Reviewer 1

This is a fascinating topic. I often find in the literature that cell cycle molecules and their regulators are only discussed within a particular context, such as senescence only, or differentiation only. Seeing alternate roles for these molecules within a single tissue type/s discussed within one publication is certainly needed and appreciated. However this is a very technical topic and spending more time and perhaps adding an additional section introducing the reader into how these molecules work (and remaking figure 1) could be helpful. This review article is currently very difficult to read.

Figure 2 is your graphical abstract, but this is not even mentioned or described in the introduction. Use Figure 2 (or adapt it in such a fashion) so that a reader can follow the structure of the text using this figure as a map. Your sub-section titles should match this abstract (and do for the most part) and you should introduce the material in the Introduction section in this order. Finally, the structure of your Discussion section should follow this same order using the same themes and terminology to summarize what you have described to us in the body of the review. For Figure 2, numbering the 4 arms (senescence, inflammation, browning…) and matching those numbers to the numbers used in your sub-titles of your sections will help immensely to guide the reader. Even directly stating “The topics of this review will cover 1….2…3…and can be found in the graphical abstract in figure 2” will work. The other figures do not help very much either. A summary figure for each of the sub-sections would improve readability.

Because of the lack of clarity, lack of a distinct structure and a lack of appropriate citations, primarily in the introduction and in Section 5 (role in adipose inflammation), I suggest a partial rewrite. In general, the content is phenomenal but presented with too much concision for the breadth of information covered. Because of this, the impact this article will have for researchers who are not already familiar with these works is limited in its current form.

As suggested by the reviewers, since the paper is mostly focused on adipose tissue, the title has been modified accordingly. In line with this, the body of the review has been substantially revised and several paragraphs have been deeply restructured in the context of adipose tissue. We would like to bring to your attention the fact that this invited review is part of a special issue about the ARF/INK4a locus entitled "Deciphering alternative functions of the INK4a/ARF locus". This special (and specialized) issue aims to collect experimental observations about the functions of both ARF and INK4a, as well as the mechanisms that control their expression, in either physiological or pathological contexts. In this context, adding an additional section introducing the reader into how these molecules work, may be redundant with other articles of this issue. The paragraph in the introduction illustrated in figure 1 may allow the reader to better understand the role of these cellular pathways controlled by this locus, even for someone who is not specifically an expert in cell cycle regulation.
We fully agree with this reviewer regarding the other comments. The manuscript was substantially revised and the text has been reorganized and/or largely rewritten. In the revised version, the text organization was clearly described and figure 2 was referenced at the end of the introduction. The sub-sections were better organized to present data in a meaningful way in explicit entitled paragraph. Accordingly, we modified figure 2. The numbering of the 4 arms of the new figure (more informative and used as graphical abstract) matches with the numbers used in the titles of the sub-sections. Thus, the reader can better follow the text organization using this figure as a map. Several parts have been rephrased and sub-sections have been better introduced (especially 2: a balance between adipogenesis and senescence and 4: a role in adipose tissue inflammation) expanded, and partially rewritten in the revised version. We have added appropriate references throughout the review accordingly (10 references were added in the new version). In general, we have tried to improve clarity and depth of the text as often as possible to make this review easier to read.

Introduction:

Good introduction with focused information to guide reader into the review well, however it appears to be missing many references pertinent to the claims made, and seems to gloss over some very technical information without enough explanation for someone who is not specifically an expert in cell cycle regulation. Line 59-79 in the introduction contains an overwhelming amount of information in a dense space. Perhaps splitting up this paragraph to contain genetic information and risk associations in one paragraph, and basic functions of cell cycle inhibition would have set me up better to receive the subsequent sections. For example, Figure 2 is fascinating and is your graphical abstract. This should be referenced at the end of the introduction and listing each of the 4 arms with a sentence for itself would help: such as “Cell cycle inhibition is important for balancing adipogenesis and senescence, but too much leads to...”

-Line 29: Reference missing from definition of Obesity. This reviewer suggests including this one, or similar:


This citation was added in the revised text.

-Line 29: Attributing Obesity solely to energy balance, although true, is an oversimplification that detracts overall from the introduction. Provide at least a few phrases describing other contributors to obesity such as genetics, obesogenic environmental influences (xenobiotics and ultraprocessed foods) that increase inflammation. This is very important for properly introducing your inflammation sub-section

This part was rephrased and a few sentences have been added.
-Line 31: Needs at least 1 citation demonstrating inflammatory profile associated with adipose tissue gain.

This citation was added in the revised text.

-Line 35: Cite types of adipose

The types of adipose tissue (visceral vs subcutaneous) are indicated in the introduction in two sentences: « WAT exists in multiple locations in the body with two major subtypes: visceral and subcutaneous [10] ». « Unlike visceral WAT (vWAT), the metabolic adaptability of subcutaneous WAT (sWAT) to changes in its environment, a process called plasticity, has been associated with increased insulin sensitivity and decreased rates of T2D [12] ».

-Many more citations needed in the introduction.

The introduction has been expanded, restructured and a few references were added. In particular, as suggested, the former section 2 (a role in adipogenesis) has been shortened, reworked and is now part of the introduction.

Section 2

This section is very important, and still part of the introduction it seems. Please rework the information from this section into Figure 1. Then switch figure order to make figure 2 (graphical abstract) figure 1, and this one the new figure 2.

See below. The figure order has been kept in the revised version because we consider that, for more clarity, the description of the INK4a/ARF locus should appear before its role in adipose tissue in the text.

Section 3

This subsection is of most interest to me, however could be enhanced and made to be more complete. Line 170 needs a citation. Line 171-172 is incomplete, and when finished will need a citation. More information on connecting aging to obesity as far as senescence, and the impact of that senescent phenotype needed. Line 176 – What happens in AT that causes failure to expand? Any information on whether the cell cycle changes are causative or resultant? Line 176 would be a good place to allude to one of your next sections (inflammation). Paragraph 2 (line 177-188) is very cool!

As suggested, this subsection has been expanded to be more complete. In particular, more information on connecting aging to obesity as far as senescence and the impact of that senescent phenotype have been provided. Specific references have been added accordingly.
Section 4

I already forgot where CDK4 comes in. This is a section that would really benefit from a diagram showing how these cell cycle regulators signal to enhance the insulin signaling pathway. You mention CDK4 acts in a cell-cycle-independent manner, but one more sentence reminding the reader of its “canonical” role in cell cycle before introducing this new role, would be helpful. Line 198: ‘exhibit’ misspelled.

As suggested, a new figure (new figure 3) was added to summarize how these cell cycle regulators signal may enhance the insulin signaling pathway. A new sentence was added to remind the “canonical” role of CDK4 in cell cycle.

Section 5

Bringing aging back into the discussion to compare phenotypes of low-grade inflammation to obesity could be a way to make this section thorough. This section is poorly cited. Start with works on meta-inflammation and fibrosis with obesity (Daniel Lark or David Wasserman), and inflammation and macrophages with aging (Micah Drummond) or obesity (Ryan O’Connell).

As suggested, this subsection has been expanded to be more complete and appropriate references have been added accordingly.

Discussion:

I appreciate the strategy of summarizing and commenting on how to target these pathways for each specific function, as well as the challenges. However, at the start of the discussion section, please restate and summarize your graphical abstract (figure 2).

A sentence was added at the beginning of the discussion that summarizes figure 2.