Longevity Genomics

Pier Giuseppe Pelicci
Istituto Europeo di Oncologia and University of Milan, Milan, Italy

Research on aging and, more specifically, on the molecular mechanisms governing life-span duration is relatively new. Yet, it has made extraordinary progress over the past 30 years.

The first breakthrough that paved the way for a new era in aging research came with the discovery of the existence of genes whose inactivation determines an increase in the maximum life span of an individual. These genes (few dozen in all) were discovered in both invertebrates (Drosophila and C. elegans) and mammals. Since their absence determines the prolongation of life, these genes are called aging genes (genes, that is, whose activity accelerates aging). The study of their physiological function has allowed their classification in three groups: i) genes that enhance the activities of insulin, a hormone that regulates cell metabolism; ii) genes that increase the accumulation of oxidative stress in the tissue; iii) genes that regulate the elongation of chromosome ends, and, thus, proliferative potential in stem cells. The existence of aging genes it is not easy to reconcile in evolutionary terms, as it is not immediately clear how genes that do not increase fitness can be selected.

A second major step forward was due to the discovery of the existence of genes whose activities prolong life (longevity genes). In particular, it is thanks to these genes if organisms are able to prolong life when subjected to calorie restricted diets (caloric restriction effect). Although detailed investigations have just begun, these genes too appear functionally connected to the regulation of cell metabolism.

Recent studies suggest that aging genes, longevity genes and caloric restriction all act on the same animal function: the capacity of an organism to adapt to the environment under conditions of nutrient deprivation. Undoubtedly, one of the big evolutionary challenges was represented by the alternation of cycles of food availability.

Finally, a third step forward came with the discovery that life extension by manipulation of aging genes or caloric restriction associates with a greater resistance to the incidence and the severity typical of aging-associated diseases (such as cancer or cardiovascular diseases). Although intuitively obvious, this suggests that the mechanisms behind the process of aging and aging-associated diseases overlap (for example, oxidative stress, insulin resistance, etc.). Applicatively, therefore, the study of the molecular mechanisms associated with aging can provide new molecular targets for the design of drugs against aging-associated diseases.

This possibility is quickly becoming very concrete. Indeed, there are at least two examples where the treatment of mice with drugs directed against the products of aging or longevity genes, respectively, has had an effect on life span or on some aspects of the aging-associated diseases. All these data, while preliminary, tell us that the study of the mechanisms regulating the duration of life may have a significant impact on aging, healthy aging or aging-associated diseases. It is likely that this knowledge will have a further acceleration in the near future. We expect further acceleration of this knowledge in the near future from studies of environmental modifications, in particular of diet, on chromatin (the complex of DNA and proteins around it). These aspects will be discussed.