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Regulation of Desaturation of Fatty Acid and Triglyceride Synthesis by Myostatin through Swine-Specific MEF2C/miR222/SCD5 Pathway

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Abstract : Myostatin (MSTN) is the master regulator of double muscling phenotype with overgrown muscle and decreased fatness in animals, but its action mode to regulate fat deposition remains to be elucidated. In this study a swin-specific pathway through which MSTN acts to regulate the fat deposition was deciphered. Deep sequenincing of the mRNA and miRNA of fat tissues of MSTN knockout (KO) and wildtype (WT) pigs discovered the positive correlation of myocyte enhancer factor 2C (MEF2C) and fat-inhibiting miR222 expression, and the inverse correlation of miR222 and stearoyl-CoA desaturase 5 (SCD5) expression. SCD5 is rodent-absent and expressed only in pig, sheep and cattle. Fatty acid spectrum of fat tissues revealed a lower percentage of oleoyl-CoA (18:1) and palmitoleyl CoA (16:1) in MSTN KO pigs, which are the catalyzing products of SCD5-mediated desaturation of steroyl CoA (18:0) and palmitoyl CoA (16:0). Blood metrics demonstrated a 45% decline of triglyceride (TG) content in MSTN KO pigs. In light of these observations we hypothesized that MSTN might act through MEF2C/miR222/SCD5 pathway to regulate desaturation of fatty acid as well as triglyceride synthesis in pigs. To this end, real-time PCR and Western blotting were carried out to detect the expression of the three genes stated above. These experiments showed that MEF2C expression was up-regulated by nearly 2-fold, miR222 up-regulated by nearly 3-fold and SCD5 down-regulated by nearly 50% in MSTN KO pigs. These data were consistent with the expression change in deep sequencing analysis. Dual luciferase reporter was then used to confirm the regulation of MEF2C upon the promoter of miR222. Ecotopic expression of MEF2C in preadipocyte cells enhanced miR222 expression by 3.48-fold. CHIP-PCR identified a putative binding site of MEF2C on -2077 to -2066 region of miR222 promoter. Electrophoretic mobility shift assay (EMSA) demonstrated the interaction of MEF2C and miR222 promoter in vitro. These data indicated that MEF2C transcriptionally regulates the expression of miR222. Next, the regulation of miR222 on SCD5 mRNA as well as its physiological consequences were examined. Dual luciferase reporter testing revealed the translational inhibition of miR222 upon the 3´ UTR (untranslated region) of SCD5 in preadipocyte cells. Transfection of miR222 mimics and inhibitors resulted in the down-regulation and up-regulation of SCD5 in preadipocyte cells respectively, consistent with the results from reporter testing. RNA interference of SCD5 in preadipocyte cells caused 26.2% reduction of TG, in agreement with the results of TG content in MSTN KO pigs. In summary, the results above supported the existence of a molecular pathway that MSTN signals through MEF2C/miR222/SCD5 to regulate the fat deposition in pigs. This swine-specific pathway offers potential molecular markers for the development and breeding of a new pig line with optimised fatty acid composition. This would benefit human health by decreasing the takeup of saturated fatty acid.

Keywords : fat deposition, MEF2C, miR222, myostatin, SCD5, pig
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