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MM9

Integrated computational and experimental approaches for the identification of new molecules with readthrough activity on premature termination codons (PTCs) in cystic fibrosis cells

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Cystic Fibrosis (CF) patients with nonsense-mutation in the CFTR (Cystic fibrosis transmembrane conductance regulator) gene generally make virtually no CFTR protein and thus often have a more severe form of CF. Recently, Ataluren (PTC124; Translarna) was suggested to induce the readthrough of premature termination codons mainly the UGA codon. However, despite promising results there is not a general consensus on efficacy and mechanism of action. The design of new small molecules (PTC124 related) together with the understanding of their mechanism of action could lead to new pharmacologic approaches for the cure of CF. This work was aimed to identify new molecules (PTC124 analogues) with readthrough activity and to evaluate their efficacy in CF cells. In particular, the experiments were conducted in different cell model systems: 1- human cells transfected with vectors containing PTCs in reporter genes; 2- primary human bronchial epithelial cells 3- immortalized epithelial cells of cystic fibrosis (CF) patients. Design and synthesis of the new PTC's read-through promoters was based on the results obtained by a virtual screening approach. We synthesized 18 analogues of the PTC124 and tested some of them in three different biological models. The FLuc assay and IB3.1 cell lines were used to test the new identified products. Three of these new compounds showed high read-through capacity in CF cells. Finally, computational studies were aimed to model the interaction between the bioactive synthesized compounds and the possible cellular target, in order to understand the mechanism of action of the new synthesized analogues.

MM10

Maternal high fat diet consumption during pregnancy and lactation: impact on intestinal morphology and function in preweaning offspring

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Different evidence supports an important role for maternal obesity in the development of childhood obesity and subsequent adult disease. This study is addressed to investigate if and to which extend maternal high fat feeding would induce compensatory and adaptative responses in gut predisposing to the eventual development of paediatric obesity. Adult female mice were divided into two groups fed with i) high fat (HF) diet and ii) standard chow (SC)diet, during pregnancy and lactation. HF mothers showed a significant weight gain, higher levels of blood glucose and an abnormal glucose tolerance compared to SC mother, indicating the establishment of metabolic syndrome. Then, offspring subdivided according to maternal diet, O-SC pups birthed from mothers fed SC, whereas O-HF pups birthed from mothers fed HF diet, and morphological and functional experiments were performed in the small intestine 2 developmental ages, early suckling (P2) and late suckling (P15) to evaluate the contribute of maternal milk in the development of obesity. O-HF at P2 and P15 did not show significant changes in the morphology of the small intestinal wall (villus height, depth of the crypt, villus width near the crypt and thickness of the muscular layer) compared to O-SC. Moreover in agreement with morphological data, no difference has been found in the amplitude and frequency of the intestinal spontaneous mechanical activity from O-HF compared to O-SC. The contractile and relaxant responses to well know drugs as the muscarinic receptor agonist, carbachol, and the □-adrenergic receptor agonist, isoproterenol, were similar in both groups of animal. This study suggested that during lactation,