Sex-Specific Role for the Long Non-coding RNA LINC00473 in Depression

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Summary: This study interrogated the sex-specific role of long non-coding RNAs (lncRNAs) in depression. Women are twice as likely as men to develop depression and exposure to stress is a key environmental factor that is strongly associated with risk for depression. Recent evidence shows that up to one third of lncRNAs are differentially expressed in the brains of depressed patients and have region- and sex-specific patterns of regulation. Using human postmortem brain samples, the authors found that the lncRNA, LINC00473, is downregulated in the mPFC of depressed females, but not males. To examine the causal role for LINC00473 in depression, they generated viral vectors expressing LINC00473 and eGFP or eGFP alone and transfected them bilaterally into the mPFC of adult male and female mice. They found that LINC00473 expression promotes stress resilience in females, but not males. Specifically, social interaction deficits were rescued and circulating corticosterone levels were lower in LINC00473 females compared to control females following social defeat. LINC00473 females displayed decreased anxiety-like behaviors on a number of behavioral tests following chronic variable stress. A possible mechanism by which LINC00473 promotes resilience is via regulation of sEPSCs in the mPFC as the authors found decreased frequency and amplitude of mPFC pyramidal neurons in LINC00473 females. Finally, the authors were able to show that LINC00473 preferentially alters gene transcription in female human neural-like cells compared to males. These data suggest that lncRNAs support higher-order brain functions such as mood and that they contribute to the risk of psychiatric conditions, such as depression, in a sex-specific manner.

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