NOTCH3 signalling as a therapeutic nexus: Bridging cerebral small vessel disease and breast cancer pathophysiology

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Abstract

The neurogenic locus notch homolog protein 3 (NOTCH3), is central in both vasculogenesis and oncogenesis and, therefore, has been considered an important factor in the development of cerebral small vessel disease (CSVD) and breast cancer (BC). Pathogenic mutations of NOTCH3 induce vascular smooth muscle cell degeneration, microvascular dysfunction and neurovascular damage in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is a genetic cause of CSVD. Meanwhile, NOTCH3 aberrant signalling in BC promotes tumour progression, metastasis and chemoresistance, especially in aggressive subtypes, such as triple-negative BC. A growing body of evidence points to a common molecular pathway whereby NOTCH3 dysregulation mediates vascular and tumour pathologies, thus providing an

important link between these conditions. This narrative review synthesises current insights into the dual role of NOTCH3, focusing on translational relevance as a therapeutic target. Targeting NOTCH3 may mitigate vascular damage in CSVD and simultaneously inhibit tumour progression and metastasis in BC. The review further discusses NOTCH3 as a biomarker for early diagnosis and risk stratification, besides novel therapeutic strategies involving γ-secretase inhibitors and monoclonal antibodies. Future directions include studies into the ligand-independent functions of NOTCH3, its role within the tumour microenvironment, and the development of therapies with dual-action potential. This review discusses, for the 1st time, common mechanisms between CSVD and BC, thereby opening new avenues for therapies that could effectively target both conditions. By translating these laboratory findings into clinical applications, this approach aims to improve outcomes for patients affected by these devastating disorders. © 2025 Author(s).

Author keywords

Breast cancer; Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Cerebral small vessel disease; Neurogenic locus notch homolog protein 3; Tumor

Indexed keywords

EMTREE drug terms

biological marker; monoclonal antibody

EMTREE medical terms

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