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LETTER TO THE EDITOR Open Access

Morphoproteomics and biomedical analytics coincide with clinical outcomes in supporting a constant but variable role for the mTOR pathway in the biology of congenital hyperinsulinism of infancy

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Abstract

We first introduced the concept of the mTOR pathway's involvement in congenital hyperinsulinism of infancy (CHI), based largely on morphoproteomic observations and clinical outcomes using sirolimus (rapamycin) as a therapeutic agent in infants refractory to octreotide and diazoxide treatment. Subsequent publications have verified the efficacy of such treatment in some cases but limited and variable in others. We present further evidence of a constant but variable role for the mTOR pathway in the biology of CHI and provide a strategy that allows for the short-term testing of sirolimus in individual CHI patients.

Keywords: Morphoproteomics, Biomedical analytics, Congenital hyperinsulinism of infancy, Sirolimus

The severe form of diffuse hyperinsulinemic hypoglycemia is mainly associated with mutations in *ABCC8* and *KCNJ11* that are unresponsive to diazoxide and/or octreotide therapy [1, 2]. This poses a threat to the infants with CHI not only by causing potential neurological damage leading to epilepsy, cerebral palsy and adverse neurological development in up to 40% of cases [3, 4] but also necessitating in some, near total pancreatectomy. Furthermore, 59% of such surgically treated patients can show persistent hyperinsulinemic hypoglycemia for up to 5 years post-surgery, and eventually diabetes mellitus will be manifested in all by the time they reach early adolescence [5].

The microanatomical characteristics of the diffuse form of CHI include non-proliferative, islet cell nucleomegaly [6]. In this context we have shown that the mammalian target of rapamycin (mTOR) protein, phosphorylated (p) on serine 2448, p-mTOR (Ser 2448) is overexpressed but variably on the plasmalemmal aspect of the acinar cells in CHI [7] and variably in the cytoplasm and nuclei of the insulin-producing islet cells, including those with karyomegaly [8] (Fig.1).

Biomedical analytics using Ingenuity Pathway Analysis and data mining of the National Library of Medicine's Medline Data Base confirms the role of the mTOR pathway [8] in the biology of CHI with actionable therapeutic targets. A CHI network was constructed using the known CHI-associated genes described by Dunne and Banerjee's associates [9]: *GLUD1, SLC16A1, HADH, UCP2, KCNJ11, ABCC8, HNF1A, GCK, HNF4A*.

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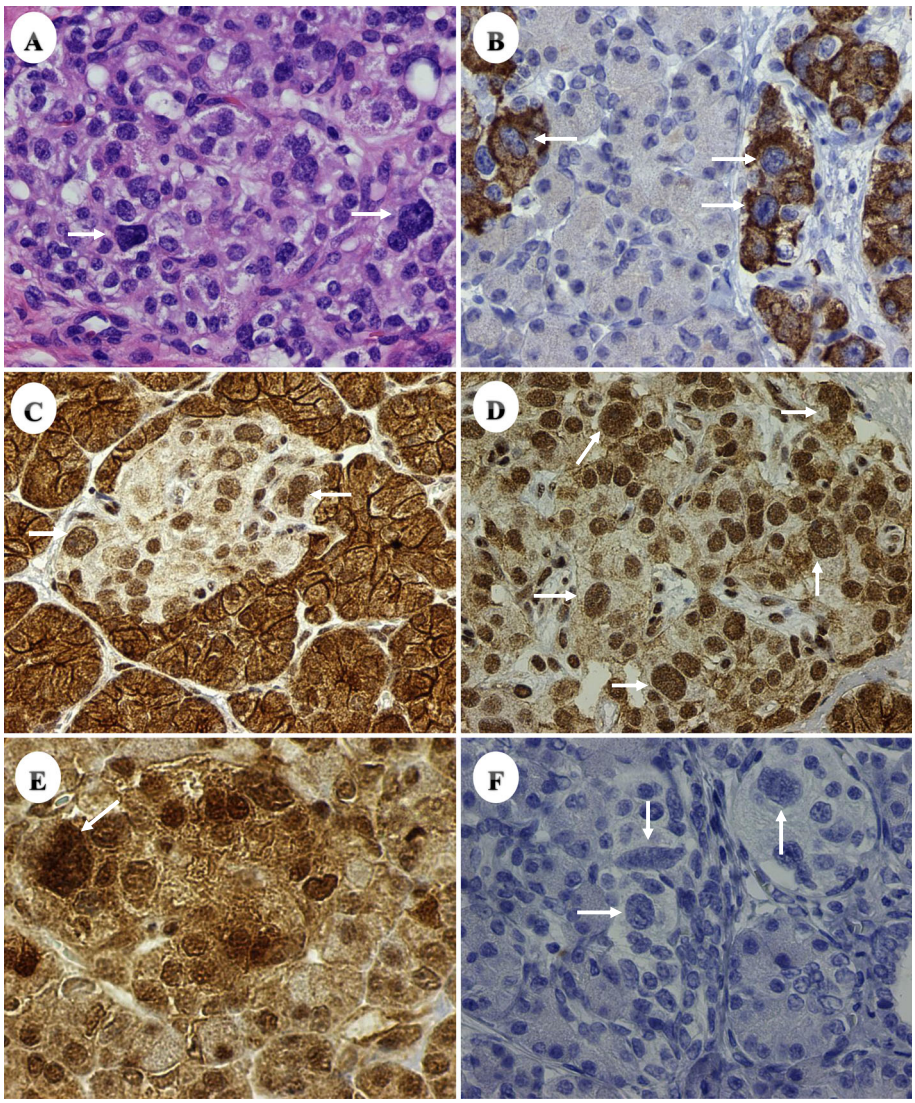

Fig. 1 Pancreas of infant with CHI and paternal ABCC8 showing nucleomegaly (arrows) in islet cells, with insulin production (Frames **a**, H&E and **b**, beta cells with insulin), p-mTOR (Ser 2448) on the plasmalemmal aspect of the acinar cells and positivity in the islet cells with nucleomegaly (Frames **c** and **d**), p-Akt (Ser 473), expression in the islet cells with nucleomegaly (Frame **e**) and contrastively, the negative control (Frame **f**) (Original magnifications frames **a**-**d** and F ×400 and ×600 for frame **e**)

The network showed that the MTOR-related molecules: MTOR, Raptor, Rictor, MTORC1 (but not MTORC2) interacted with all 9 CHI genes (Fig. 2). More than 300 interactions were identified (not shown due to complexity of image). Sirolimus modulated the MTOR group and thus, indirectly, the 9 CHI gene group. Sirolimus also increased expression of human UCP2 mRNA in the 9 CHI group [10].

Parenthetically, the contention by Banerjee and colleagues [4] that mTOR mRNA equates to *mTOR* gene in pancreases from normal, focal CHI, and diffuse CHIexpression could be accurate. Alternatively in the context of the morphoproteomic evidence of variable but constant activation and overexpression of the mTOR pathway in pancreases from diffuse CHI, it could represent the resultant of a steady state of transcription, translation and utilization of mTOR mRNA [11] following the integration of genomic, proteomic and pathway biology. Notably pathway ontology associated with the CHI disease network includes mTOR signaling [9]. Moreover, the clinical outcomes coincide with the findings of a variable therapeutic success in using sirolimus in the treatment of CHI [2, 12–18]. In the context of risk [3–5] versus benefit, we hold that severe diffuse CHI

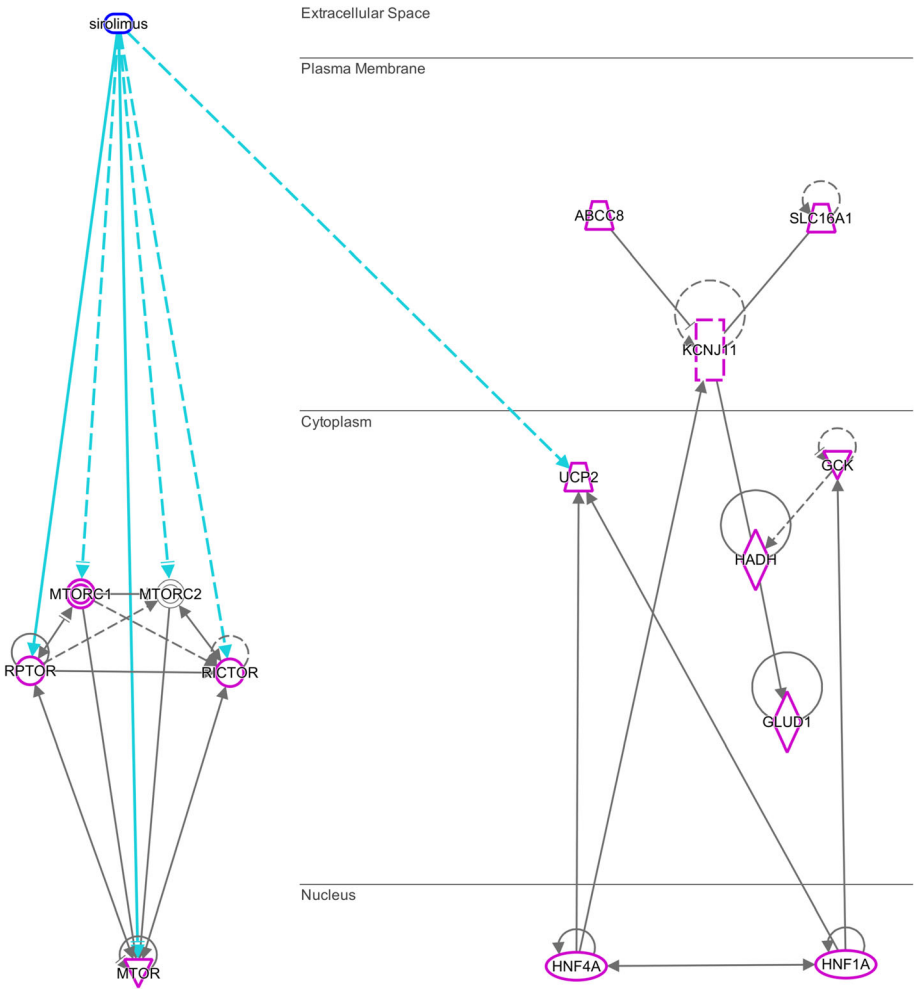

Fig. 2 MTOR-related molecules (left) have more than 300 interactions (magenta highlights) with all 9 CHI genes (right) identified by Dunne and Banerjee [9] (interactions not shown due to density.) Direct interactions: solid lines; indirect interactions: dashed lines. Activation/expression: (–→), inhibition: (–|), inhibits and acts upon: (–|>)

infants deserve a trial with an appropriate dose of sirolimus to see whether it is effective keeping in mind and monitoring for the potential immunosuppressive and adverse consequences of sirolimus [2]. We agree that sirolimus with or without other combinatorial therapies (octreotide, nifedipine, exendin-(9-39) and metformin) to counter the variable but constant activation of the mTOR biology in CHI should be explored in larger clinical trials.

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Please contact author for data requests.

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Not appropriate.

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