Finding methods for extending healthy life—life span—is a major goal of gerontologists. For a long time, the only method we knew of was caloric restriction. Although in many strains of mice and rats caloric restriction extends both life span and healthspan (in most but not all parameters measured), it is quite obvious that caloric restriction will not be widely applicable to humans unless the molecular mechanisms involved are identified and mimetics developed. Then, in the 1990s, spurred in part by the development of the Longevity Assurance Gene initiative of the National Institute on Aging (NIA), there was a significant interest in genetic manipulations that extend life span. Hundreds of such manipulations have been described in lower organisms, and they comprise a core of our current understanding of the aging process. However, applicability to humans again hinges on our ability to devise pharmacological modulators of the pathways identified. More recently, two such pathways, sirtuins and the mammalian target of rapamycin (mTOR), have led to the development of small molecule modulators that hold the promise of extending the life span, healthspan, or both. Namely, these are the sirtuin activator resveratrol and the mTOR inhibitor rapamycin.

In the current issue of the journal (pp. 580), Sharp and Strong (1) provide a very timely perspective on the seminal finding described last year that rapamycin can extend the life span of genetically heterogeneous mice, even when the supplement was started at the relatively ripe age of 20 months. The increase in life span was observed in both males and females and in all three sites where the compound was tested (2). The finding is owed to a consortium known as the Intervention Testing Program (ITP) of the NIA, which was started 7 years ago as a means to rigorously test the effect of selected compounds on mouse longevity (3). The results with rapamycin have been the most clear positive finding to date. It should be mentioned that, due to the structure of the studies, even negative or marginally positive results are also informative and have been published (4). It has been argued that limiting the ITP studies to life span, without regard to healthspan, is a flaw of the design. In a world of infinite funds, this would be a valid concern, but the ITP leadership decided to focus on meticulous life-span studies as a first step, to be followed by health studies only on those compounds that show a significant effect on life span. Such Phase 2 studies have been initiated on rapamycin, but the results will not become available for several years. In addition, the ITP is currently testing different doses of the drug, as well as earlier starting times, whereas other studies in progress are currently addressing a variety of issues related to the effect of prolonged treatment with rapamycin on health (see subsequently).

Surprisingly, preliminary data indicate that starting rapamycin treatment earlier (at 9 months of age) leads to the same level of life-span extension as was observed when the treatment was started later. It is possible that inhibition of the mTOR pathway during early adulthood might result in deleterious effects related to its role in growth, development, and the control of resource allocation. It is also possible that the immune suppression caused by rapamycin might be more deleterious in youth. In effect, as discussed by Sharp and Strong, this issue has led to significant controversy over the relevance of these findings for humans. After all, the study done by the ITP laboratories—like most mouse longevity studies published these days—was done under strictly controlled pathogen-free conditions, where suppressing the immune system might not be particularly harmful because the animals are never challenged with pathogens or need to heal wounds. Such “ideal” conditions would not be applicable to humans. And yet, rapamycin’s effects on

Guest Editorial

Rapamycin Joins the Aging Fray

Maybe Ponce de Leon Visited Rapa Nui, not Florida

Felipe Sierra

Division of Aging Biology, National Institute on Aging, National Institutes of Health, Bethesda, Maryland.

Address correspondence to Felipe Sierra, PhD, Division of Aging Biology, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892.

Email: Sierraf@nia.nih.gov

Received March 14, 2010; Accepted March 18, 2010

Decision Editor: Huber R. Warner, PhD
the immune system are not completely clear, and in some cases, it even acts as an anti-inflammatory. Further complicating the issue, there is reason to believe that the longevity effects of rapamycin might indeed require the immune modulation effect. Indeed, there is considerable evidence that suggests that most age-related pathologies are associated with a significant inflammation. Whether there is a cause–effect relationship still remains to be seen, but it is plausible that reducing the inflammation might be a critical factor in reducing age-related tissue deterioration. Significantly, at this point, we don’t yet know the origin of circulating cytokines generally observed in aged animals and humans, and which have given rise to the concept of “inflammaging.” It is possible that these proinflammatory cytokines are derived from senescent cells accumulating diffusely throughout all tissues, and rapamycin has been reported to inhibit cell senescence. In addition, rapamycin might work by restraining the response of target tissues to these cytokines. From this perspective, it is a reasonable assumption to think that, by reducing inflammaging, rapamycin administered late in life might work to extend longevity precisely because it is an immune modulator. Key questions in this regard include identification of the role of proinflammatory cytokines and inflammation in general in the aging process and age-related disease, and the distinction of the roles of the innate and the acquired immune responses in fighting infections and other stresses in aged individuals.

The two pharmacological compounds currently at the crosshairs of gerontology research are resveratrol and rapamycin (as well as their derivatives and unrelated molecules that modulate the same pathways: sirtuins and mTOR). The history of both compounds is fascinating (1,5), and their current status is slightly different. Resveratrol has been shown in several studies to have a positive effect on mouse health, but interestingly, such effects are primarily apparent under conditions of stress (mouse models of age-related disease or regular laboratory mice fed a very–high fat diet) (6). However, the compound does not seem to have a significant effect on life span of mice fed a normal diet. In contrast, rapamycin has a clear effect on the life span of mice fed a normal diet, but being a more recent finding, at this time we don’t yet know whether healthspan will be improved by rapamycin treatment.

Therefore, testing the effect of rapamycin on healthspan is of immediate interest to the field. Several studies are under way, but few have been published yet. Results so far are promising in that relatively short treatment with rapamycin (6 weeks) allows significant improvements in at least two different mouse models of Alzheimer’s disease (7,8), and preliminary positive results have been observed for both α-synuclein and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine models of Parkinson’s disease (9) and A. Richardson, PhD, personal communication, 2010. Healthspan is, however, not simply absence of disease but rather overall robust functionality of a variety of physiological systems, both under basal conditions and after subjecting the animal to appropriate stresses. Because of the complexities involved, it took more than half a century to establish that the life-span extension afforded by caloric restriction was accompanied by a corresponding increase in health parameters. But there is reason for optimism: Based on that knowledge, comparable experiments done with resveratrol were considerably faster, and it is reasonable to expect that an answer to the issue of healthspan effects of rapamycin will be available within the next 2 or 3 years. In addition to the laboratories associated with the ITP program, several others are actively engaged in this endeavor. Longer to establish, however, will be a more detailed analysis of the effects of rapamycin on life span, including dosage of the drug, timing, and frequency. Other important studies either under way or necessary in the near future include combination of rapamycin treatment with other modulators of life span, such as caloric restriction, modulators of the insulin-like growth factor pathway, and resveratrol.

In addition, we can envision rapamycin (and resveratrol) as “first hits” in a screen for drugs that affect life span and healthspan. Therefore, second-generation drugs are a major area of future research as well. In the case of resveratrol, Sirtris (Sirtris Pharmaceuticals, Cambridge, MA) has already identified additional compounds, unrelated to resveratrol but affecting the same enzymes (sirtuins) and they are actively pursuing these leads. Similarly with rapamycin, a race to identify “rapalogs” that affect life span is already under way. Although some researchers are focusing on finding mTOR inhibitors that do not have immune modulation activity, this might actually be a misleading effort if, as discussed previously, it turns out that the mechanism of action of rapamycin indeed requires this immune modulation. Nevertheless, these studies will still be informative in terms of understanding the mechanism of action of rapamycin or its analogs, as well as furthering our knowledge about the basic biology of aging.

Finally, a word about translation of these findings to the human population: Of course, the hope is that compounds such as rapamycin, resveratrol, and others soon to be discovered actually affect the basic aging process and thus will delay the appearance and/or lessen the symptoms of the entire panoply of age-related diseases, conditions, and ailments. Such compounds could be hailed as a modern “fountain of youth.” However, although extending life span or even healthspan is a worthy endeavor for academics, and, if available over the counter, such compounds will be taken up by a small number of people in the public (the same ones that already embrace other antiaging potions), it will be a hard sell for the Food and Drug Administration. For that reason, it is likely that translation of the findings on rapamycin will require demonstration of efficacy in clinical trials designed to address specific age-related diseases, as opposed to the aging process as a whole. A drug is unlikely to create a significant backlash if it happens to have an off-label beneficial effect in other aspects of the physiology of old people (e.g., if it can be approved to treat, say, wound healing, diabetes, or Alzheimer’s disease).
REFERENCES