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Review

Commonality amid diversity: Multi-study proteomic identification of conserved disease mechanisms in spinal muscular atrophy

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Abstract

The neuromuscular disease spinal muscular atrophy (SMA) is a leading genetic cause of infant mortality, resulting from low levels of full-length survival motor neuron (SMN) protein. Despite having a good understanding of the underlying genetics of SMA, the molecular pathways downstream of SMN that regulate disease pathogenesis remain unclear. The identification of molecular perturbations downstream of SMN is required in order to fully understand the fundamental biological role(s) for SMN in cells and tissues of the body, as well as to develop a range of therapeutic targets for developing novel treatments for SMA. Recent developments in proteomic screening technologies have facilitated proteome-wide investigations of a range of SMA models and tissues, generating novel insights into disease mechanisms by highlighting conserved changes in a range of molecular pathways. Comparative analysis of distinct proteomic datasets reveals conserved changes in pathways converging on GAP43, GAPDH, NCAM, UBA1, LMNA, ANXA2 and COL6A3. Proteomic studies therefore represent a leading tool with which to dissect the molecular mechanisms of disease pathogenesis in SMA, serving to identify potentially attractive targets for the development of novel therapies.

Keywords: Spinal muscular atrophy; SMA; SMN; UBA1; Proteomics

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disease, primarily characterised by loss of motor neurons from the anterior horn of spinal cord and atrophy of skeletal musculature. The disease is considered to represent a "continuum of clinical severity" [1], but is broadly subdivided into four sub-types, depending on the developmental milestones that are reached: type 1 (severe), type 2 (intermediate), type 3 (mild) and type 4 (adult-onset) [1]. Type 1 SMA is the leading genetic cause of infantile death in the western world and infants typically die before the age of two due to respiratory failure [2,3].

The cause of SMA for the majority (>95%) of patients is a loss-of-function defect in the *SMN1* gene, resulting in reduced levels of the ubiquitously-expressed survival of motor neuron (SMN) protein [4]. Although most humans possess at least one copy of an additional – and almost identical – *SMN2* gene, protein translated from *SMN2* is much less stable and unable to fully compensate for loss of *SMN1* [4–6]. The severity of the disease is largely dependent upon the number of *SMN2* copies that are present. Thus, patients with the most severe phenotypes tend to have a lower copy number of *SMN2* [7].

At present, there are no disease modifying treatments available for SMA, and palliative support is the best that can be offered to patients. However, significant progress has been made over the last two decades in terms of both basic research and pre-clinical development, leading to the identification of several promising therapeutic approaches entering clinical trials. Almost all of this therapeutic work has focused

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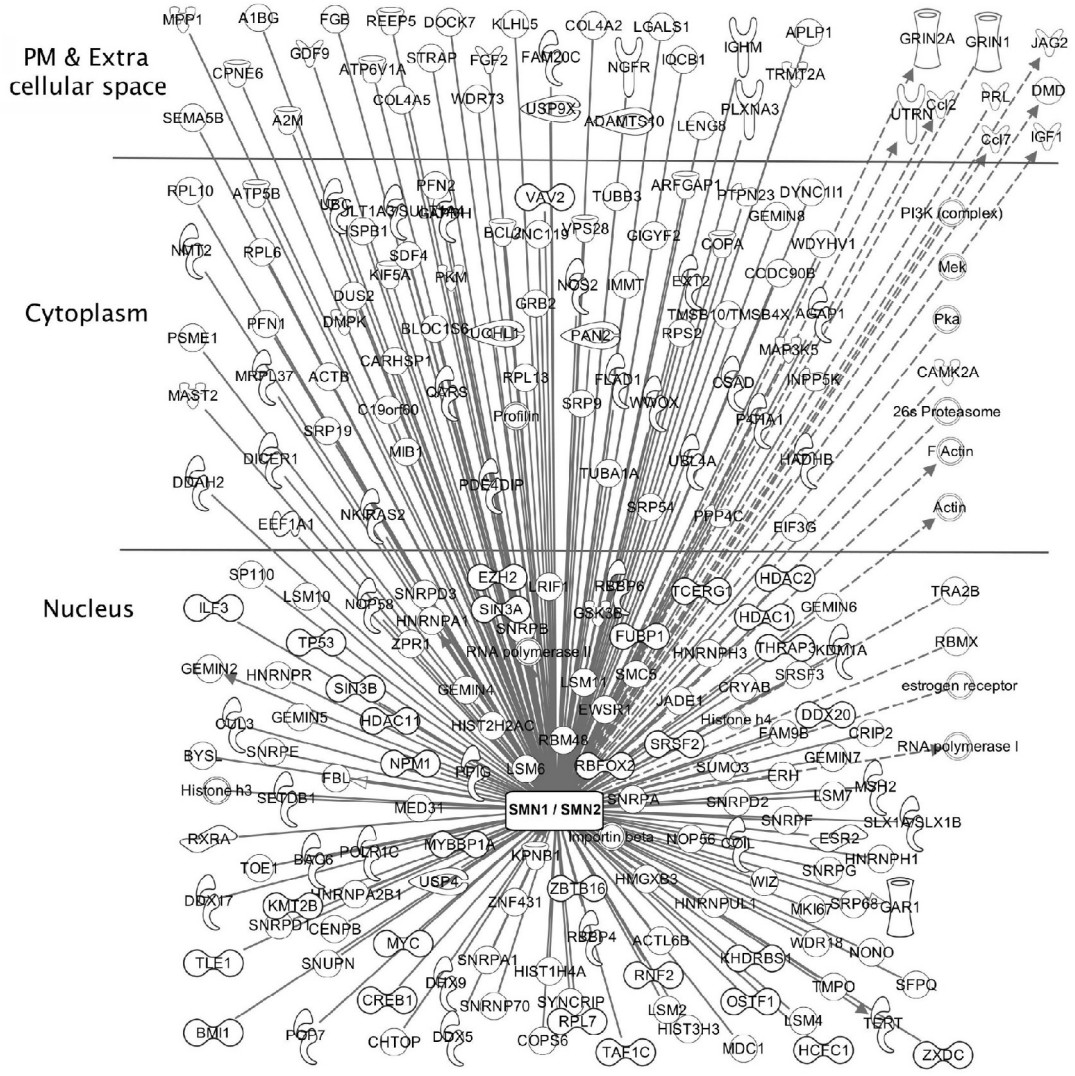

Fig. 1. The SMN interactome. Ingenuity Pathway Analysis (IPA) software-based identification of all known interacting partners of SMN protein reported in the published literature. Candidate interactors are organised based on their predominantly reported subcellular localisation and does not mean that they are exclusively restricted to these positions. These interactions are direct (solid lines) or indirect (dotted lines), and may have been reported following identification at the genomic, transcriptomic or proteomic (DNA, RNA and/or protein) level. As a result, the schematic presented here represents the known "interactome" for SMN as identified by IPA.

on identifying compounds aimed at targeting either *SMN2* promoter activation, modulation of splicing, or *SMN1* replacement gene therapy [8]. In contrast, the ability to identify potential non SMN-focused therapeutic targets has been hampered by a lack of understanding of the core molecular pathways acting downstream from SMN to modulate disease pathogenesis in SMA [9].

SMN is a ubiquitously expressed protein with a role in the assembly of small nuclear ribonucleic proteins (snRNPs) in the cytoplasm and subsequent transport into the nucleus for RNA splicing [4,10]. To do this, SMN functions as a core complex with at least eight other proteins: gemins 2–8 and unrip. In addition to this well-characterised housekeeping role, SMN appears to interact with several other proteins required for the transport and correct localisation of mRNAs in axons [11–13]. Whilst some of these SMN interactions are relatively stable (in the case of the core complex with gemin proteins), there are many other interactions that are expected to be more transient [14]. A search of two protein interaction databases, Biomolecular Interaction Network Database (BIND) and the Molecular INTeraction database (MINT), suggests that in excess of 100 proteins have the potential to interact with SMN. Given the potential size of the "SMN interactome" (Fig. 1), and the fact that each of those interacting proteins may also have their own unique "interactome", it seems highly probable that a reduction of SMN should have significant downstream molecular consequences affecting a range of different target proteins and pathways.

Recent advances in proteomic technologies have enabled researchers to take an unbiased, global view of the proteome,