

Insulin receptor condensates in insulin sensitivity and resistance

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Insulin receptor (IR) signaling is central to normal metabolic control and is dysregulated in metabolic diseases such as type 2 diabetes. Here we consider whether a condensate model for IR provides insight on the molecular basis of insulin resistance. In normal cells, insulin stimulation results in accumulation of IR in bodies that display dynamic characteristics expected of liquid-like condensates. In insulin-resistant cells, both IR accumulation and dynamic behavior are reduced, suggesting a physico-mechanical link between insulin response and the dynamic behavior of IR condensates. Treatment of insulin-resistant cells with metformin, a first-line drug used to treat type 2 diabetes, can rescue accumulation and dynamic behavior of IR condensates. This rescue corresponds with metformin's role in reducing reactive oxygen species that interfere with normal condensate dynamics. These results indicate that changes in the physico-mechanical features of IR condensates contribute to insulin resistance and have implications for improved therapeutic approaches.