RESEARCH HIGHLIGHT

# Sensing unsaturated fatty acids: insights from GPR120 signaling

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**GPR120 is a receptor that plays a crucial role in mediating the beneficial effects of free fatty acids (FAs), particularly ω-3 FAs, on metabolic and inflammatory pathways, making it an important therapeutic target for metabolic diseases. Recently, Mao et al. report the cryo-EM structures of GPR120 in complex with an ω-3 FA as well as other three endogenous FAs and a synthetic agonist, along with pharmacological investigations and molecular dynamics simulations, thereby providing comprehensive insights into the molecular recognition and biased signaling of GPR120 via various agonists**.

Free fatty acids (FAs) play essential roles in human metabolism and are involved in many physiological processes. Among them, omega-3 fatty acids (ω-3 FAs) are well-known for their potential health benefits, especially anti-inflammatory actions, and potentially improving cardiovascular and brain functions.[1] GPR120, also known as free fatty acid receptor 4 (FFAR4), has been identified as the receptor for ω-3 FAs and is responsible for mediating their anti-inflammatory and insulin-sensitizing effects.[2] This makes GPR120 a promising target for anti-diabetic therapies.[3–5] However, the molecular mechanisms underlying the recognition and activation of GPR120 by ω-3 FAs remain unknown. A recent publication in *Science* by Mao et al. sheds light on this issue through extensive pharmacological investigations, structural analyses, and molecular dynamics (MD) simulations, revealing the molecular basis for the biased signaling of GPR120 for various unsaturated FAs.[6]

Similar to many other G protein-coupled receptors (GPCRs),[7] GPR120 could couple to several transducers ($G_q$, $G_i$, $G_s$, and β-arrestins) to mediate different downstream signalings. To account for potential signaling bias in various FAs and synthetic agonists, several types of GPR120 agonists, including endogenous saturated 9-hydroxystearic acid (9-HSA), unsaturated linoleic acid (LA, ω-6 FA) and oleic acid (OA, ω-9 FA), a natural product eicosapentaenoic acid (EPA, ω-3 FA), and a synthetic agonist TUG891, were profiled against multiple transducers.[7] Notably, TUG891 displays $G_q$-biased activity, and only EPA can activate the $G_s$ signaling (Fig. 1). Additionally, other two ω-3 FAs, α-linolenic acid (ALA) and docosahexaenoic acid (DHA), could also stimulate the $G_s$ pathway. Importantly, activating $G_s$ signaling in cilia could control adipogenesis, and modulate homeostatic mechanisms in healthy fat tissue.[8] These signaling bias properties of ω-3 FAs may contribute to their potential health benefits. Intriguingly, only the short-splicing form of GPR120 could efficiently transduce G protein-mediated signalings, and there are no detectable $G_s$ and $G_q$ and much weaker $G_i$ activities for the long-splicing form of GPR120.

To gain molecular insights into ligand recognition and signaling bias, Mao et al. determined five GPR120–$G_i$ complexes bound to various ligands (9-HSA, LA, OA, EPA, and TUG891) and a GPR120–$G_q$ complex bound to TUG891. Within the binding pocket of GPR120, all FAs were found to largely adopt an "L" shape conformation (Fig. 1). Complemented with mutagenesis, structural, and MD simulation data, an aromatic array consisting of nine residues ($F27^{N}$, $F28^{N}$, $F88^{2.53}$, $F115^{3.29}$, $W198^{ECL2}$, $W207^{5.38}$, $F211^{5.42}$, $W277^{6.48}$, and $F303^{7.35}$) was identified to recognize double bonds at specific positions of unsaturated FAs (Fig. 1). Thus, compared with other FAs, additional π–π interactions between EPA and GPR120 might result in the $G_s$ signaling bias property of EPA. Specifically, MD simulations revealed a flipping of $F211^{5.42}$, which is engaged with the ω-3 FA unsaturated bond, in the simulated model of the EPA-bound GPR120–$G_s$ complex. These conformational changes of $F211^{5.42}$, $N215^{5.46}$, and $S123^{3.37}$ initiate a cascade of rearrangements in downstream residues, triggering a rotameric switch of $E135^{3.49}$, which in turn interacts with Y391 of the $G_s$ protein and promotes the engagement of $G_s$ protein with GPR120.

Moreover, as the ligand TUG891 is a selective agonist for GPR120,[9] the specific recognition mode revealed by the cryo-EM structures of the TUG891-bound GPR120–$G_i$ and –$G_q$ complexes would be valuable in the design of new selective agonists. Mutations of five residues ($F88^{2.53}$, $W207^{5.38}$, $F211^{5.42}$, $N215^{5.46}$, and $I287^{6.58}$) within the binding pocket, which are distinct from other long-chain FAs sensing GPCRs, result in decreased $G_i$ activity of GPR120 upon stimulation with TUG891. In comparison with FA ligands, TUG891 is a $G_q$-biased ligand of GPR120 and has some distinctive features. Its molecular structure consists of three aromatic rings that confer rigidity and facilitate additional π–π interactions with neighboring aromatic residues. These interactions lead to conformational changes of the residues in the binding pocket, which sequentially leads to the formation of the TM1–TM2 and TM7 conformational locks and promotes the cation–π interaction between $R136^{3.50}$ of GPR120 and $Y356^{H5.23}$ of $G_q$ protein.

In conclusion, the paper by Mao et al. offers detailed insights into the molecular mechanism underlying the signaling-biased activation of GPR120 via saturated and unsaturated FAs and selective agonist TUG891. This study reveals the binding mode of the selective agonist TUG891 of GPR120, which could facilitate the structure-guided development of future selective GPR120-targeted drugs. Moreover, the structure of the GPR120–$G_q$ complex also expands our knowledge of $G_q$ coupling modes. Notably, GPR120's relatively longer TM5 and TM6, along with disorders of intracellular loop 2 and helix 8, distinguish its $G_q$ coupling mode from previously reported $M_1R$ and $5\text{-}HT_{2A}R$ modes.[10] These insights into the complexity of GPR120 signaling may pave the way for potential therapeutic applications of GPR120 in metabolic diseases.

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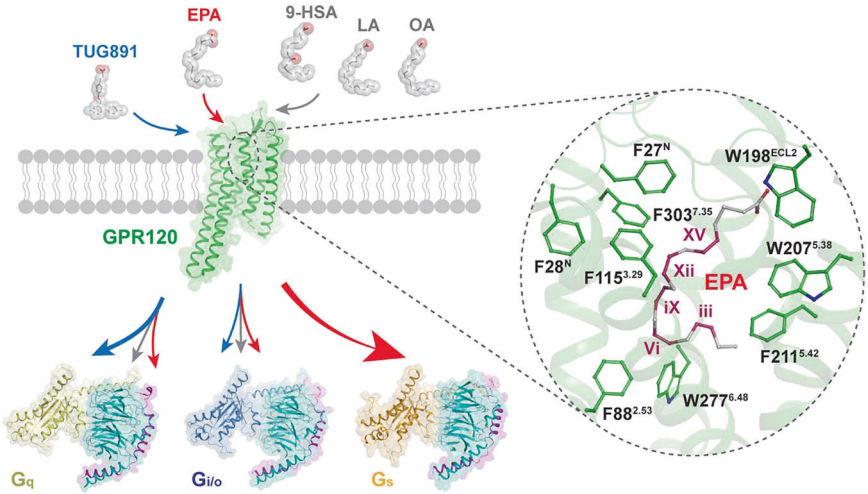


**Fig. 1 Signaling bias of GPR120 agonists and recognition of unsaturated bonds in FAs by the aromatic array in GPR120.** GPR120 agonists (TUG891, EPA, 9-HSA, LA, and OA) are shown in both stick and sphere models and colored in gray. GPR120 (PDB: 8G59), $G_q$ heterotrimer (PDB: 8G59), $G_{i/o}$ heterotrimer (PDB: 8ID8), and $G_s$ heterotrimer (PDB: 7XTC) are shown in both ribbon and surface models. GPR120, $G_q$, $G_{i/o}$, $G_s$, $G_\beta$ and $G_\gamma$ are colored in green, yellow, sky blue, orange, cyan and magenta, respectively. Signaling pathways induced by TUG891, EPA, and other FAs (9-HSA, LA, and OA) are indicated by blue, red, and gray arrows, respectively. As an example, the interactions between EPA and GPR120 in the orthosteric binding pocket are shown in the inset panel. EPA and nine aromatic residues involved in the recognition of the unsaturated bonds in FAs are shown in the ball and stick model, and colored in gray and green, respectively. Specifically, the double bonds in EPA are colored in deep purple. All the oxygen and nitrogen atoms are colored in red and blue, respectively.

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## ADDITIONAL INFORMATION

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