Neuroscience and Symptoms Related to the CADASIL Disease

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ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) disease belongs to the group of rare diseases. It is well established that Notch3 protein is primarily responsible for the development of the CADASIL syndrome. Herein, we attempt to shed light to the actual molecular mechanism underlying CADASIL syndrome via insights that we have from preliminary in silico and proteomics studies on the Notch3 protein, which is involved in many cancers and in particular lung and ovarian cancer. In this disease we always see accumulation of Granular Osmiophilic Material (GOM), which has been a hallmark for the final diagnosis based on electron microscopy (EM). Consequently, we present the regions of the brain that get affected by the disease and their functions. Finally, the symptoms of CADASIL are examined with reference to the neurological analysis that has preceded.

Keywords: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), Cognitive Problems, Infarcts, Ischemic Episodes, Leucoencephalopathy, Migraine, Notch3, Psychological Problems, Stroke, Subcortical

INTRODUCTION

The ultimate goal of our research is to provide insights into the structural properties of the Notch3 protein that promotes the CADASIL syndrome. In order to achieve this, the 3D structural properties of the Notch3 protein must be analyzed. There is evidence that controlling Notch3 protein is very important for cancer progression. We know that Notch3 affects stem cell maintenance, development and death via its control on cell survival and angiogenesis. There is also evidence that Notch3 cross-talks with other oncogenes that are very important in the anti-cancer research field. The Notch3 signaling pathway is ligand-induced, where a ligand docks and induces the exposure of the S2 domain within the negative regulatory region (NRR). Therefore inhibition of Notch3 using the knowledge derived from the CADASIL

DOI: 10.4018/ijsbbt.2013100102
experiments may also lead to the development of a new anti-cancer strategy, comprising of novel Notch 3-specific inhibitor compounds.

Notch was first reported by T.H. Morgan almost a hundred years ago (Artavanis-Tsakonas & Muskavitch, 2010; Guruharsha et al., 2012; Louvi & Artavanis-Tsakonas, 2012). However, the first significant breakthrough came with Don Poulson in the 1930s (Poulson, 1936). Poulson linked the embryonic phenotypes that he was observing to deletions in the chromosomes. One of those deletions was Notch, which is a minor X-linked mutation. The Notch3 is a receptor protein that is strategically positioned on the surface of smooth muscle cell very close to the local blood vessels. Following Poulson’s findings it was found that if Notch switches off and becomes inactive, epidermal precursors kick in that convert normal cells to neuroblasts (Artavanis-Tsakonas & Muskavitch, 2010; Guruharsha et al., 2012; Louvi & Artavanis-Tsakonas, 2012). Neuroblasts differentiate and produce embryos that have nervous system hypertrophy and epidermal structure deficiencies. Bill Welshon then studied the 3C7 region on the X chromosome, where Notch is located. It was then that a very detailed map of Notch mutations was first drawn. In flies Notch is affecting a series of biological characteristics, including the definition of boundaries between cells with developmental roles (Demerec, 1950; Go, et al., 1998). Overall it is well established that Notch activity influences differentiation, proliferation and apoptosis.

Notch has been linked mainly to three inherited diseases, one of which is CADASIL. An excess of 190 mutations of the Notch3 gene have been found to induce CADASIL. CADASIL is a hereditary disease affecting over middle-aged adults, leading them to disability and dementia. CADASIL stands for cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy. It was first identified as a disease in 1993, even though there are records pointing back in 1955, when van Bogaert characterized CADASIL as the Binswanger disease (Artavanis-Tsakonas & Muskavitch, 2010; Guruharsha, et al., 2012; Louvi & Artavanis-Tsakonas, 2012). After a series of other patient incidences, CADASIL disease was linked to the Notch homolog 3 protein. The actual prevalence of the disease is unknown. However, CADASIL has been reported in more than five hundred families around the globe. The clinical manifestation of CADASIL can be described by five distinct symptoms. Those are: migraine with aura, subcortical ischemic events, mood disturbance, apathy and cognitive impairment. The symptoms can vary depending on patient age and progression of the syndrome (Artavanis-Tsakonas & Muskavitch, 2010; Guruharsha, et al., 2012; Louvi & Artavanis-Tsakonas, 2012).

Initiation of the Notch3 function and activation is triggered by small molecular ligands that bind to certain areas of the Notch3 receptor and activate it. The trans interactions between Notch and Delta is well documented (Artavanis-Tsakonas & Muskavitch, 2010). However, it is the ratio of ligand and receptor adjacent cell expression that dictate the level of activation. Each one of those two adjacent cells will have to take active roles either as signal receiving or a signal sending cell. The mechanism behind this is the critical ratio levels between functional ligand and receptor in each cell. The signal sending cell will be the one expressing more ligand whereas the signal receiving cell will be the one expressing more receptor (Artavanis-Tsakonas & Muskavitch, 2010). This asymmetry is mediated by feedback loops, whose mechanism still remain to be elucidated.

As mentioned above, Notch is capable of influencing cell proliferation, differentiation and apoptosis. Thereby, it is directly linked to major cell anomalies such as cancer. Notch activation will definitely affect cell proliferation in a repertoire of cellular contexts. It is noteworthy that activation of Notch can even influence the proliferation patterns of non-adjacent cells. Today, the exact molecular and structural mechanism behind this phenomenon remains elusive. For example, it has been demonstrated in a mouse tumor model that Notch activation in the crypts of the adult mouse led to dramatic proliferation increase in the area
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