Ageing Research Reviews 28 (2016) 62–71

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Preserving the longevity of long-lived type II collagen and its implication for cartilage therapeutics

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ARTICLE INFO

Article history:
Received 15 April 2016
Accepted 26 April 2016
Available online 28 April 2016

Keywords:
Ageing
Long-lived type II collagen
Collagen cross-linking
Osteoarthritis
Cartilage
Polyphenols

ABSTRACT

Human life expectancy has been steadily increasing at a rapid rate, but this increasing life span also brings about increases in diseases, dementia, and disability. A global burden of disease 2010 study revealed that hip and knee osteoarthritis ranked the 11th highest in terms of years lived with disability. Wear and tear can greatly influence the quality of life during ageing. In particular, wear and tear of the articular cartilage have adverse effects on joints and result in osteoarthritis.

The articular cartilage uses longevity of type II collagen as the foundation around which turnover of proteoglycans and the homeostatic activity of chondrocytes play central roles thereby maintaining the function of articular cartilage in the ageing. The longevity of type II collagen involves a complex interaction of the scaffolding needs of the cartilage and its biochemical, structural and mechanical characteristics. The covalent cross-linking of heterotypic polymers of collagens type II, type IX and type XI hold together cartilage, allowing it to withstand ageing stresses. Discerning the biological clues in the armamentarium for preserving cartilage appears to be collagen cross-linking. Therapeutic methods to crosslink in *in-vivo* are non-existent. However intra-articular injections of polyphenols *in vivo* stabilize the cartilage and make it resistant to degradation, opening a new therapeutic possibility for prevention and intervention of cartilage degradation in osteoarthritis of aging.

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1. Introduction

Human life expectancy has been steadily increasing at a rapid rate (Oeppen and Vaupal, 2002), so that someone born in European Union today could be expected to live about 100 years (Brown, 2015). This longevity, however, is tempered with a potential for a decline in life expectancy, as exemplified in the United States, primarily due to the negative effects of obesity (Olshansky et al., 2005). Increasing lifespan also brings with it increased exposure to diseases, dementia and disability (Sander et al., 2015).

Of the 291 conditions listed in a 2010 global burden of disease study, hip and knee osteoarthritis ranked the 11th highest in terms of years lived with disability and 38th highest in terms of overall burden, as measured by estimates of daily-adjusted life years (Cross et al., 2014). Wear and tear have been argued to have a great influence on the quality of life during ageing, with joints being prime examples of organs that wear and tear during age-

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http://dx.doi.org/10.1016/j.arr.2016.04.011
1568-1637/

ing. The articular cartilage wear and tear have adverse effects and result in osteoarthritis (OA) (Felson, 2009), while the epidemic of obesity further compounds this disease. OA is characterized by erosion of the articular cartilage, osteophyte formation, subchondral bone sclerosis, ligament and synovial membrane pathologies. Of all these, pathological changes in the articular cartilage are the central to the loss of joint function and progression of OA. The articular cartilage is a complex matrix that helps in frictionless joint motions and provides tensile strength and compressive resistance. The articular cartilage consists of two components: type II collagen and the large aggregating proteoglycan (PG), aggrecan (Poole, 2005).

In this review we focus on the longevity of type II collagen in context with its biochemical, cross-linking and structural aspects. We scrutinize the reasons for the long-lived characteristic of type II collagen and its molecular interactions in relation to aging. Importantly, we use this knowledge to suggest therapeutic strategy using plant polyphenols to intervene or prevent cartilage degradation in OA and aging.

1.1. Type II collagen: structure and organization within cartilage

The type II collagen molecule is a homotrimer of three identical α1-polypeptide chains of 1050 amino acids residues each, with a large uninterrupted triple-helical region and non-triple helical telopeptides at the terminal ends. These telopeptides do not possess the Gly-X-Y repeating units observed in the triple-helical region. The type II collagen N-telopeptide and C-telopeptide consists of 19 and 27 amino acid residues, respectively. Each triple helix is formed, by an uninterrupted helical region with alternating polar and nonpolar domains, into a single collagen molecule of 300 nm lengths. Type II collagen, similarly to Type I, self-associates into a **D**-periodic fibril assembly (Fig. 1) with a characteristic 67 nm axial D periodicity (Birk and Brückner, 2011; Prockop and Kivirikko, 1995). The higher-order supramolecular structures laterally arrange in a quasi-hexagonally manner with their neighbours to form the basis of the fibril.

Type II collagen of cartilaginous tissues is heterotypically associated with type IX and Type XI collagens (Eyre, 2002a). Type XI collagen is a fibril-forming protein of the same size as type II collagen. The triple helix of type XI collagen molecules is incorporated centrally with the fibre of type II collagen (Fig. 2a) (Eyre et al., 2008). The N-terminal pro-peptides of type XI collagen are retained and are exposed at the surface of fibres (Fig. 2a) (Eyre et al., 2004a). Type IX collagen, a 'fibril-associated collagen with interrupted triple-helix' (FACIT) sub-family member, is highly evolved and plays a critical role as an adapter molecule on the surface of nascent type II collagen fibrils (Wu et al., 1992). Types IX and XI collagens are most concentrated with their highest ratio to type II collagen in developing cartilage and in the immediate pericellular zone of chondrocytes (Mendler et al., 1989). As cartilage matures, the ratio of type II collagen to collagen XI and IX rises to about 96:3:1 from 80:10:10 in foetal cartilage (Eyre et al., 2002b). In addition, with increasing cartilage maturity, type XI collagen fractions contain more a1(V) and less a2(XI) in proportion to the a1(XI) and a3(XI) found in foetal cartilage (Wu et al., 2009). The change to a1(V) has been speculated to provide a polymeric filamentous template for the thicker type II collagen fibrils that accumulate in adult cartilage (Lane and Weiss, 1975; Wu et al., 2009). Collagen fibre diameters increase with age as well as within cartilage depth (Lane and Weiss, 1975).

The stability of the fibrils and the internal order are maintained by intermolecular cross-linking between collagen molecules (Eyre et al., 2002b). Covalent cross-links are formed between lysine and hydroxylysine within both the helical and non-helical telopeptide domains of collagen molecules within a D-period. Cartilage collagen uses hydroxylysine significantly for aldehyde based cross-linking by lysyl oxidase (Eyre and Wu, 2005). Type II collagen of newly formed cartilage becomes cross-linked by divalent ketoimines between the hydroxylysine aldehyde of the telopeptide and the hydroxylysine of the triple helix. As fibrils mature, the divalent ketoimines interact spontaneously to form trivalent cross-linked hydroxylysyl pyridinoline (HP). As a part of the maturation process, ketoimines disappear from mature cartilage and HP becomes the sole cross-linked residue. Cartilage contains the highest levels of collagen HP of all connective tissue (Eyre, 1984). Eyre et al. (2010) also showed that the initially formed ketoimine cross-links of type II collagen mature by an alternative chemical reaction. In mature bovine cartilage, two-thirds of the ketoimines in cartilage collagen was shown to form trivalent HP and one-third to arginoline. The latter is a divalent ketoimine cross-link that fails to form a pyridinoline and undergoes spontaneous oxidation, followed by rapid addition of free arginine.

Type II collagen molecules have more amino acid residues for cross-linking at N and C termini when compared with type I collagen. Three potential cross-link forming lysine residues are present at the C terminus of the homotypic chain composition of type II molecules. Similarly, at the N terminus of type II collagen, Hyl-9 may form three covalent bonds with lysine residues on monomer five of the fibrils (Orgel et al., 2006). This increased potential for cross-linking leads to a higher number of covalent bonds within and possibly even between the fibrils (Antipova and Orgel, 2010). Covalent cross-linking of type IX with type II collagens and to type XI collagen molecules is also known to occur by lysyl oxidase mechanism. Type XI collagen form cross-links to primarily other type XI molecules and is divalent in nature (Wu and Eyre, 1995). In addition, the a1 (II) C-telopeptide cross-links with the amino-terminal site of the a1 (XI) triple helix (Wu and Eyre, 1995). Furthermore, the various types of reducible cross-links disappear from adult connective tissues, whether their primary formation pathway is from lysine or hydroxylysine aldehydes (Avery and Bailey, 2005; Bailey et al., 1998). Nutritional, endocrine and pharmacological factors also influence extracellular matrix crosslinking and maturation (Tinker and Rucker, 1985).

The presence of identical a1-polypeptide chains, with large uninterrupted triple-helical regions and relatively short nonhelical teleopeptides, allows for proper super coiling of type II collagen fibrils (Prockop and Kivirikko, 1995). The uniform chain length of type II collagen, combined with its alternate amino acid composition, guarantees a unique mode and distribution of intermolecular cross-links and structural conformation. In addition, a bulkier type II collagen N-telopeptide may function in sterically inhibiting the formation of large type II fibrils similar in size to type I collagen (Antipova and Orgel, 2010; Orgel et al., 2011), leading at the same time to loosely organized fibril bundles composed of small and relatively thin fibrils (Holmes and Kadler, 2006). Type II collagen molecular packing significantly differs from that of type I collagen. Type II collagen fibrils are much thinner (≈35 nm) as compared to type I fibrils (≈100–200 nm) and are approximately 300 nm long in their fibrillar form (Orgel et al., 2011). Thinner type II collagen fibrils allow greater attachment of PG molecules outside of the fibrils (Orgel et al., 2011). PGs, such as decorin, fibromodulin and biglycan, bind type II fibrils to stabilize the larger fibrils bundles (Fig. 3). Collectively, these findings indicate that cartilage collagen fibrils are even more densely cross-linked than previously appreciated for their HP content alone, and a greater potential exists for cross-linking in type II collagen within, and possibly even between the fibrils than is found in collagen type I. Therefore, the type II collagen fibril is likely to be more stable, which may translate into complex and stable tissue organization of cartilage.

Articular cartilage exhibits a zonal architecture consisting of superficial, middle and deep zones, so a different level of various crosslinks is found in different zones. For example, HP levels are