Mutations in Tumor Suppressor Genes: Links between Cancers and Autism Spectrum Disorders?

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Tumor suppressors play critical roles not only to prevent cells in a G0 quiescent state from re-entering the cell cycle for division and proliferation [1,2], but precisely promote the detachment of differentiating neurons from the neuroepithelium and regulate neural differentiation [3]. However, the functional losses in tumor suppressors result in uncontrolled cell proliferation in cancers, and as well as neural differentiation in neurodevelopmental disorders, such as autism spectrum disorders (ASDs).

Increasing evidence shows that rapid and excessive increase in head size and circumference in early childhood in children with ASDs in contrast to controls in similar age groups [4-7]. Intriguingly, the overgrowth problems in ASDs seem to be associated with some genetic syndromes involving losses of function in tumor suppressor genes, such as PTEN (phosphatase and tensin homolog), TSC1 or TSC2 (tuberous sclerosis 1 or 2) and NF1 (neurofibromin 1) [7-9]; whereas, the losses of function in those genes can lead to cancers of the breast, prostate, brain, colon, kidney and other organs [10-12]. These suggest the possible links between ASDs and cancers [13].

Recent study demonstrates that Tsc dysfunction results in increased mTOR (mammalian target of rapamycin) activity, and an mTOR inhibitor, rapamycin, whose derivatives have been used to treat cancers prevents the development of autistic behaviors in Tsc-deficient mice [8]. These experimental findings have led to an ongoing phase II clinical trials of RAD001, a rapamycin derivative, in reducing autistic symptoms in patients with tuberous sclerosis complex in Boston Children's Hospital [14]. This strongly supports the links between the two types of diseases, since the same strategy of mTOR inhibition that treats cancers has clinical potential for ASDs therapy as well.

However, there are debates on the links between cancers and ASDs, because some drugs (i.e., thalidomide, valproate) that have anti-proliferative effects on cancer cells are reported to elevate autism risk [15]. Thalidomide and valproate are known in cancer therapy for its proliferative effects on cancer cells are reported to elevate autism risk [15]. Thalidomide and valproate are known in cancer therapy for its proliferative effects on cancer cells are reported to elevate autism risk.

Although mutations in tumor suppressor genes may link cancers with ASDs, little are known about why mutations in those genes sometimes lead to ASDs and/or cancers and other times do not. It is likely that the genetic inclination associated with mutations in tumor suppressor genes toward cancers and ASDs may require some "triggers", such as environmental pollutants, to cause symptoms.

References


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