR-0) and after exercise intervention (R/NR-12). The colors changing from blue to red indicate higher abundance. The heatmap was generated after data log transformation and auto scaling (n=20). **P*<0.05, ***P*<0.01 analyzed by paired Student's t-test within group.

The differential changes of serum sIL-6R levels in exercise responders and non- responders are associated with their exercise responsiveness in insulin sensitivity and glycemic control



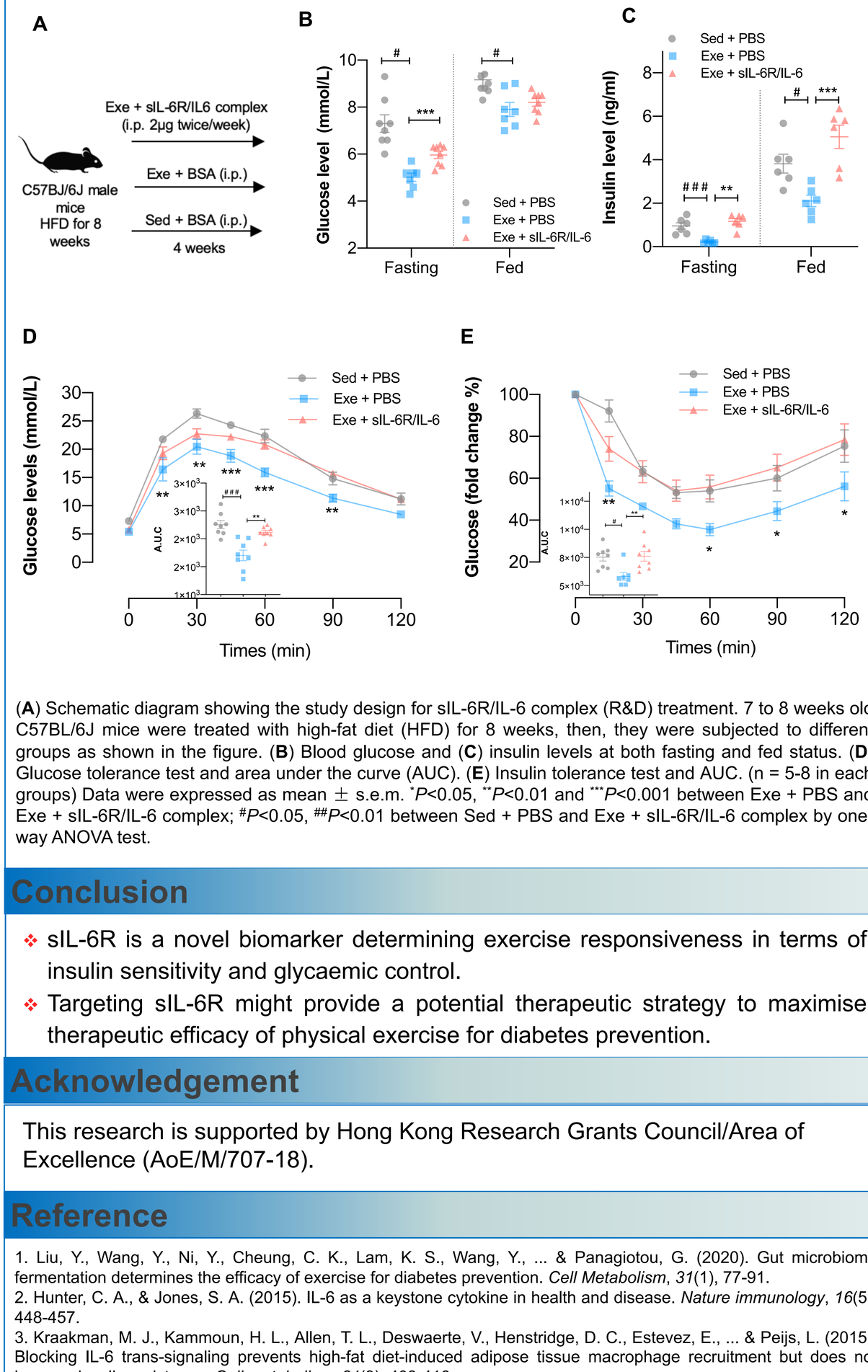
(**A**) Serum sIL-6R levels and (**B**) the relative change of sIL-6R over 12-week exercise training in exercise responders (R) and non-responders (NR). (R=14, NR=6) (**C, D**) Linear regression correlation of the alternation of serum sIL-6R and (**C**) exercise-improved fasting insulin and (**D**) HOMA-IR after 12-week training. (*n*=20). Data were shown as mean ± s.e.m., **P*<0.05, ****P*<0.001 analyzed by Student's *t*-test. *r* is correlation coefficient.

Exercise training reduces serum sIL-6R levels by down-regulating ADAM17 and IL-6R expression in white adipose tissue



(**A**) Serum sIL-6R level decreased in obese mice after exercise training. C57BL/6J mice were treated for 8 weeks high-fat diet (HFD) to induce obesity, then they were divided to exercise training (Exe) for 4-week treadmill training or sedentary (Sed) lifestyle. Lean mice were age-matched mice with standard chow feding. (**B, C**) protein expression levels of ADAM17 and IL-6R in white adipose tissue (WAT) and quantification results. (**D**) immunofluorescence staining (IF) of ADAM17 and IL-6R in WAT from different groups. (n = 5-8 in each group). Data were shown as mean ± SEM, **P*<0.05, ****P*<0.001 analyzed by one-way ANOVA test.

Administration of sIL-6R during exercise training abolishes exercise improved insulin sensitivity and glucose homeostasis in obese mice



(**A**) Schematic diagram showing the study design for sIL-6R/IL-6 complex (R&D) treatment. 7 to 8 weeks old C57BL/6J mice were treated with high-fat diet (HFD) for 8 weeks, then, they were subjected to different groups as shown in the figure. (**B**) Blood glucose and (**C**) insulin levels at both fasting and fed status. (**D**) Glucose tolerance test and area under the curve (AUC). (**E**) Insulin tolerance test and AUC. (n = 5-8 in each groups) Data were expressed as mean ± s.e.m. **P*<0.05, ***P*<0.01 and ****P*<0.001 between Exe + PBS and Exe + sIL-6R/IL-6 complex; #*P*<0.05, ##*P*<0.01 between Sed + PBS and Exe + sIL-6R/IL-6 complex by one-way ANOVA test.

Conclusion

- sIL-6R is a novel biomarker determining exercise responsiveness in terms of insulin sensitivity and glycaemic control.
- Targeting sIL-6R might provide a potential therapeutic strategy to maximise therapeutic efficacy of physical exercise for diabetes prevention.

Acknowledgement

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Reference

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