Stress kinases as potential targets to treat obesity-associated pathologies

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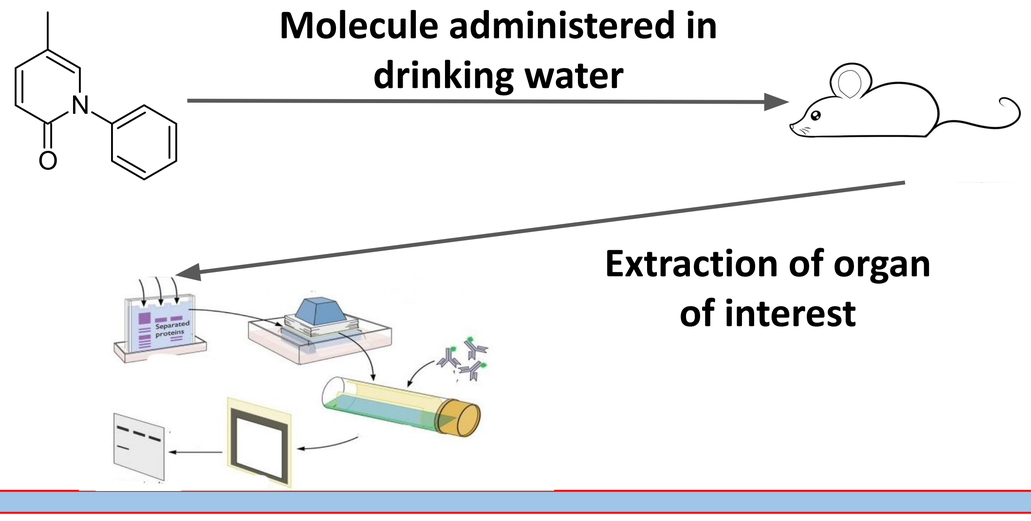
Stress-activated protein kinases (SAPK), a subclass of mitogen-activated protein kinases (MAPK), have shown their involvement in numerous pathologies such as hepatocellular carcinoma or organ development like heart growth. These proteins, as their name implies, are activated by external stimuli and are particularly sensitive to the metabolic stress induced to the organism by obesity, thus favouring the development of abnormal phenotypes in organs like heart hypertrophy or cancer as well as other pathologies. The aim of this study was to focus on the involvement of these proteins in the development of the aforementioned pathologies and the development of molecules capable of inhibiting these kinases.

I. INTRODUCTION

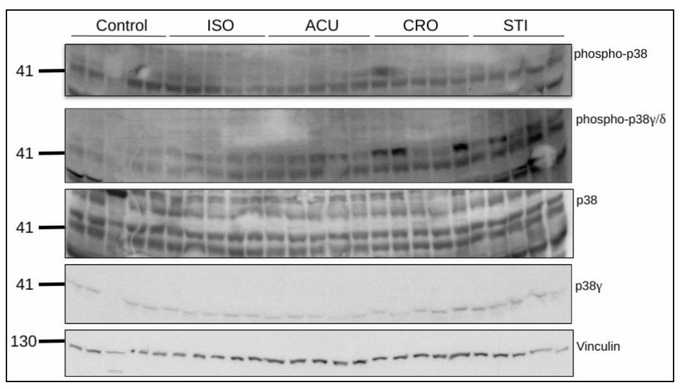
We singled out two promising inhibitor candidates, Pirfenidone and FK080, and proceeded to assess their effects on SAPK pathways. Said pathways are comprised of the JNK and p38 proteins. The complexity of the pathways and cascades tying these proteins can't be easily illustrated and are still under study.

II. METHODOLOGY

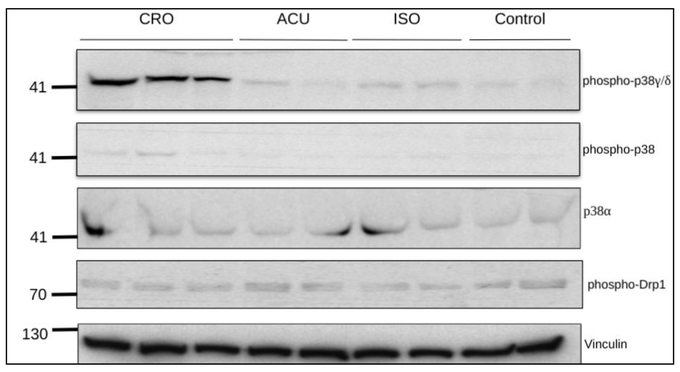


III. RESULTS

Pirfenidone increases p38γ phosphorylation in the heart

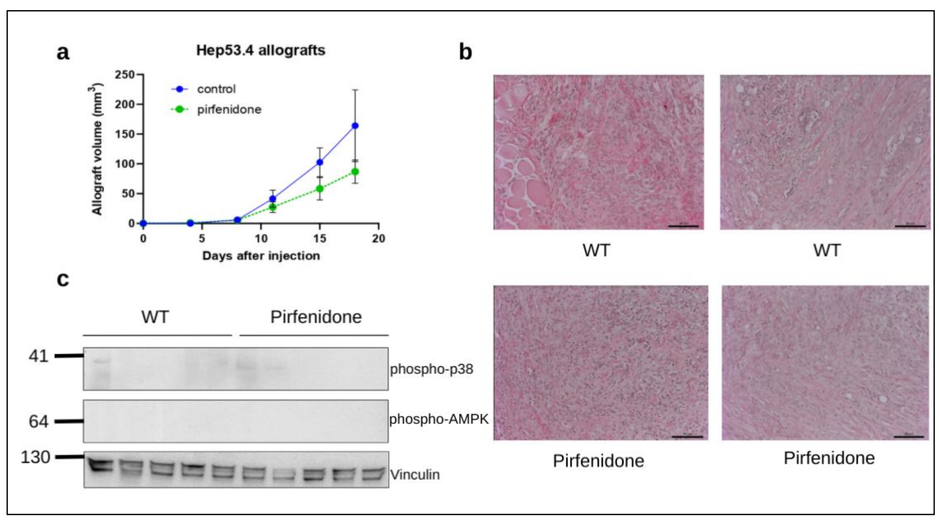


- Increased activation of p38γ in the majority of CRO mice



- No differential expression of p38α between all mice

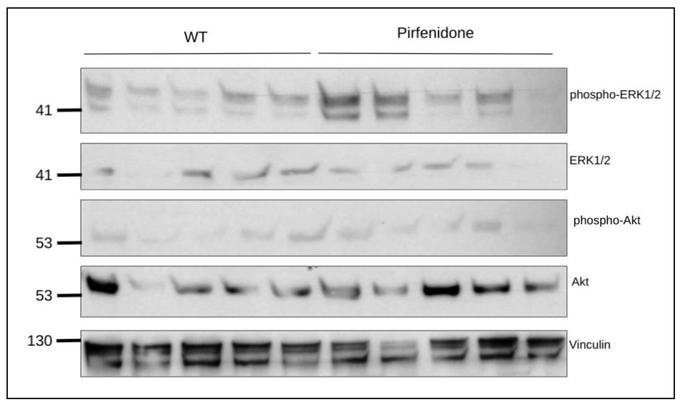
SAPKs participate in crosstalk between tissues and organs

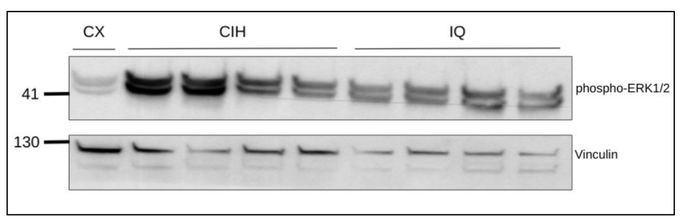


- No significant decrease in the tumoral allograft size

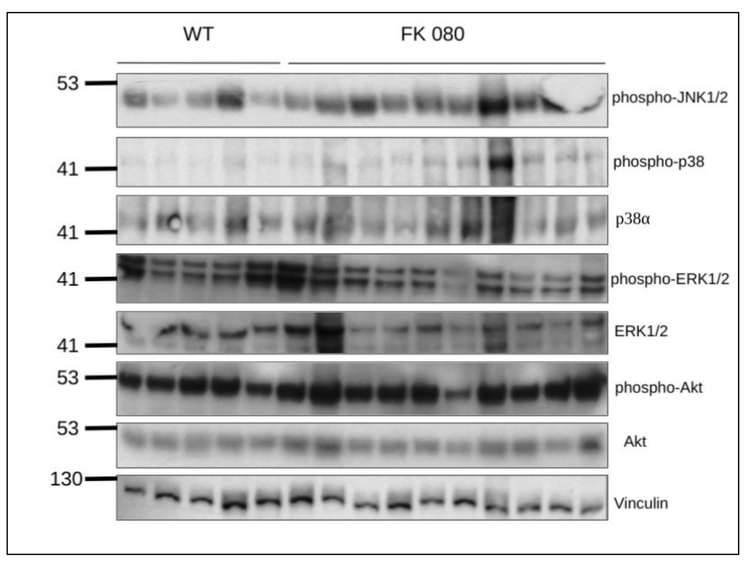
- Cell survival and growth wasn't further promoted by the tested molecule

- MAPK communicate between them and are capable of mutually induce activation of their pathways





FK 080 induces activation of stress pathways



- Results indicate that stress pathways were upregulated by the molecule's effect in treated mice

IV. DISCUSSION

Results clearly indicate that FK 080 needs more development and much like pirfenidone investigation of its effects in other extracted tissues should be made. A deeper investigation of the networking of SAPKs in the different tissues is essential to precisely understand the organisation of their pathways, and provide potential therapeutic strategies as well as finding useful molecules for the treatment and diagnosis of SAPK-induced pathologies. The tissue-specific effects of SAPKs demonstrate their tight regulation and differences. Furthermore, the molecular mechanisms that control the in vivo effects underlying these strategies are not fully understood. More studies with animal models, in which selectively one of the four p38 subclasses or JNK proteins are depleted in different tissues are required.