Journal of Bioanalysis & Biomedicine

Zhu et al., J Bioanal Biomed 2018, 10:5
DOI: 10.4172/1948-593X.1000e158

Editorial Open Access

The Role of USP18 in Insulin Resistance

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Brief Introduction to USP18

Host innate immunity is regarded as the first line of defense to fight against virus infections. Type I Interferon (IFN) is one of the main components in the innate immune response [1]. Type I and III IFNs function through activating the Jak/STAT signaling pathway and then up-regulating the expression levels of hundreds of interferon stimulated genes(ISGs) [2,3]. Many ISGs, including ubiquitin-specific protease 18 (USP18, also known as UBP43), exert important antiviral and/or immuno-modulatory effects in different stages of virus infection [4].

USP18 is a member of the deubiquitinating enzyme family [5], which removes ISG15 from its conjugated proteins (deISGylation) [6]. As a negative regulator of type I interferon signaling pathway [7], USP18 binds to the type interferon receptor sub-unit 2 (IFNAR2) to prevent JAK1 phosphorylation and thereby inhibit the type I/III IFN signaling pathways [8].

Insulin Resistance

The rates of insulin–mediated glucose disposal are varied in different populations, mainly due to adiposity, fitness or inheritance [9]. When the host's response to insulin decreases, which is named as insulin resistance (IR), insulin concentration will increase (hyperinsulinemia) to keep blood glucose level normal. Once the blood glucose derails during hyperinsulinemia, diabetes occur [10]. IR plays a fundamental role in the pathogenesis of type 2 diabetes mellitus (T2DM). In addition, IR is also related to other diseases, such as Alzheimer's disease, endometrial cancer, and inflammation [11,12].

The Role of USP18 in Insulin Resistance

USP18 alleviates insulin resistance through its deubiquitinating activity. Shimin et al. observed decreased expression levels of USP18 in the livers of non-alcoholic steatohepatitis (NASH) patients and obese mice [13]. This interesting observation indicates that USP18 is related to hepatic steatosis and glucose metabolism. In addition, the authors studied the function of USP18 in the obese mice through transgene and knockout technology. USP18 over-expression rescued insulin resistance and inflammation. On the other hand, USP18 knockout (deficiency) aggravated hepatic steatosis, insulin resistance and inflammation. Mechanistically, the authors focused their study on the upstream regulator, transforming growth factor β-activated kinase 1(TAK1), which was essential for USP18 to regulate hepatic steatosis, insulin resistance, and inflammation. They demonstrated that USP18 inhibits TAK1 activation through its deubiquitinating activity to suppress the downstream JNK and NF-KB signaling pathways. As a result, the USP18-TAK1-JNK1 axis balanced Ser/Tyr-IRS1 phosphorylation to regulate insulin sensitivity in hepatocytes. Therefore, USP18 could be a potential therapeutic target for NASH patients [13]. Furthermore, USP18 was found to directly interact with insulin receptor substrate-4(IRS4), which implied that USP18 may play an important role in insulin signaling pathway although the detailed mechanism remains to be determined [14].

Conclusion

Previously, many people thought virus infection has nothing to do with diabetes mellitus (DM). However, when people found that the diabetes mellitus was related to inflammation, the association between virus infection and DM drew a lot of attention. There is a close link between USP18 and DM as shown by the most recent study that USP18 could alleviate insulin resistance through its deubiquitinating activity. The role of USP18 induction following virus infection in IR and its underlying mechanisms remain to be determined.

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Received October 20, 2018; **Accepted** October 22, 2018; **Published** October 29, 2018

Citation: Zhu A, Chen L, Li Y (2018) The Role of USP18 in Insulin Resistance. J Bioanal Biomed 10: e158. doi:10.4172/1948-593X.1000e158

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