DISC1 promotes translation maintenance during sodium arsenite-induced oxidative stress

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Variation in Disrupted-in-Schizophrenia 1 (DISC1) increases the risk for neurodegenerative diseases, schizophrenia, and other mental disorders. However, the functions of DISC1 associated with the development of these diseases remain unclear. DISC1 has been reported to inhibit Akt/mTORC1 signaling, a major regulator of translation, and recent studies indicate that DISC1 could exert a direct role in translational regulation. Here, we present evidence of a novel role of DISC1 in the maintenance of protein synthesis during oxidative stress. In order to investigate DISC1 function independently of Akt/mTORC1, we used Tsc2?/? cells, where mTORC1 activation is independent of Akt. DISC1 knockdown enhanced inhibition of protein synthesis in cells treated with sodium arsenite (SA), an oxidative agent used for studying stress granules (SGs) dynamics and translational control. N-acetyl-cysteine inhibited the effect of DISC1, suggesting that DISC1 affects translation in response to oxidative stress. DISC1 decreased SGs number in SA-treated cells, but resided outside SGs and maintained protein synthesis independently of a proper SG nucleation. DISC1-dependent stimulation of translation in SA-treated cells was supported by its interaction with eIF3h, a component of the canonical translation initiation machinery. Consistent with a role in the homeostatic maintenance of translation, DISC1 knockdown or overexpression decreased cell viability after SA exposure. Our data suggest that DISC1 is a relevant component of the cellular response to stress, maintaining certain levels of translation and preserving cell integrity. This novel

function of DISC1 might be involved in its association with pathologies affecting tissues frequently exposed to oxidative stress.