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Sir2 and longevity:

The p53 connection

Johannes H. Bauer[1] and **Stephen L. Helfand**[2]
[1]Southern Methodist University; Dallas, TX USA
[2] Brown University; Providence, RI USA

The Sir2 deacetylase has been shown to regulate life span in yeast, worms and flies, but the mechanism for this ability remains largely unclear.[1] In our recent publication, "dSir2 and Dmp53 interact to mediate aspects of CR-dependent life span extension in *D. melanogaster*" (www.impactaging.com), we shed light on a possible mechanism for Sir2-dependent life span regulation.[2]

The cellular targets of Sir2's deacteylase activity are manifold and range from proteins controlling cellular metabolism (PGC1-α) to stress response (FoxO) and apoptosis (p53). Any of those examples may play a role in the regulation of longevity, but p53 is likely the most surprising candidate. Primarily known as a major tumor suppressor and `Guardian of the Genome', recent studies have revealed an additional role for p53 in the control of life span. Hyperactivation of p53 in mice leads to shortened life span with signs of accelerated aging, while suppression of p53 activity in animals that do not develop tumors such as *D. melanogaster* and *C. elegans* leads to extended life spans.[3] Interestingly, both Sir2 and p53 have been implied to play a role in the response to Calorie Restriction (CR), since the longevity extension by Sir2 activation or p53 suppression is not additive to the longevity extension observed by CR treatment. These data suggest that Sir2 and p53 may function in the same, CR-related longevity pathway.

In our current publication,[2] we investigated this connection further. We found that in Drosophila, longevity extensions by Sir2 over expression and p53 activity suppression are not additive, indicating that these two molecules engage similar pathways to regulate life span. Furthermore, we found that dSir2 and Dmp53, the fly orthologs of Sir2 and p53, respectively, physically interact in vivo. dSir2 was able to deacteylate Dmp53 derived peptides, and activation of dSir2 by the polyphenol resveratrol inhibited Dmp53 transcriptional activity in vitro. Therefore, just like in mammalian models, dSir2 interacts with Dmp53 and inhibits its activity through its deacetylase activity.

Previous data has shown that in Drosophila, dSir2 is up regulated in response to CR, and longevity extension due to a CR regimen is blocked in flies lacking dSir2. Our current data extends these observations to Dmp53, inhibition of which by increased dSir2 activity may be a crucial step in the CR longevity response in fruit flies.

How does inhibition of Dmp53 increase life span? The down stream events following Dmp53 inhibition remain to be worked out, but tantalizing clues have emerged. Dmp53 extends longevity only when inhibited in neurons. Thus, these mechanisms might also apply to mammals. Furthermore, inhibition of Dmp53 activity is associated with a decrease in insulin signaling activity in a major metabolic tissue of the fly, the fat body. Hence, Dmp53 may engage

jbauer@smu.edu or Stephen_Helfand@brown.edu.

the insulin signaling and/or related pathways, such as the TOR pathway, both of which are known to regulate longevity.

This `novel', life span regulating function of p53 may be more evolutionary ancient than its relatively recent role in apoptosis and tumor suppression, and is guaranteed to provide many new exciting discoveries.

References

1. Guarente L, Picard F. Cell 2005;120:473–82. [PubMed: 15734680]
2. Bauer JH, et al. Aging 2009;1:38–48. [PubMed: 19851477]
3. Donehower LA. Aging 2009;1:6–8. [PubMed: 20157591]