Intriguingly, in this issue of Aging, Anisimov et al. reported that lifelong treatment with metformin (an anti-diabetic drug with potentially anti-aging effects) was beneficial for female mice but shortened lifespan in males. Here I discuss why suppression of aging may be unfavorable in young males.

Metformin is used for treatment of type II (adult-onset) diabetes. Also, metformin and its analog phenformin prevent cancer and increase lifespan in rodents [1-7]. Yet, effects of metformin depend on mice strains and gender. In one strain (transgenic female HER-2/neu mice), metformin slowed down aging and tumor development [3]. In another strain (female SHR mice), metformin slowed down aging without inhibiting spontaneous tumorigenesis [4]. In third strain (female 129/Sv mice), metformin decreased carcinogenesis but only marginally increased life span [8]. Unexpectedly, in male mice of the same 129/Sv strain, metformin decreased the mean life span by 13% [8]. How can this be explained? There are 3 additional pieces to the puzzle. First, metformin via several mechanisms inhibits the mTOR pathway [9-15]. Second, inhibition of mTOR may explain the anti-aging effect of metformin [16,17]. Third, death rate was increased specifically in young males, thus decreasing their mean life span. Still, metformin did not affect lifespan of the last 10% of survivors and maximum life span [8].

Death from “anti-aging”

Growth and aging share a common molecular mechanism [18]. Growth factors, insulin, cytokines, nutrients, and testosterone stimulate cellular growth in part by activating the mTOR pathway [19-30]. When a cell cannot grow in size, then activated mTOR contributes to senescent phenotype [31-33]. By promoting cellular aging, mTOR is involved in organismal aging and age-related diseases [34]. mTOR is essential earlier in life but also accelerates aging and age-related diseases (cancer). (Note: This is a clear-cut example of antagonistic pleiotropy [35]. As a matter of fact, any genetic pathway that accelerates aging must be beneficial earlier, otherwise it would be eliminated by, whatever weak, natural selection). Accelerated aging can be linked to vigor earlier in life [36,37]. In agreement, size and weight is associated with faster aging [38].

However, the degree of early-life benefits is slightly different in males and females. In the wild, young males have a higher risk of death (from accidents, competition and violence) than young females. (This is still the case in modern men and women). The higher death rate earlier in life, the more important is robustness. So males need to be stronger and bigger, to fight and compete and still survive. In many mammals (including 129/Sv mice and humans), males are larger. mTOR drives cellular growth and muscle hypertrophy [22,39-41], thus providing physical strength. Noteworthy, testosterone stimulates muscle cell hypertrophy via mTOR [39]. Even further, inhibitors of mTOR decrease testosterone levels in humans [42-44]. So it is reasonable to think that mTOR contributes to vigor of young males.

While decelerating aging, inhibition of mTOR may decrease robustness, tolerance to infections, cold temp-
temperatures and famine. This may be detrimental in unprotected environment. As discussed in detail [36], hypothetically, an anti-aging drug given to young men three centuries ago (when 75% of individuals died before the age of 26) would decrease lifespan due to death from infections, starvation and violence. This would preferentially eliminate weaker (and therefore slow-aging) individuals.

For laboratory mice, the environment is not completely protected because mice do not go to a doctor to treat infections, for instance. When environment is not completely protected, anti-aging treatment earlier in life may shift death from aging to death from external causes. Without repeating all arguments published recently [36, 37], we can summarize: 1. Anti-aging agents may be harmful in young mice, when environment is not completely protected (external causes of death do exist). 2. This will affect males more than females. 3. In such conditions, this will preferentially eliminate weaker animals, who age slower. Robust, faster-aging animals will survive until aging. This effect will preclude extension of maximum lifespan, even if the aging is slowed in remaining alive (but faster aging) mice.

This may explain results by Anisimov et al published in this issue [8] and also may be applicable to other anti-aging modalities like calorie restriction (CR) and rapamycin. (Note: This may explain the lack of extension or even shortening lifespan by severe calorie restriction started early in life in some strains of inbred mice. If severe CR in young males leads to early death, then mostly fast-aging males would survive and then die relatively early too. Death of weak (slow-aging) males early in life may conceal potential anti-aging effects).

There may be other explanations. Metformin can cause side effects, which may be unrelated to its anti-aging effect and even unrelated to its “clinical” target AMPK. In humans, metformin can cause renal and gastrointestinal disturbances and other side effects. The challenge is to develop low doses of metformin (and especially their combinations with low doses of rapamycin) to suppress aging process without causing side effects. But even such modalities will not be probably indicated to healthy boys.

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