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EC PROTEOMICS AND BIOINFORMATICS
Opinion

Nuclear Transport Receptors: Moonlighting Proteins Aberrantly Expressed in Cancer

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Received: July 29, 2016; **Published:** August 23, 2016

The concept of moonlighting proteins has emerged in the last years to indicate proteins that serve more than one function, and/or act in independent processes. Moonlighting proteins are examples of "functional re-adaptation" to the changing needs of different cell types, context, biological or environmental conditions. These proteins are being demonstrated to be of growing importance in biological processes and dedicated databases are being constructed [1-3].

Some members of the karyopherin family of nuclear transport receptors (i.e., importin beta-1, alpha-1, alpha-3, beta-2/transport in, import in 13, and export in-1/XPO1/CRM1) are recognized in at least one of the moonlighting databases for having a double role. We previously illustrated the moonlighting functions of human importin beta-1 by proteomic detection of its mitotic interactors, coupled with time-lapse imaging of mitotic cells that overexpress it: we reported that importin beta-1 regulates the timing of kinetochore delivery of two proteins whose pathways are important for kinetochore function during mitosis: the RAN GTPase regulator RANGAP1, and the SUMO ligase RANBP2 [4].

Interactomic studies ongoing in our laboratory are expanding the list of both "constitutive" and cell cycle phase-specific, alternative molecular cargos that importin beta-1 is able to interact with during cell cycle progression. These findings indicate that importin beta-1's moonlighting functions are even more intricate than previously thought. In-depth analyses of the three-dimensional structures of importin beta-1 available from the Protein Data Bank [5] provided us with rational bases to build models for importin beta-1 interactions with specific mitotic targets and to predict how importin beta-1 deregulated levels might affect the function of those targets during mitosis.

We propose that all nuclear transport receptors are bonafide moonlighting proteins with distinct functions in distinct cell cycle stages or cell types. In interphase they interact with proteins tagged by nuclear localization signals (NLS) or nuclear export signals (NES), and transport them in and out of the nucleus to operate in their physiological subcellular compartments. In mitosis, when nucleo-cytoplasmic transport ceases, they are functionally "recycled" to orchestrate new functions at mitotic structures: centrosomes, asters, mitotic spindle poles, microtubules and chromosomal kinetochores [6,7] (importin beta-1 is depicted in Fig. 1). Some karyopherin family members act in specialized communication in neurons [8] and/or at a centrosome-related organelle, the cilium, present in some cell types including neuronal subtypes [9,10]. Remarkably, the pathological consequences of nuclear transport receptor dysfunction, i.e. abnormal mitosis originating genetic instability - a cancer hallmark - and complex syndromes such as ciliopathies, are attributable to their "secondary" functions.

Growing evidence indicate that nuclear transport receptors are abnormally expressed in cancer types [11,12]. Efforts are being made to develop inhibitors with potentially therapeutic purposes [13,18]. Implementation of *ad hoc* bioinformatics and proteomic studies is es-

sential to reveal the full extent of promiscuity and moonlighting functions of nuclear transport receptors and identify molecular features involved in specific interactions. This, in turn, is the required basis to rationally design compounds potentially effective in cancer contexts in which these receptors are aberrantly expressed.

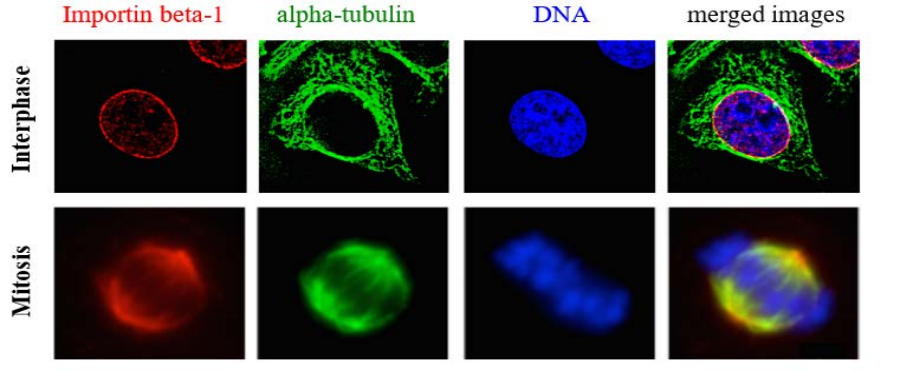

Figure 1: The localization of importin beta-1 in human cells illustrates its moonlighting functions during the cell cycle. *Top row: importin beta-1 (in red) accumulates at the nuclear envelope encircling the nucleus (blue) in interphase to perform its function as a nuclear transport receptor. Staining of alpha-tubulin (in green) depicts the interphase cytoskeleton. Bottom row: in mitosis importin beta-1 (red) associates with the spindle microtubules (green), with enrichment at the spindle poles, to regulate the activity of the mitotic apparatus and hence segregation of chromosomes (in blue). Regions in which importin-beta 1 overlaps with alpha-tubulin appear in yellow in the merged pictures.*

Acknowledgment

Our work is supported by the CNR Flagship "InterOmics" project.

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Volume 1 Issue 1 August 2016