Levels of protein SIRT6 appear to impact lifespan of mice

February 23 2012, by Bob Yirka

(Medical Xpress) -- Researchers in Israel have found that genetically altering male mice to cause them to express more of the protein SIRT6 allowed them to live up to fifteen percent longer. Haim Cohen and colleagues at Bar-Ilan University in Ramat-Gan, describe in their paper published in *Nature*, how they veered from following the crowd studying SIRT2 and instead chose to look at SIRT6. In so doing, they discovered that when the mice under study were caused to express more SIRT6, the older males tended to metabolize sugar at a faster rate than normal, which led, they believe, to protecting them from metabolic disorders and a longer lifespan.

Four years ago, scientists studying aging found that heightened levels of SIRT2 in yeast, fruitflies and nematodes tended to increase their lifespan . This discovery led to a lot of studies being conducted on SIRT2 and whether it might eventually lead to a real fountain of youth. Unfortunately, things haven't panned out as hoped, and what appeared at first to be some real breakthroughs turned out to be faulty science. Because of all this, Cohen et al chose to follow another path; there are seven kinds of sirtuin after all, why not look at one or more of the others. They chose SIRT6 because it appeared to be the least studied.

To find out what impact SIRT6 levels might have in mammals, they genetically altered a group of mice causing them to express more of the protein. Afterwards they found, after fattening them up, that the high levels of SIRT6 in the mice tended to protect them from diseases associated with obesity. Then because research by other groups had

already shown that mice with low levels of SIRT6 generally didn't live very long, they wondered if the opposite might be true.

In the next phase of the experiment, the team once again genetically altered a group of mice (245) to express more SIRT6, but this time they fed them a normal diet, then simply recorded how long they lived. They found that the median lifespan for the transgenic male mice was fourteen and a half percent longer than normal in one line and almost ten percent in another, while there was no statistical difference in the females. They also measured maximum lifespan and found it grew by nearly sixteen percent in one line of the mice and just over thirteen percent in another. This the group says, shows that mice tend to live longer if they express more SIRT6.

Other researchers aren't so sure, David Lombard and Richard Miller have also published a paper in *Nature*, but theirs is in response to the findings of the team in Israel, suggesting that the increased expression of SIRT6 in mice might be affecting other systems in the mice that allow them to live longer, rather than impacting aging directly.

At any rate, Cohen's group can only speculate on why expressing higher levels of SIRT6 only increases male lifespan, but suggest it might be that all it's really doing is allowing the males to catch up to the normally longer living females.

More information: The sirtuin SIRT6 regulates lifespan in male mice, *Nature* (2012) doi:10.1038/nature10815

Abstract
The significant increase in human lifespan during the past century confronts us with great medical challenges. To meet these challenges, the mechanisms that determine healthy ageing must be understood and controlled. Sirtuins are highly conserved deacetylases that have been

shown to regulate lifespan in yeast, nematodes and fruitflies1. However, the role of sirtuins in regulating worm and fly lifespan has recently become controversial2. Moreover, the role of the seven mammalian sirtuins, SIRT1 to SIRT7 (homologues of the yeast sirtuin Sir2), in regulating lifespan is unclear3. Here we show that male, but not female, transgenic mice overexpressing Sirt6 (ref. 4) have a significantly longer lifespan than wild-type mice. Gene expression analysis revealed significant differences between male Sirt6-transgenic mice and male wild-type mice: transgenic males displayed lower serum levels of insulin-like growth factor 1 (IGF1), higher levels of IGF-binding protein 1 and altered phosphorylation levels of major components of IGF1 signalling, a key pathway in the regulation of lifespan5. This study shows the regulation of mammalian lifespan by a sirtuin family member and has important therapeutic implications for age-related diseases.