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Original Research

Differential Gene Expression Signatures and Cellular Signaling Pathways induced by Lamin A/C Transcript Variants in MCF7 Cell Line

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Abstract

Background: Lamins are the major component of nuclear lamina. Alternative splicing of the 12 exons comprising *lamin A/C* gene creates five known transcript variants, lamin A, lamin C, lamin AΔ10, lamin AΔ50, and lamin C2. The main objective for this study was to examine the association of critical pathways, networks, molecular and cellular functions regulated by each Lamin A/C transcript variants. **Methods**: Ion AmpliSeq Transcriptome Human Gene Expression analysis was performed on MCF7 cells stably transfected with lamin A/C transcript variants. **Results**: Lamin A or lamin AΔ50 upregulation was associated with activation of cell death and inactivation of carcinogenesis while both lamin C or lamin AΔ10 upregulation activated carcinogenesis and cell death. **Conclusions**: Data suggest anti-apoptotic and anti-senescence effects of lamin C and lamin AΔ10 as several functions, including apoptosis and necrosis functions are inactivated following lamin C or lamin AΔ10 upregulation. However, lamin AΔ10 upregulation is associated with a more carcinogenic and aggressive tumor phenotype. Lamin A or lamin AΔ50 upregulation is associated with a predicted activation of increased cell death and inactivation of carcinogenesis. Thus, different signaling pathways, networks, molecular and cellular functions are activated/inactivated by lamin A/C transcript variants resulting in a large number of laminopathies.

Keywords: lamin A/C transcript variants; senescence; laminopathies; nuclear lamins; Ion Torrent

1. Introduction

Lamins are architectural protein components of the cell nucleus. Because of their ability to polymerize, they form molecular networks that anchor nuclear embedded proteins and peripheral chromatin components within the nuclear envelope, which confers mechanical stability, and thus have been implicated in the role of maintaining the structural integrity and overall mechanical stability of the nucleus [1]. Lamins participate in diverse nuclear cell functions including maintenance of the genome in a specific structural organization [2–5]. Lamins have also been shown to play a pivotal role in DNA repair, replication, and transcription, and thus affect cellular differentiation, apoptosis, and cell aging. Furthermore, lamins are classified as type V intermediate filament proteins, which can be categorized according to their sequence and structural organization as either A-type or B-type lamins [5]. The A-type lamins have 2 major isoforms (lamin A and lamin C) and three minor isoforms (lamin AΔ10, lamin AΔ50 [Progerin] and lamin C2), while the B-type lamins have two major isoforms (lamins B1 and B2). A-type lamins are expressed mostly in somatic cells, whereas B-type lamins are usually ubiquitously expressed and interact in the nuclear lamina's assembly process [5].

Lamin A, Lamin C, along with Progerin (Lamin AΔ50), Lamin AΔ10, and Lamin C2 (specific to the testis) are all derived from a single gene (*Lamin A/C*) by alternative splicing of one transcript of the gene, which contains exons 1 through 12 [2,3,6]. Consideration of Lamins as individual disease causing elements within the cell and nuclear lamina requires a deeper understanding of the Lamina network. The first 566 amino acids of human Lamin A/C, spanning exons 1–10, are identical in lamin A and lamin C. However, lamin C has six unique carboxyl-terminal amino acids [7]. Both Lamins A and C have been given the role of establishing nuclear mechano-transduction and stiffness, however, it has been found that Lamin C correlates more with mechanical properties than Lamin A. Unlike Lamin A, which has a prelamin that undergoes tail domain cleavage modification once it is inside the nucleus, Lamin C is the only Lamin that does not undergo post-transitional modifications with a farnesylated tail domain. Consequently, its expression is unaffected by certain mutations that occur in genes affecting farnesylation, which is a feature of Lamin A-specific disease [8].