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1 Obesity and metabolic disease

2
3 **Diving deep – multi-pronged investigations into *RIPK1* as risk factor for obesity.**

4
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10 *A recent study by Karunakaran et al. has suggested RIPK1 is important in obesity and related metabolic*
11 *traits. With genetic variation associated with expression and the risk of obesity, and repression of activity*
12 *leading to a favorable metabolic profile in an obesogenic model, is there evidence for a potential*
13 *therapeutic role?*

14
15 Receptor-interacting serine/threonine-protein kinase 1 (RIPK1) is a regulator of autoinflammatory
16 systems and appears intimately involved in the coordination of events around cell death. There is a body
17 of evidence which marks out RIPK1 as an important regulator for inflammatory events in both normative
18 settings and disease. RIPK1 is able to play a role in the triggering of cell death, but it also can act to
19 regulate inflammatory signaling and promote cell survival¹. Indeed, in atherosclerosis, it has been
20 suggested that pathways involved in necrosis are triggered and that this can predispose weakness in
21 plaques/lesions². This flags such regulators for therapeutic interventions and RIPK1 has received recent
22 attention. RIPK1 is not only a potential route to the modulation of key biological systems important in
23 common complex disease¹, but it is also an exciting and tractable target². This is because of the
24 kinase structure of RIPK1 being an excellent target for the development of potentially effective specific
25 pharmacological small-molecule inhibitors.

26
27 The present work ([*ref](#)) suggests that genetic variation at the *RIPK1* locus (or nearby) is associated with
28 expression of the coded protein and that these events are also associated with the risk of obesity in
29 human. Whilst the finding of an association between cis variation and expression is not entirely
30 surprising, the authors are also able to show that one of the associated single nucleotide polymorphisms
31 is within a transcription factor binding site associated with promoter activity and *RIPK1* gene expression
32 in adipose. This is then further advanced by the observed effects of therapeutic silencing in a model of
33 diet induced obesity - associated with fat mass, total body weight, improved insulin sensitivity, reduced
34 macrophage count and promoted invariant natural killer T-cell accumulation. These events, which are of
35 course subject to the limitations of system level interpretation are fascinating and more-so flag the
36 importance of multi-pronged assessment of likely biological function. This type of evidence triangulation
37 has been promoted in other fields^{3,4} and is the hallmark of exceptional science looking to start breaking
38 down biological complexities into real understanding. In this new work on *RIPK1*, there is a refreshing
39 combination of human genetic epidemiology, model and cell work which builds on the story of this gene
40 and the potential role it has in a range of important biological processes (**Figure 1**).

41
42 More generally, this paper forms part of a growing collection of studies looking to use genetic variation to
43 increase the functional understanding of underlying biological events. It is increasingly clear that there is
44 breadth in the shape of genetic contributions to disease⁵ and whilst the associations with outcomes and
45 intermediate traits are reliable, the architecture of these genetic contributions varies wildly. That said, it is
46 clear that the differing types of genetic association study are useful and capable of yielding insight into
47 pathways of interest. What is less clear, however, is how one navigates the difficult path of moving from
48 signal to biological understanding.

49
50 This tricky road has been walked by papers which really have started to use sensible collections of
51 existing resources to unpick the deeper stories behind association results. For example, the strong
52 association between genetic variation at *FTO* on chromosome 16 and adiposity uncovered in part
53 through its logical relationship with type 2 diabetes^{6,7} has been well cross-examined and by those able to
54 deploy existing collections of deep genomic data to explore why and how the association might exist⁸.
55 Indeed, some of the earliest association signals for adiposity coming first from familial studies of extreme
56 phenotype are now being explored with both a view to the existence of common and well explored rare
57 genetic variation⁹. Despite these advances, the bridge between reliable signal and function – which
58 theoretically can lead to an ability to consider possible therapeutic value – is one which remains
59 extremely difficult to cross, but is the paradigm of the work discussed here.

60

61 Finding genetic variation at, or around *RIPK1* (some of which looks to be regulatory) which is associated
62 with expression in the appropriate tissue and which is associated with a risk of elevated adiposity is
63 compelling. The combination of this with analysis of therapeutically knocked down expression in an
64 overweight model and the observation of the right “milieu” of biological events (inflammatory,
65 immunological, body composition and glycemic profile) is exciting and brings a clear addition to an
66 existing literature. However, one is constantly reminded that there are rarely enough tools to fully assess
67 a complex regulatory network such as that involving RIPK1. The suppression of a key regulator seems
68 likely to inevitably yield systemic changes and the qualification of specific genetic variants as useful
69 proxies/handles for understanding the impact of RIPK1 on obesity leaves a cautionary feel to the new
70 work. Furthermore, with inflammation and body composition in particular, one enters the murky waters of
71 reverse causation and likely bidirectional effects, which would require careful examination before
72 embarking on work setting out to measure clinical effectiveness.

73
74 This work clearly has not refuted the likely importance of RIPK1 and at worst has marked it as a sentinel
75 or reporter for a network of regulatory events which are coincident in a number of complex diseases.
76 Evidence presented by Karunakaran and colleagues furthers the hypothesis that there is likely to be a
77 meaningful biological read out of specific therapeutic manipulation of RIPK1 (even if subject to the
78 complexities and redundancies of the systems targeted). Furthermore, the work has delivered a multi-
79 pronged attack on trying to understand the potential role of RIPK1 across cell, model and human
80 investigation. There is potential in this attractive target to deliver increased metabolic control in the
81 context of a prevailing obesogenic environment and population level obesity control aside, this parallel
82 development is a tantalizing prospect.

83
84 The author declare no competing interests.

85
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90 (C18281/A19169).

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Figure 1. Triangulation of evidence around RIPK1 as a candidate for a role in body composition related cellular pathways.

Schematic representing multiple independent sources of evidence highlighting the likely importance of RIPK1. **A** – human studies relating genetic variation at *RIPK1* associated with expression, risk of obesity and suggesting a causal role for RIPK1 in adiposity, **B** – murine studies suggesting that the specific repression of RIPK1 expression affects a suite of metabolic traits in a diet induced model of obesity. **C** – evidence that genetic variation relating to human studies resides in a transcription factor binding site for E4BP4 and influences RIPK1 promotion. Green arrows indicate evidence from Karunakaran *et al.* and from different sources supporting important roles for RIPK1 in obesity and metabolic traits. Red arrows are indicative of important followup work which can be prompted by that reported by Karunakaran *et al.* ASO refers to Anti-sense oligonucleotide, MR refers to Mendelian randomisation and eQTL refers to expression quantitative trait locus. METSIM¹ gives reference to Metabolic Syndrome in Men Study which was used to examine the relationship between genetic variation at RIPK1 and RIPK1 mRNA (eQTL discovery)¹⁰. OTTAWA² refers to a cohort of participants recruited for the study of genetic variation at the FTO locus, but used by Karunakaran and colleagues for the analysis of genetic association between RIPK1 variation and the risk of obesity¹¹.

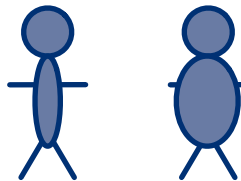
A

METSIM¹
eQTL → mRNA

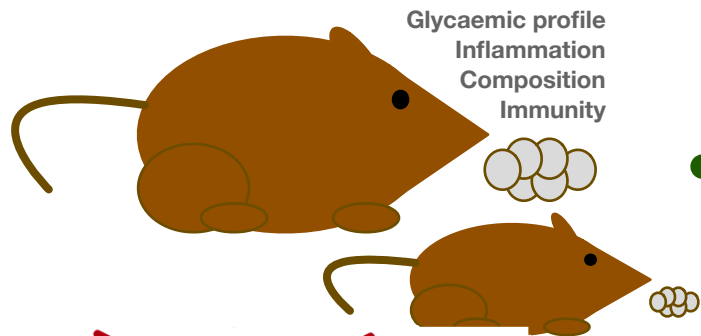
OTTAWA²
↑ risk obesity

eQTL MR → obesity
Multiple cohorts

AAGGTCCA(A/G)ATCCAAA

**B**

Further followup - Murine expression studies



Triangulation of evidence

Further followup - Human expression studies

C

AAGGTCCA(A/G)ATCCAAA

TFBS
(E4BP4)



Further followup - ASO direction and cell function