MAPK15 PROTECTS AGAINST DIET-INDUCED PROGRESSIVE METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Background:

Large epidemiological and health impact assessment studies indicate that environmental exposures we are subjected to throughout our life are important risk factors for the development of most non-communicable diseases, overall accelerating the natural aging process. Luckly, numerous genes evolved to efficiently counteract the deleterious effects of the human exposome. Among them, MAPK15 has repeatedly demonstrated a key role in protecting cells from both endogenous and exogenous sources of cellular damage.

Methods and Results:

By taking advantage of a novel *MAPK15* knockout (*MAPK15*$^{-/-}$) mouse model, we investigated the protecting role of this gene against liver steatosis and the correlated metabolic dysfunction-associated steatotic liver disease (MASLD), which represents the most common chronic liver disease worldwide. Specifically, we show that *MAPK15*$^{-/-}$ mice presented a typical MASLD phenotype, with increased accumulation of lipids in the liver, overweight phenotype, dyslipidemia and insulin resistance. Importantly, we demonstrate that dysregulated accumulation of intracellular lipids was caused by increased expression and membrane localization of the CD36 fatty acid translocase, which controls the rate of exogenous lipid uptake into cells. Strikingly, feeding *MAPK15*$^{-/-}$ mice with a western-style diet to increase the availability of exogenous lipids, strongly accelerated MASLD progression to metabolic dysfunction-associated steatohepatitis (MASH).

Conclusions and Significance:

Overall, we demonstrate that MAPK15 can strongly mitigate some of the deleterious effects of one of the leading health risk factors for several cardiometabolic human diseases, represented by impaired diet quality and composition and excessive food intake, which is estimated to cause, every year, millions of premature deaths worldwide. Our results also suggest that pharmacological modulation of *MAPK15* expression and/or activity may successfully prevent MASLD onset and its most devastating clinical consequences, i.e. cirrhosis and HCC.

Keywords:

Western diet; steatohepatitis; CD36; Lipid droplets; Knockout mice.

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