



## OPINION ARTICLE

# Defining “FGF21 Resistance” during obesity: Controversy, criteria and unresolved questions [version 1; peer review: 1 approved, 2 approved with reservations]

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## Abstract

The term “FGF21 resistance” was first used to describe increased circulating FGF21 levels concomitant to decreased FGF21 receptor complex expression in white adipose tissue of obese mice. Since this initial report, the term has been associated with a wide range of pathological states, including human obesity, in which circulating FGF21 levels are elevated. However, the notion of “FGF21 resistance” has been controversial partly due to difficulty in delineating the mechanisms underlying the physiological versus pharmacological effects of FGF21. Here, key aspects of the term “FGF21 resistance” are discussed including; the origin and experimental context surrounding the term “FGF21 resistance”, new criteria for evaluating FGF21 sensitivity *in vivo* and finally, crucial unresolved questions regarding the function of FGF21 during obesity.

## Keywords

FGF21 resistance, fibroblast growth factor 21, obesity, insulin sensitivity, FGF21, beta-klotho, insulin resistance

## Open Peer Review

Approval Status

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<b>version 1</b>			
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University School of Medicine, New York, USA
2. **Junichiro Sonoda**, Genentech Inc., South San Francisco, USA
3. **Andrew C. Adams**, Eli Lilly and company, Indianapolis, USA

Any reports and responses or comments on the article can be found at the end of the article.

**Corresponding author:** Kathleen R. Markan ([kathleen-markan@uiowa.edu](mailto:kathleen-markan@uiowa.edu))**Author roles:** Markan KR: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing**Competing interests:** No competing interests were disclosed.**Grant information:** The author is funded through a NIH K01 DK111758 award.*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.***Copyright:** © 2018 Markan KR. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**How to cite this article:** Markan KR. **Defining “FGF21 Resistance” during obesity: Controversy, criteria and unresolved questions [version 1; peer review: 1 approved, 2 approved with reservations]** F1000Research 2018, 7:289  
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Fibroblast Growth Factor 21 (FGF21) has pleiotropic metabolic effects including increasing insulin sensitivity and energy expenditure, while decreasing body weight and sugar intake<sup>1,2</sup>. Paradoxical to these beneficial metabolic effects, circulating FGF21 is increased during obesity potentially suggesting a state of “FGF21 resistance”<sup>3</sup>. This hypothesis, however, has generated controversy within the field. In light of this and in response to a recent call for a unified definition of “FGF21 resistance”<sup>4</sup>, I would like to discuss the controversy surrounding “FGF21 resistance” during obesity, highlight unresolved questions and outline additional criteria for its definition.

“FGF21 resistance” was first used to describe decreased expression of the FGF21 receptor complex in epididymal white adipose tissue, increased plasma FGF21, blunted ERK phosphorylation, and attenuated reduction in plasma glucose following low dose administration of FGF21 that occurred in obese mice<sup>3</sup>. Shortly thereafter, an independent group also reported decreased FGF21 co-receptor expression in white adipose tissue and increased plasma FGF21 levels in obese mice<sup>5</sup>. However, based on dose response studies, these investigators concluded that circulating FGF21 is increased during obesity to maintain insulin sensitivity, and not due to “FGF21 resistance”<sup>5</sup>. Hence, the existence of “FGF21 resistance” during obesity has remained controversial with the prevailing question: how can “FGF21 resistance” exist if pharmacological dosing is still efficacious<sup>1</sup>? Potentially, FGF21 sensitivity during obesity may be akin to insulin resistance whereby the biological effect of endogenous FGF21 is lacking yet pharmacological dosing elicits an effect. Therefore, although effects of exogenous FGF21 should be evaluated in testing FGF21 sensitivity<sup>4</sup>, consideration of the dose, functional readout, and time-course of FGF21 action should be taken.

Although plasma FGF21 levels, FGF21 co-receptor expression and downstream signaling should be evaluated in defining “FGF21 resistance”<sup>4</sup>, it is difficult to interpret tissue-specific decreases in receptor and signaling activation without understanding how that specific tissue mediates FGF21’s effects. For example, what is the relevance of decreased co-receptor expression in white adipose tissue? Adipose tissue is necessary for FGF21’s acute insulin sensitizing effect<sup>6</sup> yet, different results have been reported *in vivo* when either overexpressing or maintaining physiological levels of  $\beta$ -klotho during obesity<sup>7,8</sup>. Furthermore, brown adipocytes mediate the acute insulin sensitizing action of FGF21<sup>6</sup>; meaning, that although decreased white adipose co-receptor expression has been used as a marker of

“FGF21 resistance” we still do not understand the pathological relevance of this event.

How then, should “FGF21 resistance” during obesity be defined? Different experimental designs are required when evaluating the acute insulin sensitizing action of physiological levels of FGF21 versus the chronic effects on body composition of pharmacological doses of FGF21. Acute FGF21 sensitivity should be determined via insulin tolerance test following co-injection of insulin and FGF21 in addition to assessing tissue specific glucose uptake and activation of the FGF21 signaling cascade in brown adipose tissues<sup>6</sup>. To test chronic FGF21 sensitivity, weight loss and energy expenditure should be evaluated, although FGF21 signaling is difficult to assess since the specific tissue(s) mediating these effects of chronic FGF21 treatment remain undetermined.

Finally, caution is warranted in translating rodent studies to man. Although plasma FGF21 is elevated in obese and diabetic humans<sup>9</sup>, human FGF21 is proteolytically cleaved *in vivo*<sup>10</sup>. Therefore, the bioactivity of increased circulating FGF21 in humans remains unknown. It is possible that increased circulating FGF21 during obesity could serve a yet uncharacterized role. FGF21 has been shown to have central effects<sup>11–13</sup>, however whether or not central FGF21 co-receptor expression and signaling are altered during obesity remains unreported.

There is still much to discover regarding FGF21 action but consideration of the points outlined here can help avoid ambiguity in defining “FGF21 resistance” during obesity. Undoubtedly, the definition of “FGF21 resistance” will continue to evolve as new physiological and pharmacological studies help unravel the mechanisms underlying FGF21’s metabolic actions.

### Data availability

All data underlying the results are available as part of the article and no additional source data are required

### Competing interests

No competing interests were disclosed.

### Grant information

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*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

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# Open Peer Review

Current Peer Review Status:   

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Version 1

Reviewer Report 26 June 2018

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**Andrew C. Adams**

Lilly Research Laboratories, Eli Lilly and company, Indianapolis, IN, USA

The opinion presented by Dr. Markan discusses an important topic in the FGF21 field, which has persisted as an unresolved issue for quite some time. While the report presents a balanced view, I would suggest the following potential additions/revisions:

- In the context of a discussion of FGF21 resistance and proteolytic cleavage, it is important to discuss recent developments as they pertain to the various circulating forms of FGF21. Specifically, it would be warranted to mention that it has been recently demonstrated that the ratio of 'active' FGF21 to total FGF21 can be modulated in humans (for example, in the GTT setting) and that in certain disease states, expression of the protease FAP are altered.
- It would be helpful to mention the composition of the FGF21 receptor complex early in the manuscript, prior to discussion of tissue specific effects later in the article. Indeed, it is possible that there is local FGF21 resistance in specific tissues, as measured by pERK vs. traditional systemic hormonal resistance.
- When discussing translation of FGF21 results to man, it is important to consider that many of the proposed clinical candidates in this area have the site of FAP cleavage mutated, thus negating C terminal truncation (likely the most dramatic inactivation by endogenous proteases). While N terminal cleavage may still occur, it is likely that truncation would not impair action, unless the treatment was with wild type human FGF21.
- Inclusion of discussion of more current findings from numerous groups on tissue specific ablation/overexpression of FGF21 receptor components would add significantly to the manuscript, specifically, detailed discussion of central vs. peripheral action might be relevant to the topic of 'FGF21 Resistance'.
- Another potential explanation for increased FGF21 in states such as obesity is that it may be a sustained homeostatic response to chronic insult. Indeed, FGF21 appears is elevated by a number of stressors (both acute and chronic), including oxidative stress, lipopolysaccharide (LPS), ethanol/alcohol and dietary stress (Fructose etc). Interestingly, when these stressors

are removed, FGF21 levels typically normalize relatively rapidly.

**Is the topic of the opinion article discussed accurately in the context of the current literature?**

Yes

**Are all factual statements correct and adequately supported by citations?**

Yes

**Are arguments sufficiently supported by evidence from the published literature?**

Yes

**Are the conclusions drawn balanced and justified on the basis of the presented arguments?**

Yes

**Competing Interests:** Current employee and shareholder of Eli Lilly & Company.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 08 June 2018

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**Junichiro Sonoda**

Department of Cancer Immunology, Genentech Inc., South San Francisco, CA, USA

Markan KR discusses the controversial “FGF21 resistance” in obesity. It is an important topic for discussion given the crucial role of FGF21 signaling in health and disease. However, I feel that the discussion should also incorporate more recent findings, especially the results of tissue-specific CKO studies which have shed light on the sites of FGF21 action (instead of just stating “the specific tissue(s) mediating these effects of chronic FGF21 treatment remain undetermined”). Also, highlighting examples of local FGF21 resistance (e.g., pERK as a marker) vs. systemic FGF21 resistance (e.g., whole body metabolic effects) would be necessary since the receptors for FGF21 are located in various cell types.

When the notion of “FGF21 resistance” was first introduced, it was an attractive idea to explain the “paradoxical” elevation in plasma FGF21 in obesity by analogy to other more established examples of hormone resistance where hormone insensitivity is associated with a feedback hormone production (e.g., insulin resistance, growth hormone resistance, leptin resistance, thyroid hormone resistance etc.). Around that time, the site of receptor expression important for the

metabolic action of FGF21 was poorly understood, but the receptor complex expressed in adipocytes was thought to be responsible for many of the chronic metabolic effects. A decrease in Beta-Klotho protein expression in white adipose tissues in obese mice was thus considered to be a potential mechanism for “FGF21 resistance”. More recently, mouse genetic studies have uncovered that the induction of weight loss, glucose lowering, stimulation of energy expenditure, and increased water consumption, are mediated by the receptor complex expressed in the nervous system, rather than adipocytes (Owen et al. 2014 Cell Metab, etc.). This notion is completely overlooked by Markan KR, but in my view, is important when discussing “FGF21 resistance”.

Other comments:

- Beta-Klotho was introduced in the 3rd paragraph without an explanation. For readers who are not familiar with FGF21 signaling, it should be explicitly noted that FGF21 acts by activating membrane-bound FGFR/Beta-Klotho receptor complex.
- In the second paragraph, “blunted ERK phosphorylation” – which tissues were examined?

**Is the topic of the opinion article discussed accurately in the context of the current literature?**

Yes

**Are all factual statements correct and adequately supported by citations?**

Yes

**Are arguments sufficiently supported by evidence from the published literature?**

Yes

**Are the conclusions drawn balanced and justified on the basis of the presented arguments?**

Partly

**Competing Interests:** I am a paid employees of Genentech/Roche and hold shares.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 27 March 2018

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Moosa Mohammadi 

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In this article, Dr. Markan expresses her opinion on the ongoing controversy surrounding FGF21 resistance in obesity. This issue has not been explicitly addressed in the past publications so the commentary piece should be a refreshing read for the researchers in FGF signaling field in particular and obesity in general. Having said so, I recommend revising the text along the points below:

- 1) In the Abstract, I suggest changing the verb “used” to “introduced”.
- 2) First paragraph: I am wondering if the word “paradoxical” is the appropriate term to use here. Surely one could argue that the observed increases in FGF21 serum level in obese mice/human subjects represent a natural feedback mechanism in response to the progressive worsening of insulin resistance. Are there any published literature which correlate the severity of obesity with serum levels of FGF21? If there are, they should be discussed.
- 3) Clearly articulate/elaborate the difference between the two studies under scrutiny by putting particular emphasis on the different interpretations of dose response curves of FGF21 in these two studies. Also, please discuss how differences in experimental approach might possibly have influenced the disparate conclusions reached by the authors of these two studies. Explain whether only b-klotho co-receptor or both b-klotho and FGFR1c show reduced expression in obesity. Clearly identify tissues that lose expression of b-Klotho and/or FGFR1c and provide information on the extent of these expression losses if known.
- 4) For the sake of general readership, please introduce b-Klotho co-receptor and FGFR1c, the cognate receptor of FGF21, early on in the text perhaps even in the abstract. Please state that unlike classical paracrine FGFs, FGF21 operates through a dual receptor system.
- 5) The point brought up on the inactivating proteolytic cleavage of FGF21 is interesting and worthy of further discussion. Please identify whether the reported increases in FGF21 levels measure the levels of full length bioactive form. I.e. are the assays used capable to differentiating between full length “active” and cleaved “inactive” forms.

**Is the topic of the opinion article discussed accurately in the context of the current literature?**

Yes

**Are all factual statements correct and adequately supported by citations?**

Yes

**Are arguments sufficiently supported by evidence from the published literature?**

Yes

**Are the conclusions drawn balanced and justified on the basis of the presented arguments?**

Partly

**Competing Interests:** No competing interests were disclosed.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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