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Commentary

Chronicles of an FGF chimera: The odyssey continues

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According to Greek mythology, the Chimera (also Chimaera) was a monstrous hybrid creature which Homer described in the *Iliad* as having the head of a lion and behind of a snake. In this issue of *EBioMedicine*, Zhao *et al.* have given birth to a new Chimera, the fibroblast growth factor "(FGF) Chimera," but instead of destruction, have harnessed its power for good – to fight metabolic disease. Consistent with the mythological Chimera, this FGF chimera is also hybrid in nature containing structural elements of two metabolically potent FGF proteins: FGF21 and FGF1. FGF21 is an endocrine hormone derived primarily by the liver which regulates energy homeostasis and markedly reduces body weight and lipid levels in both rodents and humans [1]. FGF1, on the other hand, is expressed in many tissues but functions in an autocrine/paracrine manner through interactions with various FGF receptors and heparan sulfate [2]. FGF1 also has potent metabolic effects to dramatically reduce plasma glucose levels and lower food intake [3]. To overcome deficiencies in potency and half-life of FGF21, the authors developed a unique chimerization approach to replace the low affinity receptor binding core of FGF21 with a high affinity receptor binding core derived from FGF1 [4]. To put the importance of this strategy and its functional implications into context, however, we must delve into the backstory of FGF21 and FGF1 signaling as potential therapeutic targets.

The discovery that a subset of FGFs act as endocrine hormones to regulate metabolic processes opened the gates for studies to explore these exciting new factors. The endocrine FGFs, which consist of FGF15/19, FGF21, and FGF23, lack an affinity for heparan sulfate like traditional FGFs and therefore can diffuse away from their tissue of origin. FGF21, in particular, garnered significant interest for its potent insulin sensitizing effects and ability to promote weight loss in rodents [1]. FGF21 signals to target tissues which express a receptor complex composed of a traditional FGF receptor, FGFR1c, and a co-receptor, β-klotho [5]. Numerous groups have developed or are developing FGF21 analogs to treat obesity and diabetes, utilizing various approaches to increase the stability and half-life of FGF21 which is known to be degraded and inactivated in humans by fibroblast activation protein (FAP) [6]. The potential therapeutic benefits of FGF21 have been highly touted, but the weak affinity of FGF21 for FGFR1 relative to other FGFs (i.e., FGF1) may contribute to some of its off-target effects.

More recently, a modified FGF1 protein was investigated as a potent glucose lowering agent that did not cause hypoglycemia [7,8]. Unlike FGF21, FGF1 is mitogenic, but this effect on cell proliferation, can be eliminated by removal of specific residues [7]. FGF1, however, is not designed to circulate and signal to specific tissues like FGF21. Since FGF1 can signal to multiple FGF receptors and since FGFR1 expression is largely ubiquitous, a major potential concern for FGF1-based analogs as therapeutics is the lack of signaling specificity. Thus, both FGF21 and FGF1 have strengths and weaknesses in their pharmacological properties. With that in mind, Zhao and colleagues sought to generate a chimera to harness the strengths of each protein: FGF21's metabolic effects and ability to function as an endocrine hormone and FGF1's high affinity for the FGFR1 receptor. The authors took advantage of structural differences between FGF21 and FGF1 in designing a chimeric version of FGF21 which exhibits improved efficacy and half-life relative to wild-type FGF21. Specifically, the authors replaced the atypical β-trefoil core of FGF21 responsible for binding to FGFR1 with a core region in FGF1 which has a strong binding affinity for FGFR1 [4]. Notably, the FGF21/FGF1 chimera maintained signaling specificity to the same tissues as wild-type FGF21 but impressively exhibited

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enhanced effects on preventing body weight gain, improving glucose homeostasis, and lowering hepatic triglyceride levels in diabetic mice compared to wild-type FGF21 [4]. Interestingly, while FGF1 significantly reduced food intake in obese mice, the chimeric FGF21/FGF1 protein did not alter food intake nor did it exhibit the worrisome mitogenic properties of FGF1 alone. Finally, in addition to studies in rodents, the authors also determined that the FGF21/FGF1 chimera improved glucose homeostasis in type 2 diabetic (T2D), non-human primates [4].

Beyond demonstrating the biological potency of the chimeric protein, these comprehensive studies also provide novel insight into how structural differences between these two FGFs contribute to their paracrine and endocrine functions and illustrates the potential significant clinical impact of FGF chimeras. Additional work is needed to determine the intracellular mechanism for FGF21 signaling and whether the FGF21/FGF1 chimera operates through the same mechanism as wild-type FGF21. More importantly, future studies are needed to determine whether this FGF21/FGF1 chimera fails to possess the side effects observed with other FGF21 analogs in humans (i.e., diarrhea, increased blood pressure) [9,10]. We believe these studies set the stage for a new chapter in the illustrious journey for FGF21-based therapeutics as we envision multiple chimeric or FGF21 fusion proteins being developed going forward.

Declaration of Competing Interest

Dr. Matthew Potthoff published a paper with Dr. Moosa Mohammadi in 2014 (PMID: 25008183).

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