nanomedicine is determined by its efficiency in each step A nanomedicine efficiently accomplishing the whole CAPIR cascade should have a high therapeutic index.

A vast number of classes of nanoparticulate delivery vehicles have been reported. As demonstrated by Huynh et al., drug-loaded delivery vehicles are attractive because they can be passively or actively targeted to cancer tissues to improve anticancer drug selectivity and thereby reduce severe side effects. Liposomes are perhaps one of the most advanced delivery vehicles concerning clinical translation, with several formulations approved by the U.S. Food and Drug Administration (FDA). Liposome-based systems encapsulating drugs are already used in some cancer therapies. However, liposomes have some significant drawbacks: they have a low capacity to encapsulate lipophilic drugs, they are manufactured through processes involving organic solvents, they are often leaky and are unstable in biological fluids and aqueous solutions.

Conclusions. New NPs tuned for nanomedicine applications are emerging, especially in the fields of drug delivery, antibiotic resistance, imaging, diagnostics, and cancer therapies. Recent studies have shown that the use of multiple nanomaterials (i.e., NDs and proteins) or a single nanoplatform functionalized with several therapeutic agents can successfully image and treat tumors with improved efficacy. NPs-based drug delivery has been included in the rational, biomimetic, and systematic design of optimal therapeutic combinations.

Nanomedicine in cellular, preclinical, and clinical studies has led to many important advances, both fundamental and translational. Many of these advances, however, have been in the field of cancer diagnosis and treatment. This disproportionate focus is expected to be addressed in upcoming years with research focuses expanding to other medical challenges such as antibiotic resistance and artificial organs. Nanomedicine is poised to be of benefit in these areas by virtue of the versatility of the nanomaterial platform design, be it through multimodal therapeutic approaches or through highly specialized multifaceted design for relevant biological applications.

Although nanomedicine has raised exciting expectations for many medical problems, scientific challenges have arisen as well, mainly due to the lack of knowledge about the behavior of nanomaterials inside living organisms. However, due to the basic research focused on these issues, we are now closer to solving them and to reaching “real” medical solutions based on nanomedicine.

EFFECT OF OMEGA-3 FATTY ACIDS ON TELOMERES

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Introduction. Telomeres are complexes consisting of tandem repeat DNA combined with associated proteins that play a key role in protecting the ends of chromosomes and maintaining genome stability. They are considered a biological clock, as they shorten in parallel with aging. Furthermore, short telomeres are associated with several age-related diseases. However, the variability in telomere shortening independent of chronological age suggests that it is a modifiable factor. In fact, it is regulated inter alia by genetic damage, cell division, aging, oxidative stress, and inflammation. A key question remains: how can we prevent accelerated telomere attrition and subsequent premature replicative senescence?

Aim. To study the possible effect of omega-3 fatty acids on telomere shortening.

Materials and methods. A literature search was conducted in PubMed, Scopus and Web of Science databases using keywords.

Research results. The cornerstone of studies on the impact of omega-3 fatty acids on telomere length was the work of Farzaneh-Far et al. They examined cohort studies of more than 600 patients with coronary artery disease (CAD), which showed strong evidence for an association between omega-3 fatty acid consumption and telomere length, and more precisely, an inverse relationship between the baseline blood levels of omega-3 fatty acids (DHA and EPA) and changes in leukocyte telomere length over five years. Studies by Cassidy et al. focused on the impact of diet and lifestyle factors on telomere length and were published in the same year. The authors examined over 2000 women and estimated their PUFA levels on the basis of a lifestyle questionnaire. They found no significant association between omega-3 fatty acid intake and telomere length. The two newest cross-sectional studies, published by Chinese groups, are in line with the work of Farzaneh-Far et al. Chang et al. examined 711 patients with nested CAD and 638 CAD-free controls. Using linear regression, they tested the association between omega-6 and omega-3 fatty acids and leukocyte telomere length. The plasma levels of omega-3 fatty acids, particularly EPA and DHA, were found to be positively correlated with telomere length. Similarly, a lower omega-6/omega-3 fatty acids ratio was significantly associated with longer telomeres. However, it should be highlighted that this correlation was mainly driven by elevated levels of omega-3 fatty acids, while omega-6 fatty acids, considered separately, had no effect on telomere length. The positive effect of omega-3 fatty acid content on telomere length has also been observed in obese children. Forty-six 3- to 4-year-old preschool children with obesity were included in the study, with equal numbers of age- and gender-matched children of normal weight as controls. The obese children exhibited lower levels of DHA, and this parameter was positively correlated with a shorter leukocyte telomere length.

Supplementation with omega-3 fatty acids affected leukocyte telomere length in patients with chronic kidney disease (CKD). In studies by Barden et al, 85 patients suffering from CKD were divided into four groups and received omega-3 fatty acids (4 g), CoQ (200 mg), both supplements, or the control (4 g of olive oil) every day for 8 weeks. The capsules of omega-3 fatty acids contained 460 mg of EPA, 38 mg of docosapentaenoic acid (omega-3 DPA), and 380 mg of DHA. The intervention with omega-3 fatty acids was associated with an increase in neutrophil telomere length, which was corrected for the neutrophil count.

In addition to the reports indicating the anti-inflammatory and antioxidant effect of omega-3 fatty acids in the context of telomere protection, there are studies that show a diversified effect of omega-3 fatty acids on telomerase, a ribonucleoprotein that adds the tandem arrays of TTAGGG repeats to telomere ends. In humans, the enzyme is composed of hTR (human telomerase RNA component), TP1 (telomerase-associated protein 1), and hTERT (human telomerase reverse transcriptase), the last of which plays a key role in telomerase activation. Telomerase was thought to be expressed only in germ cells, stem cells, and cancer cells. Indeed, most human somatic cells do not actively express this enzyme. This holds true with the exception of peripheral blood mononuclear cells, which can upregulate telomerase activity when activated. Eitsuka et al. found that fatty acids (C_{18} – C_{22}) directly inhibit telomerase activity. The IC50, the concentration at which 50% of telomerase activity is inhibited, indicated that the inhibitory potency of fatty acids increases with the number of double bonds. Accordingly, PUFAs, such as EPA and DHA, can strongly prevent telomerase's enzymatic activity. A Lineweaver–Burk plot revealed that EPA is a competitive inhibitor relative to the telomerase substrate primer, implying that fatty acids may interact with the primer-binding site of telomerase. Moreover, they demonstrated that physiological concentrations of EPA and DHA downregulate hTERT and c-Myc mRNA via PKC inhibition, thereby repressing telomerase activity. These results indicate that fatty acids, especially EPA and DHA, not only inhibit the enzymatic activity of telomerase directly but also downregulate telomerase at the

transcriptional level. Unexpectedly, others have also reported that both PUFAs and fish oil effectively inactivated testicular telomerase and inhibited c-Myc-mediated telomerase reverse transcriptase expression, whereas omega-3 PUFAs rather than omega-6 PUFAs protected the liver and testes against telomere shortening within the ranges of 13-25% and 25–27%, respectively. This finding is probably associated with the "double-edged sword" property of telomerase. Telomerase is canonically responsible for telomere length maintenance, though its activation may favor tumorigenesis. Nevertheless, both omega-3 and omega-6 PUFAs significantly reduced telomerase activity independent of telomere length. Numerous scientific papers have indicated the possibility of modulating TERT expression through epigenetic regulation. In cancers, DNA hypermethylation with the TERT promoter is a prevalent telomerase-activating mechanism that can act independently of or in conjunction with promoter mutations. Liu et al. found that erythrocyte DHA content was decreased in a cohort of 46 obese vs. 46 lean preschool children, and it had a positive association with leukocyte telomere length. Unfortunately, no association between erythrocyte DHA and DNA methylation of the TERT promoter was shown, although DHA functions to regulate DNA and histone methylation by affecting methyl group metabolism.

Conclusions. While the results of the presented cross-sectional and randomized human and rodent studies are not entirely consistent, the overwhelming number of them have demonstrated the beneficial effects of omega-3 fatty acids on telomere length (Fig. 1).

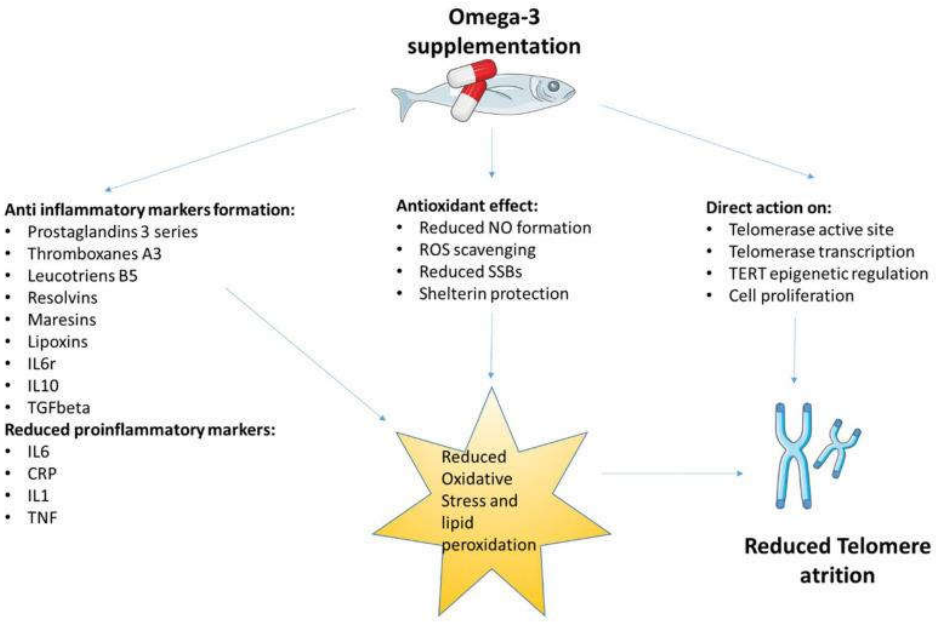

Figure 1. Indirect and direct effects of omega-3 fatty acid supplementation on telomere attrition

The factors that are strongly associated with accelerated telomere shortening and dysfunction are oxidative stress and inflammation. The ability of omega-3 fatty acids to reduce these negative effects is related not only to their well-documented beneficial effect on a number of 'lifestyle' diseases but also to their beneficial effects on telomere biology, which have both been raised in this review. The use of omega-3 fatty acids to reduce accelerated telomere attrition and, consequently, counteract premature aging and reduce the risk of age-related diseases raises high hopes. However, discrepancies in the presented results still indicate the need for a careful evaluation of the type of omega-3 fatty acids, their origin, dose and the timing of administration, as well as age, gender, regional and ethnic diversity, and health status.