A novel regulation of DNA repair in neurons: the complex of DISC1, GSK3β, and TRAX

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Mental disorders affect millions of people around the world, and account for a significant proportion of medical burden. Although tremendous efforts have been devoted to the development of therapeutic treatments for mental disorders in the past decade, many important mechanistic details remained elusive. Elevated oxidative stress that results in oxidative DNA damage and insufficient repair of DNA damage may cause abnormal neurotransmission and compromise neuronal survival, and aggravate the development of psychotic disorders. We recently reports that inhibition of GSK3β, by either agonists of the A_{2A} adenosine receptor ($A_{2A}R$) or inhibitors of GSK3β, enhances DNA repair activity via regulating the TRAX/DISC1/GSK3β (TDG) complex. Activation of $A_{2A}R$ leads to dissociation of the TRAX/DISC1/GSK3β complex (TDG complex). This is of great interest because TRAX plays a critical role in detecting DNA damage by directly interacting with ATM to trigger DNA repair machinery. Dissociation of the TDG complex facilitates the release of TRAX from the TDG complex and allows TRAX entering the nucleus to facilitate DNA repair and subsequently enhance neuronal survival. Collectively, the TDG complex might serve as a potential therapeutic target for the development of novel treatments for diseases with defects in DNA repair.