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Commentary

Costello Syndrome: The Challenge of Hypoglycemia and Failure to Thrive

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Costello Syndrome (CS) is a rare genetic disorder caused by germline gain of function mutation in the proto-oncogene *HRAS* (Aoki et al., 2005). Most of the affected individuals show p.G12S autosomal dominant mutation (~80% of cases reported to date), however different amino acid changes have been reported in minority cohorts and an attempt to assign genotype/phenotype correlation has been provided (Gripp and Lin, 2012).

CS is a multiple congenital anomalies syndrome mainly affecting cardiac, musculoskeletal, cutaneous and central nervous systems. Facial dimorphisms are distinctive and an aged phenotype usually develops from the first years of life. Severe failure to thrive from postnatal onset, sometimes associated to hypoglycemia and growth hormone (GH) deficiency, is one of the most challenging clinical problems to manage (Gripp and Lin, 2012). Most patients require nasogastric tube or gastrostomy during the first years of life to be fed. Although most affected children improve by gaining weight after 3 to 4 years of age, the final growth in terms of weight and height still remain under the normal centiles compared to the general population (Gripp and Lin, 2012).

It has been speculated that growth delay in Costello syndrome likely arises from multiple issues, in particular low caloric intake after birth, feeding difficulties, delay in oro-motor function and gastro-esophageal reflux (Leoni et al., 2016). Recently, increased resting energy expenditure measured by indirect calorimetry in a cohort of individuals affected by CS, provided evidence of a new possible mechanism underlying failure to thrive in this condition (Leoni et al., 2016). In the same patient cohort the Authors detected low glucose and high cholesterol levels in the blood and described normal/high daily caloric intake in the CS cohort compared to the recommended levels of nutrients, excluding low caloric intake as a reason for poor weight gain. In particular a high protein and lipid, and low carbohydrate diet was observed. Whereas fasting hypoglycemia has been previously reported in CS linked to GH and cortisol deficiency (Gregersen and Viljoen, 2004), pancreatic hyperplasia and hyperinsulinemic hypoglycemia (Alexander et al., 2005), Leoni and co-workers were the first to observe high cholesterol concentrations as a frequent metabolic finding detected in CS.

Since the germline gain of function mutation in the *HRAS* gene have been reported to cause CS by Aoki and Co-Workers in 2005, few research groups have generated animal models to better elucidate the roles played by *HRAS* mutations. To date four groups have developed CS mouse models, all expressing the Hras G12 V mutation (Schuhmacher et al., 2008; Chen et al., 2009; Viosca et al., 2009; Schreiber et al., 2017). It is worth noting that to date, all researchers have focused their attention on the description of facial phenotype (Schuhmacher et al., 2008; Chen et al., 2009), cardiac abnormalities (Schuhmacher et al., 2008), the understanding of cognitive deficits (Viosca et al., 2009; Schreiber et al., 2017) and explanation of mechanisms leading to tumor development (Chen et al., 2009).

Although the HRAS p.G12S mutation represents the most frequent amino acid change causing CS, no one scientific group have developed an $Hras^{G12S}$ knock-in mice so far. Moreover, even though the failure to thrive and hypoglycemia do represent respectively the first severe clinical and metabolic challenge to manage CS-affected individuals soon after birth, no one had studied the metabolic profile and biochemical changes on animal models until the paper presented in this issue by Oba et al. (2017).

Oba and co-authors, generated an HRAS G12S knock-in mouse and evaluated changes in its facial, cardiac and kidney morphology and focused their attention on metabolic assessment. Their mouse model exhibited craniofacial features overlapping with CS in humans, cardiomegaly with cardiomyocyte hypertrophy and kidney fibrosis. No papilloma or angiosarcoma development was observed until the age of 1 year. The authors accurately described the growth phenotype, the

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metabolic changes and the liver findings occurring in $Hras^{G12S/+}$ mice fed under a controlled diet before and high fat diet (HFD) subsequently. Interestingly $Hras^{G12S/+}$ knock-in mice developed a peculiar metabolic profile and growth impairment only after prolonged fasting under HFD. On the contrary, children affected by CS do not need to be induced with HFD regime to show severe feeding difficulties and failure to thrive. In fact they usually present with these findings soon after birth.

The evidence of metabolic changes in $Hras^{G12S/+}$ mice when consuming HFD reported by Oba et al., led the authors to support the hypothesis that oncogenic RAS signaling in mice modulates energy homeostasis in vivo. Leoni et al., first detected high blood cholesterol levels and high protein/lipid diet profile in a CS cohort, however did not provide data on mitochondrial function tests, and in particular on fatty acid oxidation metabolites.

To conclude, the paper by Oba et al., represents the first attempt to define possible mechanisms underlying hypoglycemia and failure to thrive in CS, using mouse models. Not all findings reported by the authors have been reported in individuals affected by CS to date (i.e. normal weight under control diet, cystic kidney, hepatic steatosis), nevertheless they provided new insights about mechanisms underlying metabolic changes and energy homeostasis in this condition.

Although many issues still need to be addressed, this paper should incentivize physicians and basic scientists to confirm present findings on HRAS G12S knock-in mice, to clarify the pathophysiology of metabolic profile (specifically hypoglycemia) and failure to thrive in CS, and to carry out possible overlapping results on energy homeostasis in relevant animal models and humans.

Disclosure

The author declared no conflicts of interest.

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