FBXW7 E3 ubiquitin ligase ameliorates insulin sensitivity in equine metabolic syndrome-affected liver by targeting Fetuin-A hepatokine

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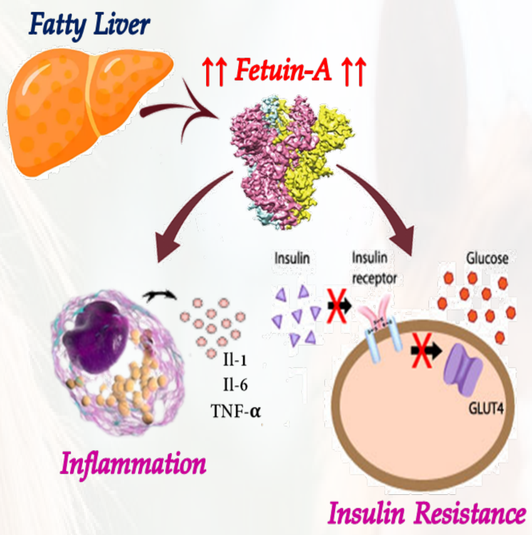
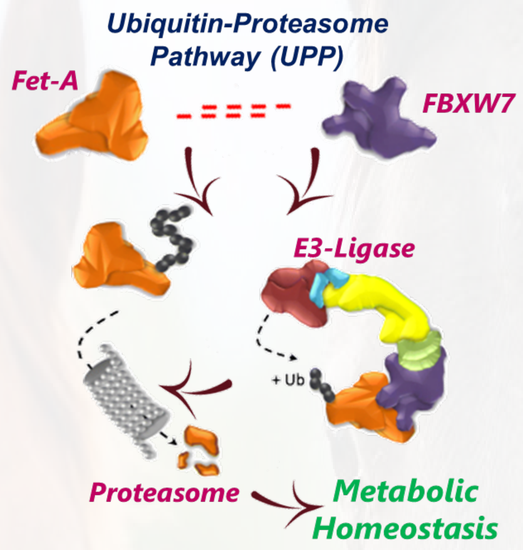
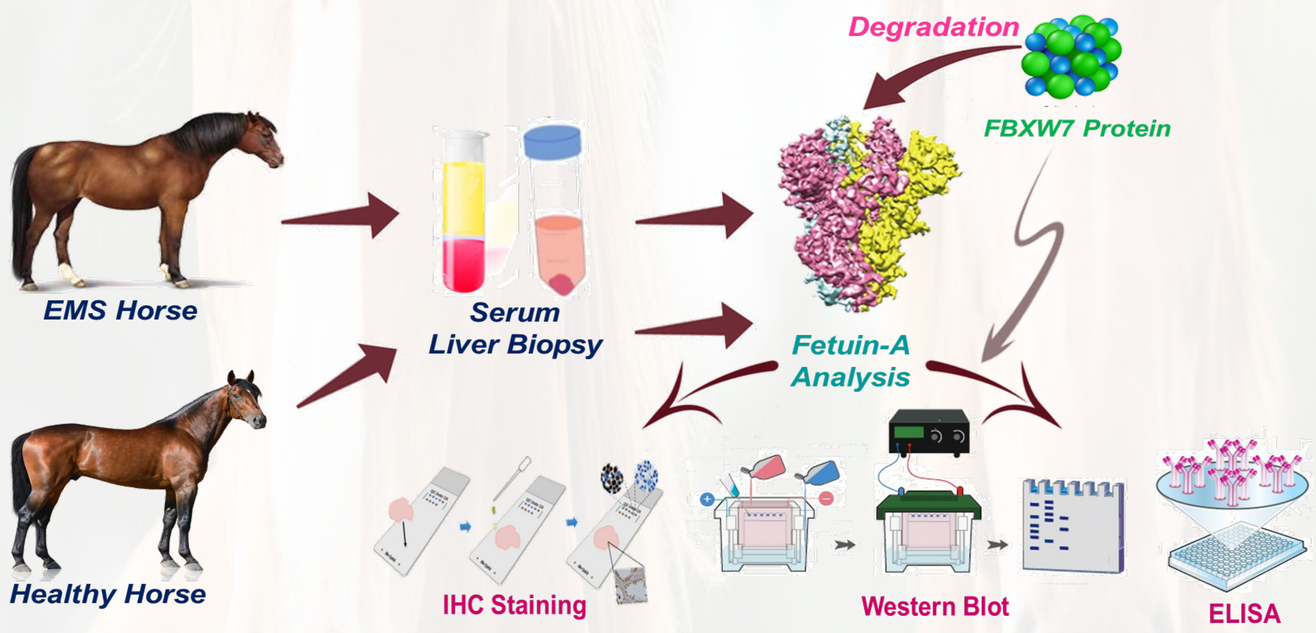
Fetuin-A is a glycoprotein dominantly produced by the liver. It has been the subject of research in relation to insulin resistance and inflammation, particularly in the context of metabolic disorders such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease.
Research has suggested that elevated levels of fetuin-A may be associated with insulin resistance and inflammation, although the exact mechanisms involved are still a subject of investigation.





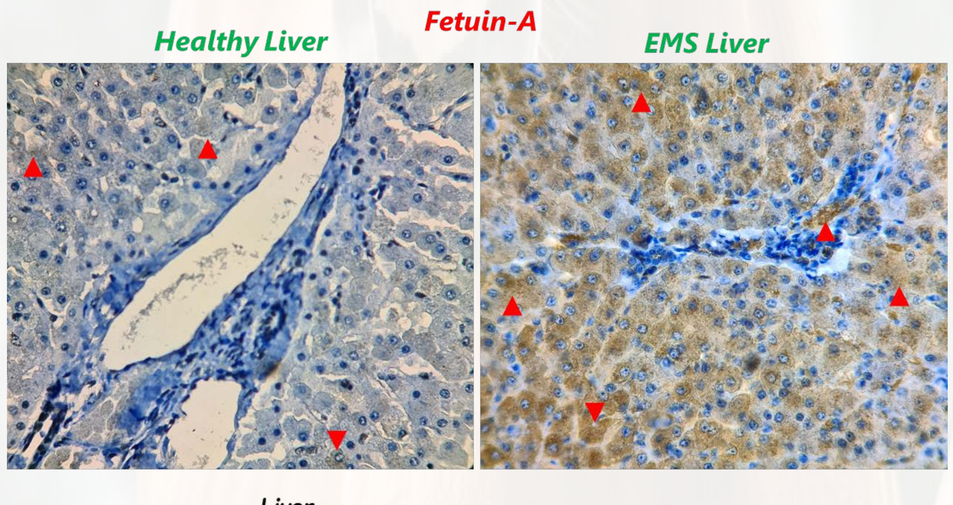
Fetuin-A hepatokine turnover is regulated by the ubiquitin-proteasome pathway involving the FBXW7 protease.
While FBXW7 has been proposed as a crucial mediator maintaining proper glucose and lipid homeostasis, recent data underlined the considerable loss in FBXW7 protein expression in obese individuals in favour of increased Fetuin-A protein and underlying insulin resistance development.

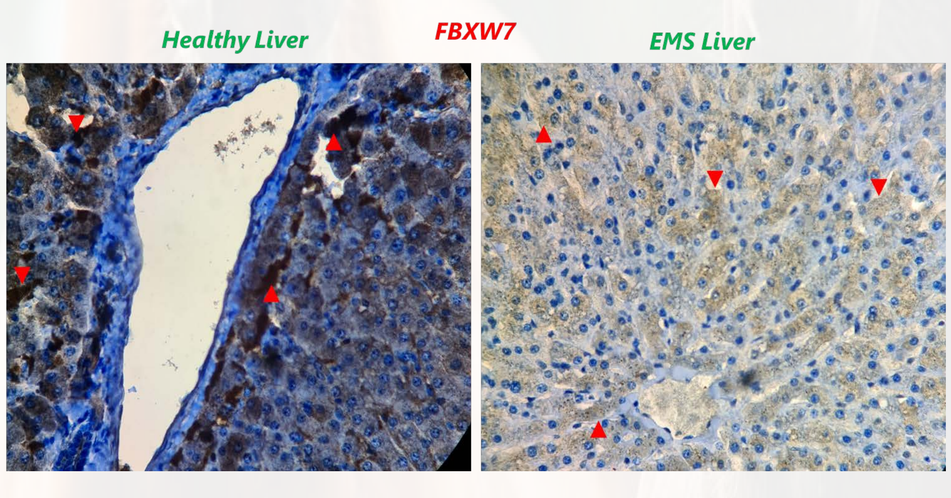
This study aimed at verifying the potential use of FBXW7 as a therapeutic tool for the efficient management of metabolic disorders by targeting Fetuin-A hepatokine

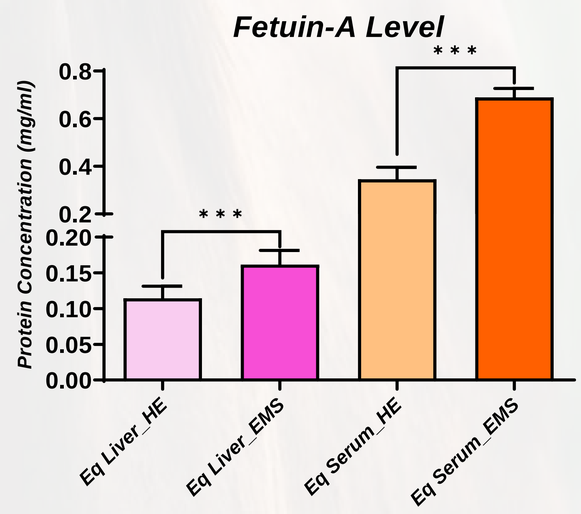


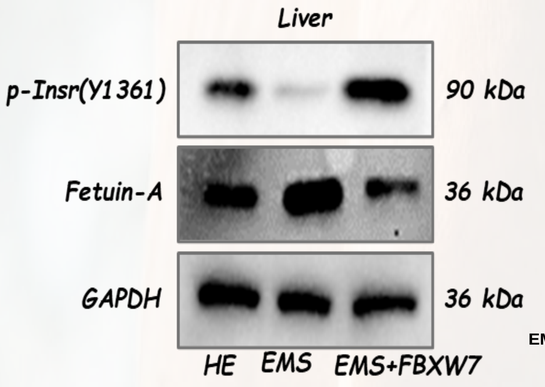
Liver explants and Blood samples were collected post-mortem from Polish cold-blooded healthy (HE, n=6) and EMS (Obese/IR, n=6) horses from a local slaughterhouse (Targowa, Rawicz, Poland).
Fetuin-A and FBXW7 levels have been measured in Serum and liver using western blot and ELISA assay, while FBXW7 has been stained by immunohistochemistry in liver tissue. Moreover, the effect of FBXW7 E3 ligase on Fetuin-A/INSR axis has been evaluated by measuring the changes in Fetuin-A and INSR phosphorylation levels.

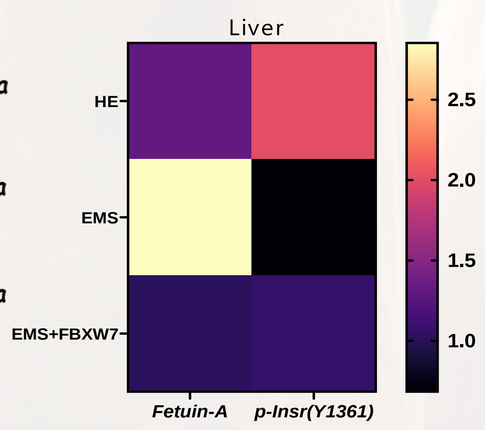
EMS horses display suppressed FBXW7, elevated Fet-A and depleted insulin signaling pathway. FBXW7 application restored INSR-mediated signal transduction which correlates with reduced Fet-A protein in EMS liver explants.

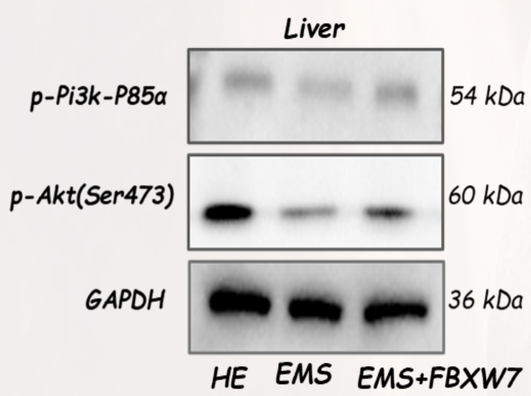


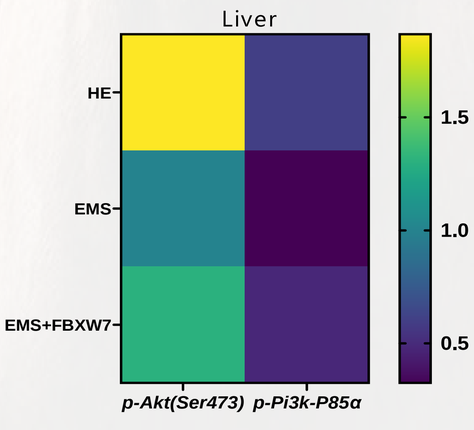












EMS horses display increased circulating and tissue Fetuin-A levels compared to control animals. Healthy tissue shows significantly higher FBXW7 levels by contrast to EMS livers.

Incubation of EMS liver with exogenous FBXW7 decreases Fet-A expression and restores proper INSR, AKT and Pi3K phosphorylation

FBXW7 E3 ligase deficiency participates in insulin resistance onset and could serve as a new potential therapeutic lead for insulin sensitivity restoration in EMS horses by targeting liver Fetuin-A protein.

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