Please find a point-by-point rebuttal

First of all, we really want to thank warmly the reviewers who spent their time to review our manuscript in a constructive and useful way. We have taken into account all the suggestions carefully and made modifications accordingly.

Reviewer 1

This is a great article of a very difficult topic. This reviewer appreciates the authors’ efforts to (greatly) improve the readability.

One thing I’m still confused about is CDK4 (pRB) vs MDM2 (p53) regulation. Is it as simple as the pRB arm promoting differentiation of adipocytes, whereas activation of the p53 arm results in early senescence? I struggle with the regulation/fate decision between senescence and differentiation specifically. I wonder if it’s possible that maybe senescence is a form of premature differentiation due to epigenetic changes preventing suppression of differentiation transcriptional program (inability to maintain quiescence)? This can be due to inflammation and other cues eventually causing histone reductions within stem cells, for example. If you think this question makes sense or could be relevant, please add 1-2 sentences addressing it in section 2 or the discussion to make this portion of the review more satisfying.

This is an interesting point of view. To our knowledge, no data are available to support this hypothesis in adipocyte. However, we cannot rule out that the adipose stem cell fate decision between senescence and differentiation in obese individuals relies on epigenetic mechanisms that regulate differentiation transcriptional program. As suggested, a few sentences (line 174 to 179) and one reference (new ref 66, Beerman et al 2016) have been added in the sub-section 2 as follow:

“The mechanistic basis for aging or obesity-associated adipose stem cell decline linked to elevated p16INK4a/p53 expression is not completely understood. However, increasing evidence suggests that epigenetic dysregulation is an important mechanistic driver of stem cell fate during these processes (66). Thus, it is tempting to speculate that epigenetic mechanisms regulating differentiation transcriptional program may account for the adipose stem cell fate decision between senescence and differentiation in obese individuals.”

Minor comments:

Line 73: DT2 should be changed to T2D for consistency

Line 235-236: Fix Grammar: “Although metabolic insults directly up-regulates…yet the underlying”

Line 295-296: “In short” not needed for figure legend description.

This is now corrected.