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Review

Unique structural features of the pentameric matrix protein COMP sustain its dynamic regulation of extra- and intracellular activities: A review

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ABSTRACT

The macromolecule COMP –Cartilage Oligomeric Matrix Protein– was originally discovered as an essential regulator of the assembly, integrity and homeostatic remodeling of cartilage tissue ECMs. Later, however, it was found to have a more widespread distribution, to attain different subcellular topographies and play a pivotal role as an integral component of fibrotic and cancer-associated matrices. The homopentameric configuration of COMP remains distinctive within the human proteome and confers to the protein a multivalent functionality exploitable by the cells under physiological and pathological conditions. The structural-functional properties of COMP show limited overlap with those of other members of thrombospondin family and its multifaceted nature extends beyond its function in matrix assembly to embrace signal transducing interactions with the cell surface, the sequestering of signaling molecules, and the binding of components of the immunological/complement system. Mutated chondrocyte variants of COMP and isoforms aberrantly expressed by transformed cells are retained intracellularly to engage interactions with a variety of cytoplasmic molecules and convert the macromolecule from a structural ECM component to a regulator of homeostatic and transformative events. We discuss here how the unique structural traits of COMP may endow it with multifunctionality and explain its active participation in highly diverse biological processes.

1. Protein family community and regulation of the COMP gene

Cartilage Oligomeric Matrix Protein (COMP) was first isolated from bovine cartilage as a multimeric complex of an estimated size of 524 kDa and was rapidly baptized as being a predominant component of the ECM of cartilage and specialized connective tissues [1,2]. The expected fallout of the discovery was that the macromolecule proved to be a key contributor to the turnover and pathogenesis of these tissues. In this review we discuss how the unique structural features of COMP translate into an array of functional properties that underlie the role played by the macromolecule in the maintenance of the homeostasis of cartilage tissues and its involvement in inherited and acquired diseases.

Nucleotide sequence determination of human COMP [3], and later of the mouse orthologue [4,5], revealed a significant sequence homology with thrombospondins (TSPs) but a reduced size of the gene product (Fig. 1). In fact, COMP is an official member of the TSP family that stands out because of the lack of an *N*-terminal segment of 84 amino acids yielding a 40 % shorting of that domain [3]. By contrast, the glycoprotein maintains a high conservation degree (53-82 %) within the "signature domain", typical of the TSP family and encompassing a distinct *C*-terminal domain, and within the so called "Type III TSP repeat" segment [6]. Human COMP is derived from an 8533 bp long gene localized on chromosome 19p13.1 and encoding an open reading frame of 757 amino acid residues (Fig. 1). These are translated from 19 exons to build up the single monomeric units of the pentamer, each having a molecular weight of 82.860 Da and a mere of two putative glycosylation sites at positions 121 and 742. Each monomer further harbors 23 highly conserved cysteine residues for intra- and

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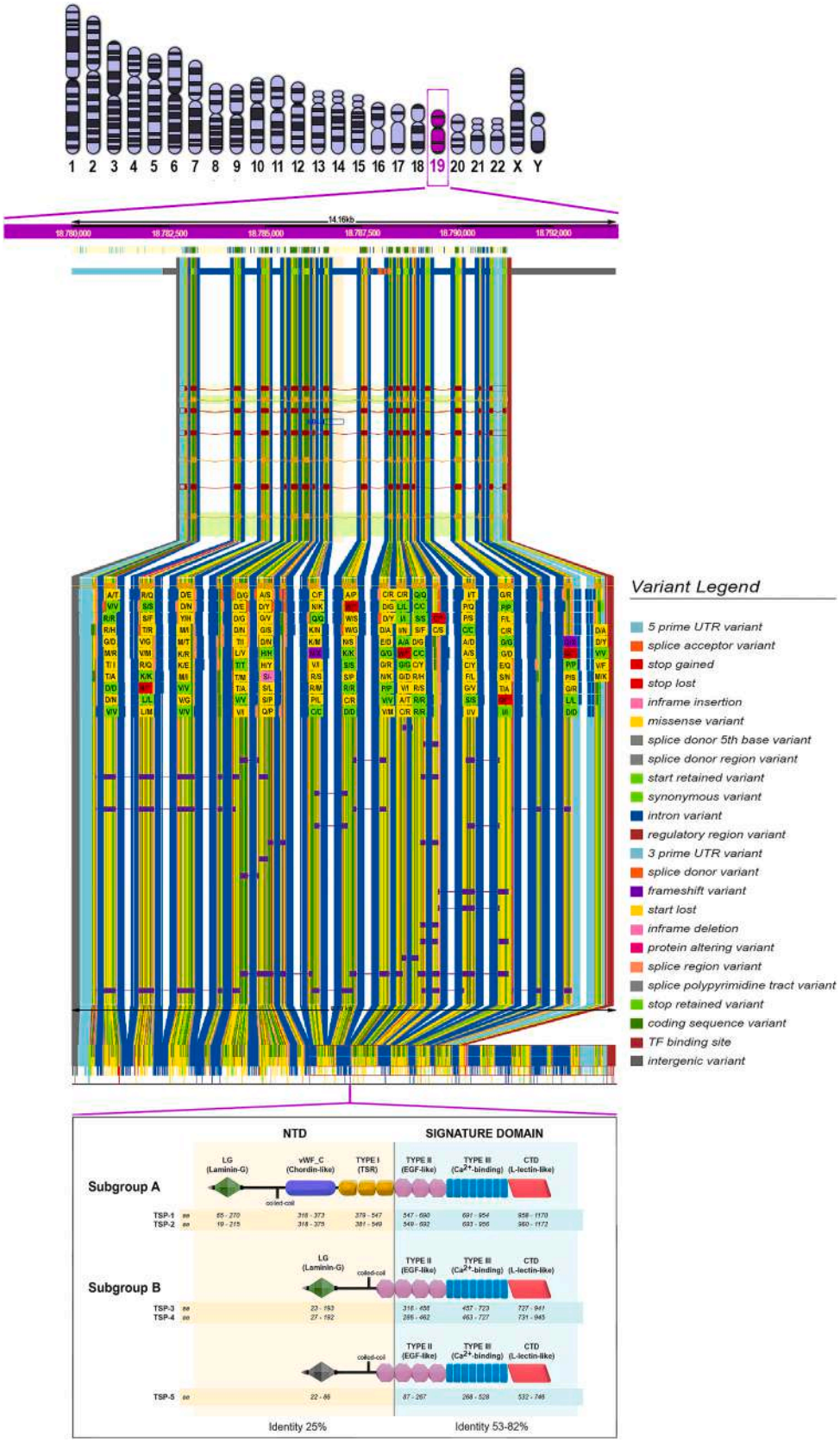

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Fig. 1. The human COMP gene resides on chromosome 19 and displays a wide genetic variation. COMP belongs to the thrombospondin family which is divided into two subgroups based on differences in their structural and oligomerization characteristics. TSP-1 and -2 are homotrimers belonging to *Subgroup A*, whereas TSP-3, -4, and -5/COMP are homotypic pentamers included in *Subgroup B*. COMP is the most distinct member of the family because of the lack of the *N*-terminal laminin-G superfamily domain. In *Subgroup A*, the conserved oligomerization domain forms an a-helical coiled-coil structure stabilized by disulfide bonds adjacent to the *N*-terminal domain, whereas in *Subgroup B* disulfide bonds are found *C*-terminally. Family members of *Subgroup A* further encompass a von Willebrand Factor Type-C domain (also known as *Chordin-like cysteine-rich repeat domain*) and three thrombospondin type-I repeats (also known as *properdin-like repeats*). The *C*-terminal region of thrombospondins ("*signature domain*") is the most conserved across vertebrate species (53–82 %) and embodies only three thrombospondin Type II EGF-like repeats, eight Ca^{2+}-binding thrombospondin Type III repeats (characterizing the family) and a globular *C*-terminal domain.

intermolecular disulfide bonding. The *N*-terminal domain accounts for solely 8 % of the full-length sequence but is both structurally unique and pivotal for the macromolecular organization of the pentamer. Comprehensively, the COMP polypeptide includes 4 Type II TSP repeats, which are build up by EGF-like motifs and occupy 24 % of the sequence; 8 Type III TSP repeats characterized by Ca^{2+}-binding motifs analogous to those found in calmodulin and accounting for 35 % of the protein; and the globular *C*-terminal domain stretching a total of 29 % of the length of the COMP molecule [7] (Fig. 1).

Tissue distribution of COMP in the human body extends somewhat beyond articular cartilage as the protein is a primary component of the ECM of synovium, ligaments, tendons [8] and the vitreous body of the eye [9]. COMP is also weakly transcribed in dermal fibroblasts and in some subpopulations of vascular smooth muscle cells, while it is markedly over and/or ectopically expressed in fibrotic conditions and in an ample array of tumor types. Gene regulation of COMP has been approached in mouse where two conserved silencer regions have been identified in the COMP promoter [5,10,11]. During the process of chondrogenesis these sites seem to be controlled by the POZ-domain-containing the transcriptional repressor leukemia/lymphoma-related factor [12]. The two implicated 30 bp-long negative regulatory elements of the COMP promoter are counterposed to a 51 bp-long positive regulator element, which has been shown to correspond to the binding site for the transcription factor Sox9. However, the later chondrogenic factor is not capable of controlling COMP transcription alone but requires the concurrent activity of two other members of that family, i.e., Sox5 and Sox6, and the co-activators CBP and p300 histone acetylase. Collectively, these factors counteract the repressor function of the leukemia/lymphoma-related factor [13].

Modulation of the COMP gene regulation machinery is likely to cooperate with the transcription-promoting activity of FOXM1 [14] in eliciting upregulations and/or de novo expressions of the pentamer upon neoplastic transformation. It could be hypothesized that these gene orchestration operates down-stream of epithelial-mesenchymal transitions propelling neoplastic transformation. Another intriguing control mode of COMP transcription, impacting on homeostasis and cancer

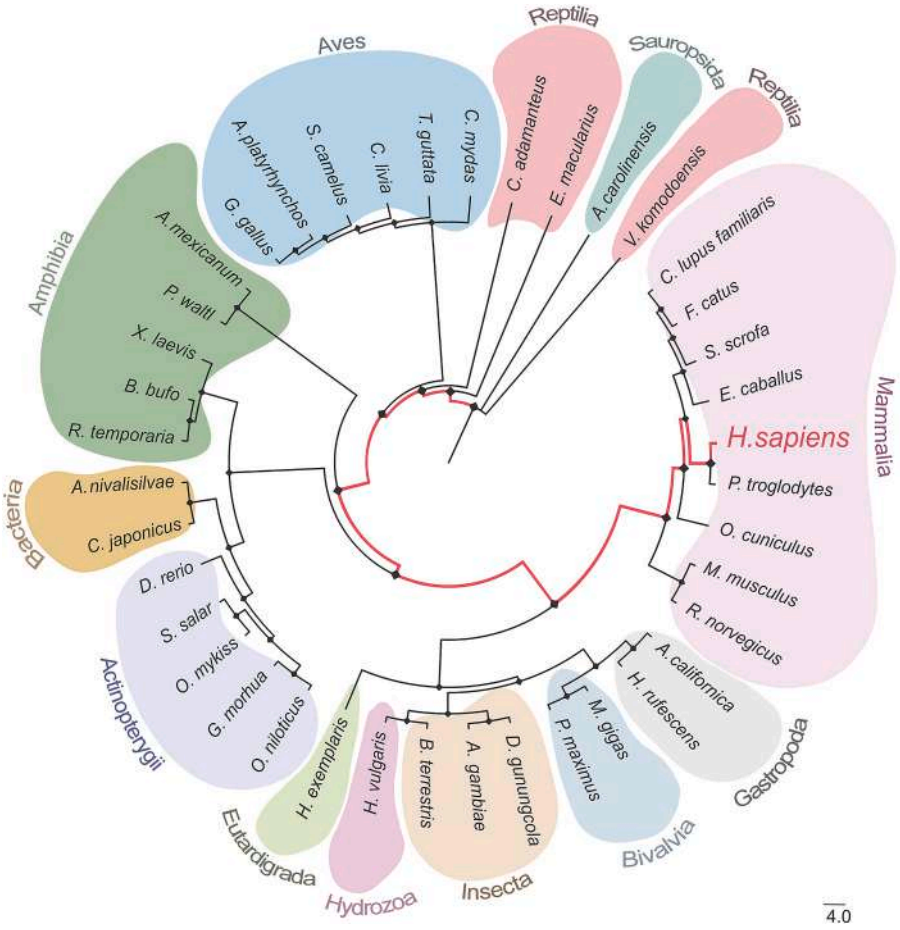

Fig. 2. Evolutionary relationships of COMP across diverse taxonomic groups. Radial phylogenetic tree illustrating the evolutionary relationships of COMP pentamers across the taxonomic classes: Amphibia, Aves, Reptilia, Sauropsida, Mammalia, Gastropoda, Bivalvia, Insecta, Hydrozoa, Eutardigrada, and Actinopterygii. The tree also includes the bacteria *Aquarufa nivalisilvae* (class Cytophagia) and *Cellvibrio japonicus* (class Gammaproteobacteria), the later collectively referred to as "Bacteria." Protein sequences were aligned using ClustalX [18] and the phylogenetic tree was generated with the Figtree v1.4.3 [19] software tool using standard parameters.

conditions, is that entailing endonuclear circular RNA-calmodulin-4 complexes, which also act as transcriptional repressors and affect the susceptibility to hypoxia-induced ferroptosis [15].

2. The evolutionary structural conservation of COMP hints functional conservation

Phylogenetic analyses demonstrate that TSPs are encoded by ancient genes and it is speculated that the primitive members of *Subgroup B* were the first to originate (Fig. 2). In metazoans, a single gene coding for a pentameric TSP was already present and through gene remodeling and duplications it gave rise to new genes in deuterostomes encoding a pentameric TSP-B, a dimeric TSP-A, and a monomeric TSP-DD containing a *discoidin domain*. Except for TSP-DD, which was lost in the vertebrate lineage, the other genes underwent gene duplications leading to the array of proteins constituting the current TSP family [16]. COMP appears to have originated from gene duplications that date 750 million years back, giving rise to a unique gene sequence (not derived from alternative splicing) truncated in the *N*-terminal region. A TSP-4-like sequence can be found in fish and is claimed to correspond to an orthologue of the tetrapod gene. It is further believed that through duplication events causing loss of coding exons, this ancestral gene may have given rise to the current COMP gene sequence, which was further stabilized under selective pressure [17].

The widely studied murine COMP orthologue is located on chromosome 8 [4,20,21] and is similarly composed of 19 exons spanning an 8.4 kb region of the genome. The translated sequence of murine COMP comprises 757 amino acids, shares 90 % homology with the human sequence (differing only by 6 nucleotides and lacking two amino acid residues) and encodes a protein of 82,342 Da (the rat homologue measures 82,664 Da). In addition to the bovine, rat and mouse orthologues, COMP of zebrafish has been specifically studied, also because of its involvement in developmental processes distinct from chondrogenesis. The protein is slightly shorter, is composed of 749 amino acids and is encoded by a genomic region of 19 exons located on chromosome 11 of this fish species. It shows 74 % similarity with the murine COMP gene and shares the multidomain arrangement of tetrapods [22]. Overall, the most conserved exons of the COMP gene across vertebrate species are those encoding the Type II, EGF-like TSP repeat domain and the Ca^{2+}-binding, calmodulin-like sites within the Type III TSP repeat domain. Conceivably, this evolutionary conservation highlights the importance of COMP as a structural ECM component, both during embryogenesis and in the context of tissue assembly and remodeling, spanning from that of simpler organisms such as *Drosophila* [22] to mammal [23].

3. The molecular architecture of COMP defines a multivalent pentamer with unique ECM reservoir functions

The first structural analysis of COMP was performed by Matthias Mörgelin in the early 90s when adopting rotary shadowing and negative staining TEM techniques at a 0.2 Å resolution [2,24,25]. Through this approach it was possible to visualize the typical "bouquet-like" constellation of COMP, further also visualized by AFM (Fig. 3A; [26]) and highlighting the five constituent monomeric chains radiate from a cylindrical pentamerization (globular) domain. The five-armed configuration of COMP could be confirmed by biochemical/biophysical analyses of a recombinant fragment corresponding to the *N*-terminal pentamerizing domain and the covalent (chemical) linkage of the constituent five polypeptide chains [27]. This *N*-terminal part of the COMP molecule is a highly uncustomary protein module within the vertebrate *Matrisome* because of its configuration and due to unprecedented thermal stability. It is composed of a coiled-coil motif region (COMPcc) formed by the folding of 230 residues into five parallel a-helices that intertwine to create a left-handed superhelix [28]. The biological implication of the exceptional thermodynamic properties of COMP's pentamer assembly domain has remained veiled but the same traits are presumably shared by TSP-3 and -4.

Jurgen Engel's group generated the first crystal preparation of this oligomeric region and demonstrated that the homopentameric structure of COMP is stabilized by hydrophobic interactions which are facilitated by residues Gln54 and Asn41, in conjunction with disulfide bridges between Cys71 and the adjacent Cys68 [29,30]. It was further found that COMPcc is structured by the 63 *N*-terminal amino acid residues (amino acids 20-83) of each monomer containing seven heptad repeats $(a\text{-}g)_n$. Remarkably, this arrangement creates a central hydrophobic channel whose biophysical properties are dictated by the hydrophobic nature of the amino acid residues at positions "*a*" and "*d*" within each heptad, while the remaining positions ("*b*", "*c*", "*e*", and "*g*") are amphipathic. The coiled-coil structure of the pentamer was further found to be primarily stabilized by hydrophobic interactions between adjacent helices, which are arranged to form four types of "knob-into-hole" interactions. In this configuration, the side chains of the amino acid residues at positions *a*, *d*, *e*, or *g* project into the structure, creating knobs that fit into complementary cavities formed by the side chains of the residues in neighboring helices at positions *a-g*, *e-d*, *c-d*, and *a-b*, respectively. Notably, the residues pivotal for the molding of the pentamerizing COMP domain, i.e., residues Gln54 and Asn41, are highly conserved in TSP-3 and -4, suggesting their specific contribution to pentameric assembly of other TSPs as well. More specifically, residue Asn41 has been shown to be indispensable for the pentameric arrangement since its substitution with a leucine residue promotes the formation of tetramers rather than pentamers [28–32].

The orientation of the hydrophobic residues building the COMPcc determines the formation of a hydrophobic axial pore measuring 73 Å in length and having a diameter that varies between 2 and 6 Å. This variation is due to regular constrictions created by the rings of the side chains at positions *a* and *d* along the entire structure. In this extended hydrophobic channel running through the COMPcc, the presence of an internal ring of hydrogen bonds formed by residue Gln54 and the anions of nearby residues endow COMP with the ability to act as a putative "ion trap" and thereby exhibit similarities with the transmembrane ion channels phospholamban and acetylcholine receptor. Structuring of a channel has led to the alluring hypothesis that COMP could function as a matrix container for small hydrophobic molecules, such as Vitamin D3 and retinoids. Indeed, these polar molecules have empirically been demonstrated to be retainable within COMPcc of individual pentamers [31–33]. Although COMP has tangibly been detected on the surface of chondrocytes and tumor cells, there is currently no evidence that it may occasionally be incorporated into the lipid bilayer, such as to serve as a functional transmembrane ion channel.

4. Structural properties of the "signature domain" reveals the presence of high-affinity cation-binding sites

The "*signature domain*" of COMP shows 41-63 % homology with other TSPs depending on the number of Type II, EGF-like and Type III Ca^{2+}-binding TSP repeats constituting the TSP homologue (Fig. 1). The segment spanning approximately 200 amino acid residues and encompassing the most *C*-terminal Type II EGF-like TSP repeat, the Type III Ca^{2+}-binding repeat domain and the *C*-terminal domain was resolved in 2009 by Tan and colleagues using X-ray crystallography at a resolution of 3.15 Å [34]. The last Type II EGF-like TSP repeat of COMP, which is analogous to the corresponding repeat of TSP-2, seems to interact with the *C*-terminal domain. By contrast, the fourth most *C*-terminal Type II EGF TSP repeat does not seem to establish direct contacts with the Type III Ca^{2+}-binding TSP repeats. The 4 Types II EGF-like TSP repeats of this domain, two of which are Ca^{2+}-binding, are followed by a region comprising 13 asparagine-rich Type III repeats with 26 putative Ca^{2+}-binding sites believed to be indispensable for proper folding of the molecule. These residues, extending from Pro746 to Ala757, form a short α-helix that crosses the β-sheet of the *C*-terminal domain and establish multiple interactions with other parts of that domain. For

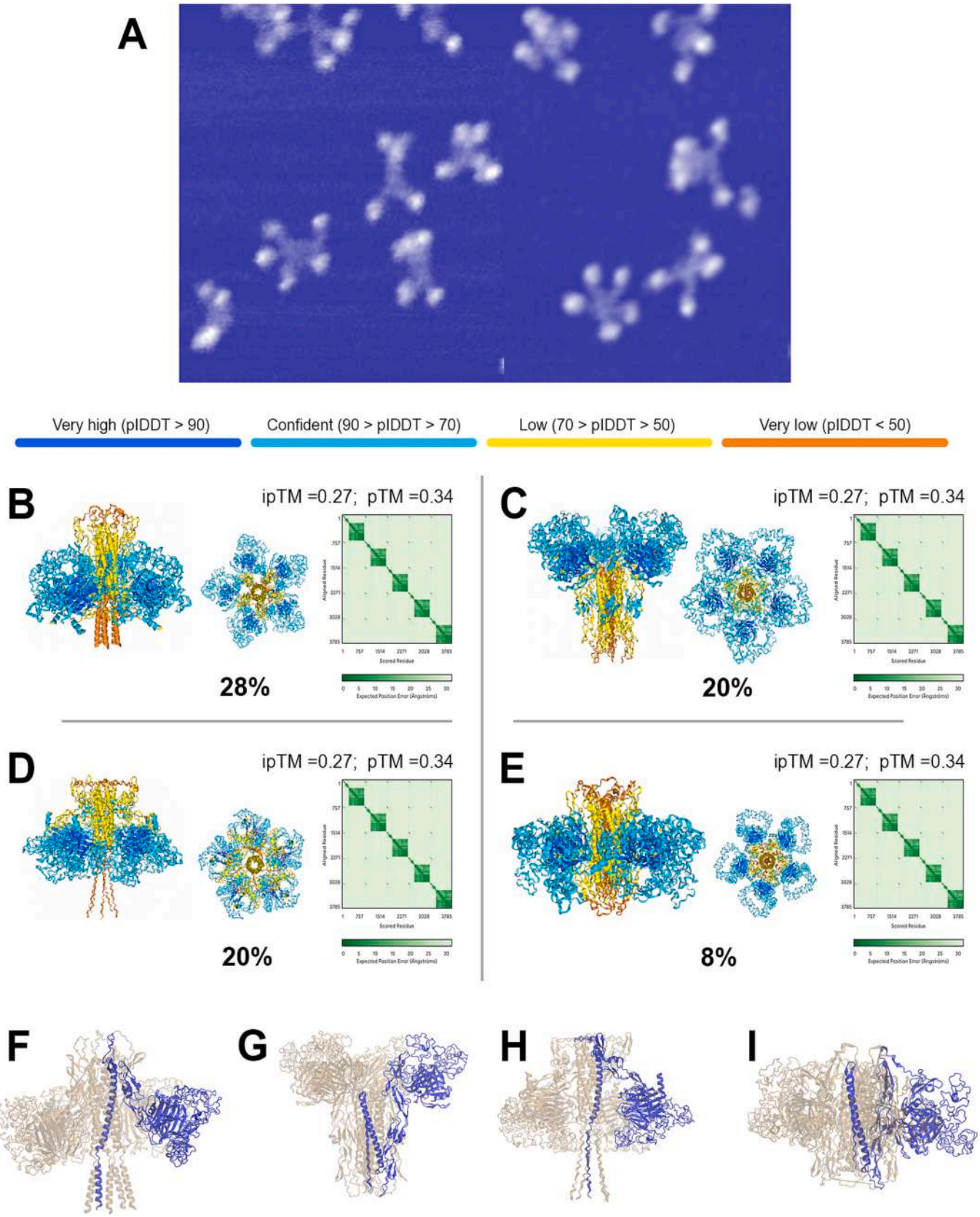

Fig. 3. Representative atomic force microscopic (AFM) and in silico defined structural models of COMP pentameric macromolecule. (A) AFM topographic images of human COMP macromolecules bound to a mica surface (0.5 × 0.5 mm; Courtesy Domenik Haudenschield and Gang-yu Liu). (B) AlphaFold3-based computational prediction models of the possible 3D configurations assumed by the pentameric COMP assembly. Probability scoring highlights the configuration of *Complex A* as the most likely to be followed by those of *Complexes B* and *C*, while configuration exhibited by *Complex D* seems to be the least likely to be assumed.

instance, residue Asp748 forms a hydrogen bond and a salt bridge with residues Tyr694 and Arg696 on the β12 strand of the β-sheet. The amino acids Pro746, Tyr749, and His752 located on this α-helix also contribute to the hydrophobic interactions within the *C*-terminal domain. It emerges that this helical tail is a unique feature of the COMP *C*-terminal end and may influence the ligand accessibility of the exposed β-sheet in this region [34].

The Type III Ca^{2+}-binding TSP repeats of COMP can be divided into 8 *C*-type sequence motifs and 5 *N*-type motifs, each capable of binding up to two calcium ions. Empirically it has been established that the 8 Type III TSP repeats of COMP bind cumulatively 14 Ca^{2+} ions in the native molecule (i.e., 14 of the 26 possible sites have been demonstrated to be occupied) and do so with moderate affinity and high cooperativity [35]. Meanwhile, computational analyses propose that once bound, these ions are relatively inaccessible to solvent and molecular ligands. In fact, one ion is predicted to be completely coordinated by protein atoms, while the other is coordinated by a water molecule. This polypeptide segment, consisting of a core of metal ions, is unique as it lacks secondary structure [34,36]. COMP contains two additional calcium-binding sites within the 5 *N*-type motifs. In this case, however, the first calcium ion is coordinated by a water molecule, while the second is exposed to the solvent. Because of being located within an "open" site, this cation can be lost upon amino acid substitution that may occur in inherited genetic disorders and/or mutational processes associated with neoplastic transformation (see below). Computationally, it can be predicted that only 5 of those are open, while the closed ones turn out to be the most conserved among TSPs [34].

Three additional "open", highly conserved Ca^{2+}-binding sites are located at the *C*-terminal end. The first two are approximately 4 Å apart and are structured by the triple aspartate motif (Asp593–595) on the β5–β6 loop and the residues Asn565, Gln619, Ser728, Gln616, and Asp678. In contrast, the third Ca^{2+}-binding site is formed by the residues Gln616 and Asp678, together with two main chain carboxyl groups from the β5–β6 loop [34]. This L-lectin-like globular domain consists of 15 antiparallel β-sheets [36] and is believed to be fundamental for the interaction of COMP with other ECM components. Proper folding of this globular domain exposes a conserved Metal Ion Dependent Adhesion Site (MIDAS), which allows COMP to bind to the carboxylic groups of its molecular ligands with each of the five assembled monomers [34].

5. Predictable molecular orientations of the COMP pentamer

The original ultrastructural analyses of the pentameric COMP molecules highlighting the "stellate" configuration of the macromolecule with the 5 arms extending out in different directions from a central globule presumably provided a rather static view of a surface-immobilized COMP. However, this static view was later challenged by computational modeling of the five-stranded coil-coiled structure of the pentamerizing domain [37]. Meanwhile, the advent of sophisticated software for in silico simulations of protein structures and protein-protein complexes has provided the computational tools for structure-function prediction studies and can effectively be exploited for simulating the possible arrangements of homotypic oligomers complexes within proteomes across species [38]. In different databases (e.g., the Ensembl database) it is possible to find computational models for the single monomers of COMP generated with early versions of the AlphaFold software tool. However, in silico simulations are of a more limited capability when attempting to provide reliable predictions of the molecular configuration of the intact COMP pentamer. The current version of Alphafold-3 (AF3) [39] harbors the ability to identify aggregate-prone regions and return macromolecular complexes, whereas. Interface predictions are less performant.

Reliable prediction of the pentameric structure of COMP must consider two primary metrics as particularly critical, predicted Local Distance Difference Test (plDDT) Scores and Predicted Aligned Error (PAE). Satisfactory statistical robustness can be achieved by performing a sufficiently high number of predictions using different initial seeds. We used AF3 through its web interface, (https://alphafoldserver.com/about) to collect 50 different structural predictions, each obtained with a different random seed, to enhance the statistical reliability of the resulting models. These pentameric complexes were clustered by structural similarity, highlighting four main groups of models covering 76 % of the total predictions, with the remaining modelled structures may be classified as outliers (Fig. 3B). According to this approach, the COMP pentamer can be deemed to adopt at least four distinct quaternary assembly geometries (Fig. 3B–E). All predicted models still exhibit a pentagonal symmetry, as observed in the native pentamer by TEM/rotary shadowing/negative staining and atomic force microscopy [26]. This suggests that the different conformations assumed by the pentamer arise from variations in interchain interactions. Notably, the different predicted multimeric complexes are associated with distinct 3D folding conformations of the monomeric units within the four pentamers, as depicted in Fig. 3F–I. Among the molecular structures generated by AF3, the most frequently occurring configuration, Cluster A, appears in 28 % of the models (Fig. 3B). The other two dominant clusters are observed with equal frequency, each comprising 20 % (Fig. 3C–D), whereas a fourth cluster is observed in a mere 8 % of the predictions (Fig. 3E). This variability highlights the structural flexibility of the COMP pentamer and emphasizes the importance of considering multiple models when interpreting its computationally derived quaternary structures.

The most probable pentamer model currently definable by AlphaFold3 indicates a strong intrachain confidence, with consistently low diagonal PAE values (0.76 for each chain) and a faithfully delineated monomer folding. However, off-diagonal PAE values, which measure inter-subunit interactions, exceed 5 across the pentamer, reflecting low confidence in the overall structure prediction of the correct assembly (Fig. 3B–E). The discrepancy puts in evidence the fact that AlphaFold3 may reliably predict folding of the individual monomeric subunits of COMP, as also highlighted by the inter-chain predicted Template Modeling (ipTM) and predicted Template Modeling (pTM) scores (0.27 and 0.34, respectively), but cannot yet efficiently be exploited for prediction of more complex features associated with the pentameric assembly of the macromolecule. In fact, it seems possible to predict with fidelity the configuration of discrete monomeric units, whereas interfacial and assembly-critical sites display much lower confidence.

6. The matrix creator, stabilizer and remodeler

The widely documented matrix-assembly function of COMP is strongly influenced by its interplays with key *Matrisome* components belonging to all primary categories, i.e., collagens, glycoproteins and proteoglycans (Fig. 4; [40]), which are brought about by distinct interactions of the ECM molecules with different structural domains of COMP. Noteworthy, a frequently unappreciated asset of COMP in this context is its dual activity as a "*creator/stabilizer*" and "*remodeler*" of both healthy and diseased interstitial matrices. This asset thereby attributes to the macromolecule a pivotal role in what may be referred to as "*matricrine signaling*". In healthy conditions, the exemplary case of a bivalent "*creator-remodeler*" role is that related to the assembly and turnover of the articular cartilage ECM. There, COMP produced by chondrocytes is co-secreted with the primary collagens making up the scaffold of that matrix, and this co-secretion is accompanied by the concurrent release of Matrilins into the meshwork of multimeric complexes of Hyaluronan-Link protein-Aggrecan.

Evidence for an intimate relationship between synthesis and secretion of COMP and Matrilins is afforded by studies of COMP, Matrilin-3 and Collagen type IX null mice. In these mutants, loss of Matrilin-3, or ablation of Collagen type IX, significantly perturbs the matrix levels of COMP, decreases the levels of several Matrilins (in addition to Matrilin-3) and impacts collagen fibrillogenesis [41,42]. This would infer that COMP serves as an adaptor protein during synthesis and elaboration of cartilage matrices. Accordingly, among the best characterized molecular

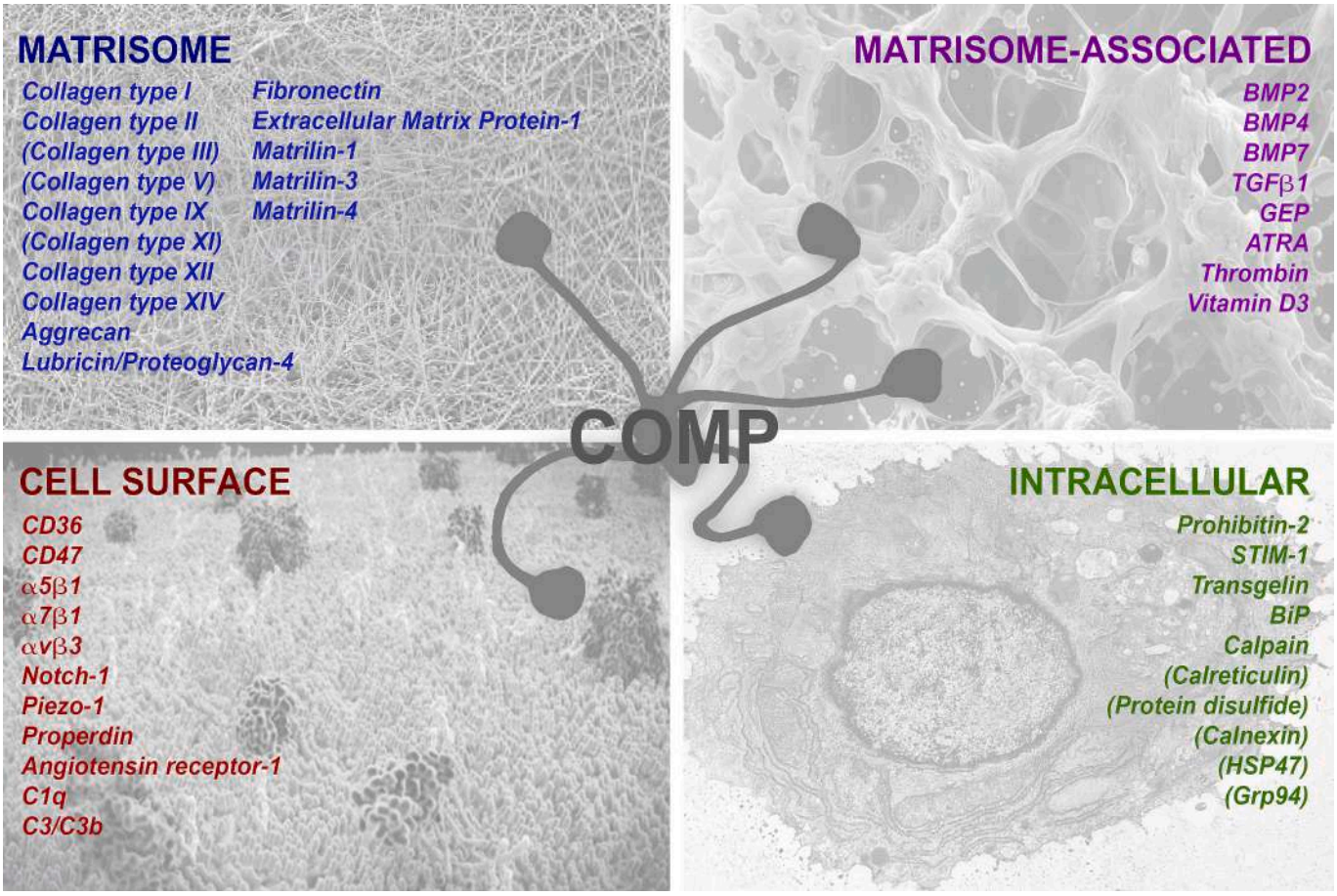

Fig. 4. Schematic overview of the currently definable COMP interactome. Highlighted are the associations of the pentamer with core *Matrisome* components, to build up, stabilize and remodel intricate matrices, and the sequestering and storage of *Matrisome*-associated molecules involved in signaling cascades. Whereas the binding of COMP to Collagen types II and IX is thoroughly documented, binding to Collagen type XI contained by the heterotypic collagen fibers of cartilage remains to be more convincingly demonstrated. Similarly, binding of COMP to the fibrillar collagen motif GXKGHR predicts a linkage of the pentamer with Collagen types III and V. Chondrocytes, subsets of smooth muscle cells and cancer cells may anchor to COMP through integrins, integrin co-receptors and other cell surface-associated component, while wild type and mutated COMP also engages a remarkable array of intracellular interactions with molecules known to be implicated in mitochondrial metabolism, cytosolic calcium fluxes and dynamics of the actin cytoskeleton. Chaperon-assisted accumulation of COMP variants harboring mutation that impedes its normal intracellular routing and secretion may favor the participation of COMP in the formation of intracellular biomolecular condensates. The central schematic illustration of the pentameric configuration of COMP is reproduced from the schematized views of the TEM/rotary shadowing images reported in Mörgelin et al. [24].

interactions of COMP are those involving fibrillar and FACIT collagens and further engaging Matrilins and the proteoglycan Aggrecan (Figs. 4, 5). In the former case, COMP shows an apparently equal affinity for 3 of the 4 known Matrilins, i.e., Matrilin-1, -3 and -4. This binding is strongly dictated by structural constraints for bringing about the associations as only the native, intact pentamer seems capable of linking to these proteins [43]. There is a consensus idea that coincident deposition of these interacting matricellular proteins and collagens is the key to assure proper ordonnance of spatially intricate matrices, such as those of cartilage tissues.

7. COMP's promotion of collagen fibrillogenesis and network assembly

Attachment of COMP to Aggrecan may involve a Ca^{2+}-dependent interaction of the "*signature domain*" of the pentamer with the glycosaminoglycan chains of the proteoglycan. However, no evidence has been provided implicating the keratan sulfate chains of Aggrecan in this interaction as only soluble chondroitin sulfates have been reported to compete out binding to COMP. Nevertheless, these investigations have portrayed the central segment of Aggrecan as the primary region of the proteoglycan responsible for its interaction with COMP. Based on these observations it can be further concluded that, alongside Matrilins, COMP is a primary candidate for the stabilization of the linkage between the collagenous skeleton of cartilage matrices and their hyaluronan-proteoglycan-enriched "ground substance". Hence, an undisputable biological explanation is provided for the detrimental clinical consequences of the extensive fragmentation of COMP by metalloproteinases and ADAMTs (i.e., MMP-19, -20 and ADAMTS-4, -7, and -12) in degenerative diseases and traumatic damages that may afflict bone and cartilage tissues [44–51].

A catalyzing role of COMP in collagen fibrillogenesis was originally demonstrated using Collagen types I and II as model fibrillar collagens. Interplays between Collagen type I and COMP seem highly relevant when addressing the role of COMP in fibrillogenesis and arrangement of fibrillar collagen structures since it is markedly enriched in diverse types of fibrotic matrices [52], as well as a documented central element of the tumor microenvironment in a myriad of cancer types [53]. Early studies of the COMP-collagen interaction evidenced that in the presence of the pentamer, extracellular collagen fibril formation was accelerated by a direct effect of the macromolecule. COMP promotes this enhancement by bringing the proteolytically processed collagen trimers in proximity to each other, such as to facilitate their assembly, while no COMP can be seen associated with isolated, terminally assembled fibrils [54].

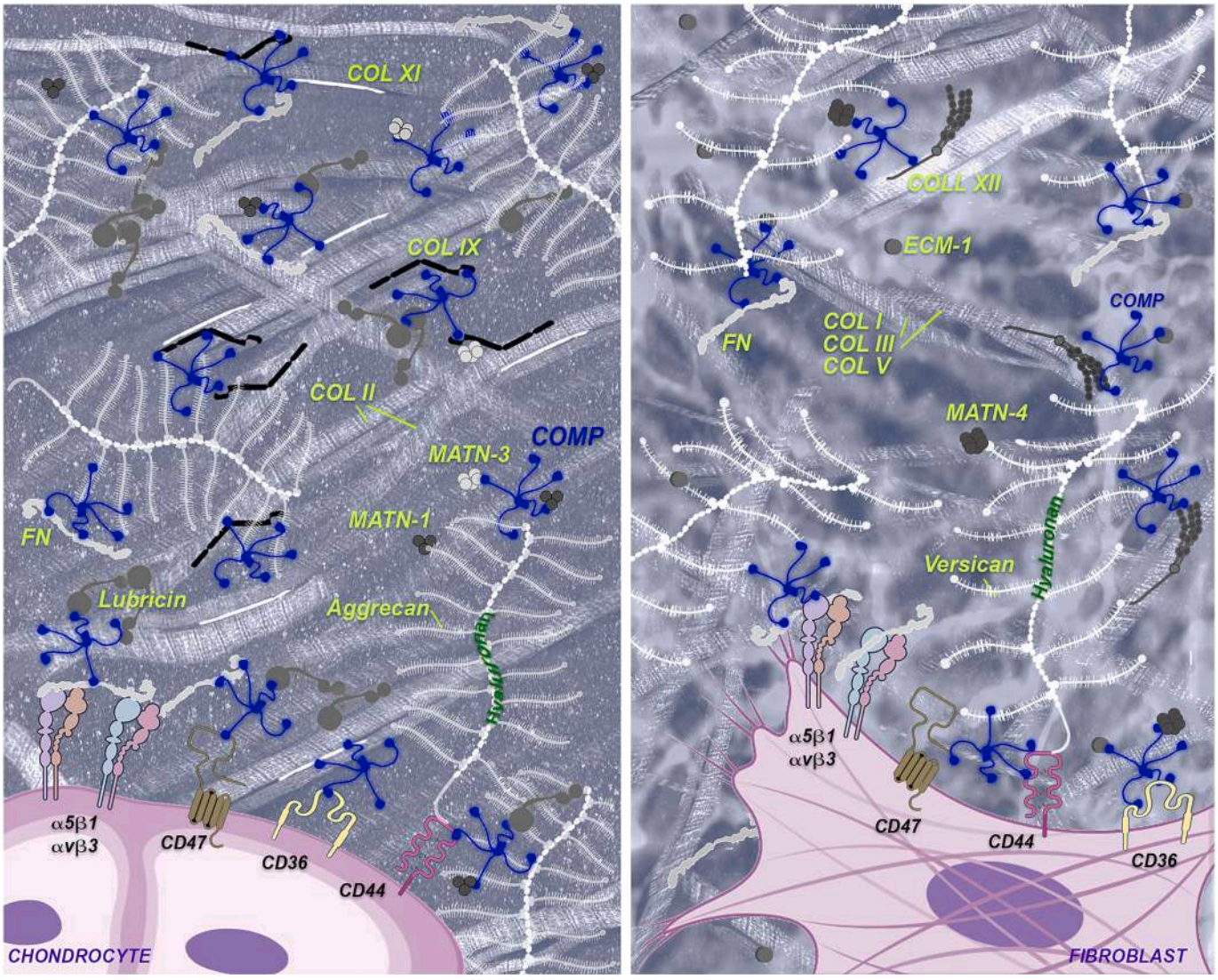

Fig. 5. Diagrammatic representation of the topographical organization of COMP in the two types of ECMs prevalently featuring a marked accumulation of COMP: the cartilage ECM and ECM associated with fibrosis and tumor microenvironment. In articular cartilage, COMP is believed to contribute to the assembly of the collagenous network and its linkage to the hyaluronan-aggrecan-link protein complexes, while assuring a close connection of chondrocytes with the matricellular protein network through a binding mediated by integrins and non-integrin cell surface receptors. The precise topographical arrangement of COMP in fibrotic and tumor-associated ECMs is less known but the presence in such matrices of established COMP *Matrisome* ligands is prospecting of similar matrix assembly functions as those observed in cartilage. This includes the ability of COMP to mediate the interaction of fibroblasts and cancer cells with the ECM networks.

Interestingly, although COMP is predicted to act as a Ca^{2+} chelator within interstitial ECMs, because of its highly conserved calcium-binding Type III TSP repeats and the lectin-like b-sandwich structure of the *C*-terminal domain [36], Zn^{2+} has been proposed to be the preferred cation for the promotion of COMP's pro-fibrillogenic function [55]. As a corollary, the cation-regulated collagen-binding site of the *C*-terminal domain of COMP shows sequence identity with the MIDAS motif found in collagen-binding integrins [34]. Furthermore, consistently with what has been proposed integrins, COMP binding to collagens may be further modulated by an adjacent Ca^{2+}-binding site designated ADMIDAS (ADjacent to MIDAS) and believed to affect ligand docking [23,34]. Most recently it has also been shown that the fibril-forming catalyzing activity of COMP is initiated intracellularly where the pentamer appears to potentiate the synthetic processing and secretion of the collagen trimers [56,57].

Linkage of COMP to fibrillar collagens is believed to be mediated by its *C*-terminal domain which establishes contacts with the triple-helical fibrillar surface at apparently 4 distinct sites [54]. This mode of interaction then allows the five arms (subunits) of COMP to be projected away from the fibril surface (Fig. 3): an orientation that concords with the topology deduced from ultrastructural analyses of the isolated macromolecular complexes. A recent attempt to pinpoint the interaction sites of COMP within the triple-helical domain of fibrillar collagens has identified the motif GXKGHR at the *N*- and *C*-termini of the collagens [58]. The presence of definable binding sites at the extremities of collagen molecules, disclosed using an overlapping triple-helical (foldon) peptide library of Collagen type II, is partly consistent with the ultrastructural data. However, it leaves veiled the nature of the other two, more centrally located areas of COMP apposition on the fibrils [54]. It is plausible that these intermediary contact points residing within an intrinsically disordered region of the collagen molecule were not reproduced by the 27-mer peptides used for the screening. Nonetheless, given the repetitive sequence of fibrillar collagens it could be expected to be able to track this COMP binding motif in other fibrillar collagens and indeed it turns out that it is harbored by Collagen types III, V and XI [58]. To note, however, no experimental data are available demonstrating the ability of COMP to bind to these collagen types. It remains therefore undetermined whether the binding of COMP to these collagens

may depend on the ECM type-specific supramolecular arrangement of the scaffolding collagenous network.

COMP has also been found to bind to Collagen type IX (Figs. 4, 5), but this interaction seems to be promoted by the non-collagenous domains of the collagen and to preferentially involve the *C*-terminal portion of COMP [59]. Then, to further increase the complexity of the interwoven linkages of COMP to ECM ligands, there is experimental evidence for a non-covalent binding of the native pentamer to Lubricin/Proteoglycan-4 (Figs. 4, 5), which seems to be mediated by its *C*-terminal segment spanning residues 518-757. This linkage can further be stabilized by cross-molecular disulfide bonding of COMP's cysteine residues with discrete *N*-terminal cysteine residues of Lubricin/Proteoglycan-4 (residues 64-82;[60]) In proximity of the chondrocyte surface, Lubricin/Proteoglycan-4 also links to Fibronectin and Collagen type II fibrils [61], completing thereby a tri-molecular sub-network within the chondrocyte lacunae. Altogether, these findings establish a framework for the more global definition of the multivalent contribution of COMP in crafting the precise supramolecular organization of cartilage and non-cartilage matrices (Fig. 5).

In the fibrotic skin, the *Matrisome* partners of COMP may be somewhat different than those prevailing in cartilage ECMs (Figs. 4, 5). With high probability, in the former matrices COMP is preferentially paired with Collagen types I, III and V and with the FACIT Collagen types XII and XIV [57,62]. COMP may further associate with Fibronectin [63] to organize matrices with the unique supramolecular architectures that are characterizing sclerotic lesions and keloids. Since COMP binds chondroitin sulfates through the heparin-binding central segment of the protein, by inference, it could be assumed that in fibrotic matrices COMP could potentially also bind the proteoglycan Versican, carrying similar chondroitin sulfate chains as those attached to Aggrecan. However, this specific molecular interaction has not yet been experimentally demonstrated. Remarkably, COMP has been discovered to be abundantly distributed throughout the stroma of several tumor types, including breast, ovarian, lung, prostate colorectal, urogenital, gastroenteric, thyroid and pancreatic carcinomas, as well as neuroendocrine tumors [64–68]. The precise molecular interactions engaged by COMP in the ECM of the tumor microenvironment remain to be detailed but it is plausible that they may be analogous to those ruling in fibrotic matrices (Fig. 5). This is deducible from the fact that many of the primary binding partners of COMP are shared by these two types of matrices.

8. Modulation of the ECM-controlled growth factor storage and receptor accessibility

The interactions of COMP with the *Matrisome* are multifaceted not only because they implicate a wide array of its components (Fig. 4) and are explicated in a dynamically intricate manner, but also because they involve both core *Matrisome* proteins and molecules classified as "*Matrisome-associated proteins*" [40]. In fact, COMP effectively associates with latent TGF-β1, BMP-2, -4 and -7 [26,69–71] and the likelihood is that COMP may sequester and store other highly homologous members of the TGF superfamily and molecules belonging to other families of signaling factors. The lifetime of this putative growth factor storage has not been defined. It remains therefore unknown whether COMP serves as a *bone fide* ECM-resident, long-term reservoir, or whether it provides a transient scaffold for rendering such factors bioactive and more accessible to the receptors. Evidence of this possibility is afforded by observations on mesenchymal stem cell aggregates and primary chondrocyte clusters in vitro, in which the above growth/differentiation factors strongly promote differentiation, maturation and phenotypic stability through an intermediary interaction with COMP. Curiously, when the COMP-TGF-β1 interaction was originally described, a distinctive feature was noted which could have not been pertinently interpreted at that time: optimal binding occurred at pH 6.75 and was virtually lost at pH 7.25 [69]. Since COMP is now known to be an abundant component of the tumor microenvironment and this milieu is characterized by a slightly acid pH, it is conceivable that tumor-associated COMP may benefit from this condition for optimally retaining members of the TGF superfamily within the tumor ECM. Whether this finetuned pH-dependence of binding may be utilized to create concentration-dictated growth factor/morphogen gradients is also an obvious subject for further investigations.

In pathological conditions such as systemic sclerosis, there is a concomitant increase of TGF-β(s) and COMP expression and in isolated sclerodermal fibroblasts in which TGF-β1 stimulation markedly upregulates COMP [56,62,72–78]. A similar phenomenon has been observed in cancer-associated fibroblasts of ovarian and colorectal tumors [67,79] to substantiate the TGF-response pattern observed in chondrocytes and involving a sequential upregulation of COMP and Collagen type II [69]. Thus, in sclerotic circumstances, and presumably in neoplastic conditions, there seems to be a cell-autonomous autocrine COMP-TGF-β loop controlling the construction of the associated matrices. Such a loop would involve a TGF-induced increase in the production of COMP which then potentiates the presentation of the growth factor to its receptor to further enhance secretion of the pentamer.

By taking advantage of high-resolution atomic force microscopy, it has been possible to visualize COMP homopentamers (Fig. 3A) linking up to five BMP-2 molecules (one for each monomeric subunit;[26]). Through the same approach it has also been possible to visualize the resulting topographical changes undergone by the pentamer following these associations. In analogy with the situation previously reported for TGF-β1, grouping of five BMP molecules on a single COMP homopentamer was predicted to facilitate the presentation of the morphogenetic proteins to their receptors and thereby promoting the triggering of more sustained SMAD-mediated signal transductions [71]. However, although COMP has been proposed to sustain BMPR-2 expression [80], the lack of a formal evidence for growth factor-binding to cell surface-associated COMP impedes at present to corroborate an incontrovertible role of COMP in the potentiation of growth factor signaling. It also remains uncertain, but of particular interest, the extent to which COMP may counteract and/or neutralize the action of the plethora of BMP antagonists that normally accumulate within tissues. This such as to balance the cells' availability to the morphogenetic proteins in the healthy and diseased states in which COMP is either entirely lost or strongly upregulated.

Notably, the growth factor binding abilities of COMP are not restricted to members of the TGF superfamily because the pentamer also interacts through its Type II EGF-like TSP repeat domain with the granulin-epithelin precursor (GEP; also referred to as Progranulin/Acrogranin/PCDGF; Fig. 4): a factor that has been proposed to act as a natural inhibitor of ADAMTS-7 and -12 [49,81] and to be a strong promoter of hepatic and ovarian carcinogenesis (with both processes featuring overexpression of COMP). Binding of GEP to COMP seems to be critically involved in the regulation of the growth-promoting effect of GEP on chondrocytes. It may have an analogous significance in the progression of the above tumors, where GEP has been identified as a prognostic factor and putative therapeutic target. In this specific context, intriguing remains the intersected relationship between the modulatory effect of GEP-COMP binding on the activity of the matrix-degrading enzymes for which COMP is recognized to be a preferred substrate.

9. The matricellular nature of COMP accounts for its induction of "matricrine signaling" events

The matricellular traits of COMP are thoroughly supported by its ability to interact with the cell surface, to sustain stable cell-ECM adhesions and to contribute to the eliciting of matrix-induced signal transduction [82,83]. Attachment of chondrocytes and synovial fibroblast to COMP seems to involve at least two RGD-directed integrins (Fig. 5), i.e., the α5β1 and α5β3 integrins [84–89]. These ECM receptors may be differentially involved in COMP binding according to the

conformation assumed by the pentamer. They are prospected to recognize the RGD motif formed by Arg367-Gly368-Asp369 as part of the symmetric motif Asp365-Arg367-Gly368-Asp369 within the 5th Type III TSP repeat [34]. In fact, the crystal structure of the *C*-terminal domain of COMP has revealed that, within the RGD motif, the amino acid Arg367 is exposed to the solvent, Gly368 is completely hidden, and Asp369 is responsible for binding a Ca^{2+} ion via a bridging water molecule. An experimentally introduced G368D mutation of the RGD motif disrupts the proper folding of the protein and impairs its ability to bind integrins [34]. Further evidence for the binding of the a5β1 integrin to the *C*-terminal portion of COMP derives from immunoprecipitation experiments on endothelial cells and the use of a peptidomimetics designed such as to antagonize the integrin interaction with that portion of the pentamer [86].

Given the intricacy of the molecular interactions that COMP engages and the complexity of the resulting matrix networks, it is difficult to envision how the RGD adhesion site on COMP could become properly exposed for cellular interactions. Similarly, it is well-established that the α5β3 integrin primarily recognizes RGD motifs with low-affinity and following unfolding of the molecules containing this ligand motif, rendering therefore this type of interaction a rare event in fully assembled matrix molecules. Notably, the α5β3 integrin may be assisted in its COMP binding by the canonical integrin co-receptor CD47 (Fig. 5), which has been proposed to bind to the *C*-terminal COMP sequence SFYVVMWK [85]. Curiously, CD47-dependent attachment of cells to COMP produces substrate-binding geometries that markedly differ from those evoked by Fibronectin substrates. On COMP substrates cells appear less spread but surrounded by articulated, highly ramified filopodial processes ending in numerous microspikes. The significance of this CD47-dependent adhesive behavior is not understood, and it is not reproduced in vascular smooth muscle cells proposed to alternatively use the α7β1 integrin to adhere to COMP [90,91].

In certain tumor types, cancer cells upregulating COMP tend to stably retain the pentamer on their membranes, in a manner that may simulate the situation seen in articular cartilage chondrocytes. Even if assuming that COMP-binding integrins are abundantly expressed on the surface of cancer cells, it seems improbable that these receptors may alone be capable of a tenacious and durable sequestering of COMP in proximity of the cell membrane because of their low-affinity ligand binding dynamics. Thus, ancillary receptor mechanisms, possibly acting in concert, are likely to operate for bringing about the phenomenon. One such mechanism may be contributed by CD36, which dimerizes upon ligand binding to function as a putative COMP receptor. COMP binding to CD36 activates the MEK1/2-pERK1/2 and PI3K/Akt signal transduction pathways [92–95] and may even affect cell fate, indicating that the COMP-CD36 interaction causes cytoskeletal arrangements and a reinforcement of cell surface-anchorage of the pentamer. High-resolution cryo-EM studies are probably needed to better understand the topology and dynamics of the cell surface retention of COMP and the modes through which it may impact on cell behavior.

Because of the potential to directly or indirectly induce signal transduction events, COMP has been postulated to actively contribute to epithelial-mesenchymal transitions implicated in the formation of different tumor types and the maintenance of cancer stem cell-like phenotypes. In addition to growth factors and morphogenetic proteins, several other signal transducing molecules have been proposed to partner up with COMP in this context (Fig. 5). This is because of the tight correlation between the activity of these factors and a direct impact of COMP on their effects on cancer cells. These presumptive ligands include Resolvin-D1, Notch-1 and -3 (primarily activated by Jagged-1) and transgelin. However, measurable interactions between COMP and Notch-3, COMP and the two Resolvin D1 receptors, lipoxin A4 receptor/formyl peptide receptor 2 and the G-protein-coupled receptor GPR32, or COMP and the Notch ligands Jagged-1-2 and Delta-1-4, have not yet been documented. This gap leaves thereby unresolved the modes and precise patterns of COMP modulation of these signal-transducing interactions [14,67,96–98].

10. Mutations in COMP alter its subcellular organization and redefine its biological functions

An exuberant number of mutations has been identified along the entire COMP transcript of individuals suffering from pathological conditions, as well as individuals not presenting a recognizable clinical phenotype. Depending on the data set that is considered, there are some differences in the reported quantities of COMP protein variants. The most embracive annotation indicates a compendious amount of 1605 protein variants [99], while UniProt [100] reports 1074 transcript variants. To safely exclude redundant annotations, the number of currently known COMP mutations covering both those leading to severe congenital malformations and those not yet associated with a distinct clinical phenotype amounts to 983 (Fig. 6).

In individuals carrying genetically inherited aberrations of the COMP gene, it was originally disclosed that discrete mutations were associated with two distinct autosomal dominant skeletal dysplasia, pseudo-chondrodysplasia (PSACH) and multiple epiphysial dysplasia (MED) [52,101,102]. However, two additional COMP mutations have recently been identified in subjects affected by familial carpal tunnel syndrome [103], in further support of the notion that the preponderant quantity of COMP mutations are directly linked to skeletal malformations. Studies on chondrocytes isolated from cartilage of PSACH patients reveal an excessive intracellular accumulation of the mutated forms of COMP and the formation of profoundly enlarged cisternae of the endoplasmic reticulum (ER). These are detectable alongside cytoplasmatic inclusion bodies [104–110], which jointly are believed to trigger apoptotic cell death. Indeed, colocalization of mutated COMP with chaperon proteins denotes an unfolded protein response connected to oxidative stress and misexpression of cell-cycle and apoptosis regulators. However, not all identified mutations are reported to cause conventional unfolded protein responses [111]. These pathological conditions, primarily linked to COMP mutations in patients with PSACH and MED, are predominantly localized within the Type III calcium-binding TSP repeat domain. However, recent studies have also identified missense mutations associated with MED or milder PSACH phenotypes in the C-terminal domain of COMP, accounting for approximately 15 % of all known COMP mutations [112]. The mutations lead to intracellular retention of COMP and may significantly affect the synthesis, processing, and secretion of its *Matrisome* ligands essential for the supramolecular assembly of cartilage ECMs (Fig. 7).

The substitution Y361N (MED mutation) seems to cause only milder changes in the overall secondary structure of the COMP monomeric subunits but reduces the number of bound Ca^{2+} ions and significantly affects the binding of COMP to collagens [35,113]. On the other hand, deletion Δ469del (PSACH mutation) reproduced in chondrosarcoma cells or bovine chondrocytes causes a marked intracellular accumulation of COMP and an aberrant matrix organization [114,115]. The same applies to the mutations D375N, H587R and D361Y, albeit the latter two cause retarded secretion or simply a lower degree of intracellular retention. This condition seems consistent with a milder phenotype of the pertaining chondrodysplasias [115]. Notably, the mutation H587R appears to also affect Collagen type I fibrillogenesis [116], suggesting that during embryonic development this mutation may interfere with endochondral ossification and contribute to the ensuing of skeletal anomalies at two different levels. It remains unknown how many mutations may co-exist in a single patient affected by skeletal malformations and whether mutations established to be disease-causing concur with mutations for which a clinical correlation has not been discovered.

Comprehensively, 34 mutations of the COMP gene discovered to be associated with skeletal abnormalities have been experimentally assayed in vitro and/or in vivo (transgenic mice). Reproduction in cultured cells and animal models of the COMP mutation patterns strongly indicates a putative correlation between the extent of

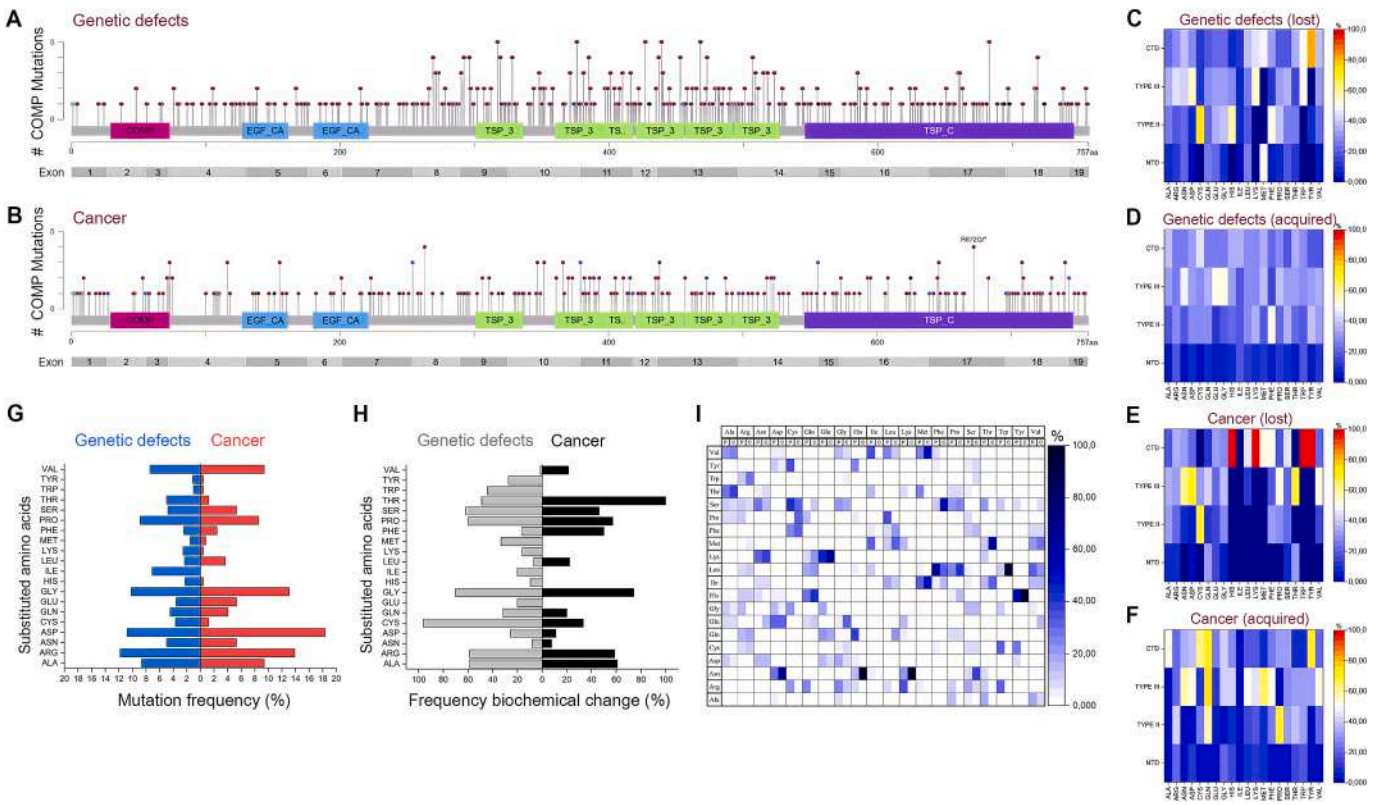

Fig. 6. Overview of the mutational spectrum of COMP in disease states. (A–B) Distribution along the COMP (monomeric) protein of mutations identified as inherited genetic defects, and most commonly causing skeletal malformations, and mutations detected in cancer lesions. (C–F) Heat maps illustrate the quantitative patterns of amino acid substitutions in the single domains of COMP, as detected in individuals harboring genetic defects and in cancer specimens. The maps show the patterns of residues hit by the mutations ("*lost*") in the two conditions and the patterns of the residues replacing the lost one ("*acquired*"). (G) Overall percentage of mutations affecting each of the amino acids and (H) percentages amino acid replacements involving substitutions with a change of the chemical property of the replaced residue. (I) Relative levels of overlap of amino acid substitutions in the two disease conditions.

intracellular retention of the pentamer, and its ligands Collagen type IX and Matrilins-1 and -3, and the severeness of the manifested skeletal malformations. Accordingly, a systematic *vitro* assaying of 12 mutations identified in dysplastic patients reveals a variable degree of disturbance of the intracellular trafficking of COMP, but again a clear relationship with the clinical features and overall severity of the diseases [117]. Loss of Collagen type IX secretion in chondrocytes transcribing/translating mutant COMP is highly compatible with the observation made in COMP or Collagen type XI null mice and double knock-out mice depleted of both genes [118]. A closer analysis of the content of the ER enlargements (cisternae) in chondrocytes synthesizing mutant COMP reveals macromolecular complexes prematurely formed by the interacting nascent matrix molecules Collagen types II and IX and Matrilins. Curiously, this would suggest a remarkable influence of the mutated COMP on intracellular fibrillogenesis [119], which would seem disconnected from the normal collagen processing within the Golgi apparatus. Undoubtedly, this observation dramatically complicates the interpretation of the role played by wild type and mutant COMP on the biosynthesis and assembly of the molecular complexes structuring connective tissue matrices.

More detailed ultrastructural analyses of the intracellular trafficking and ER retention of mutated COMP have highlighted the COMP superimposition with at least 7 chaperon proteins within the ER cisternae. These include BiP, CHOP/GADD153, calnexin, HSP47, calreticulin, Erp72, protein disulfide and Grp94 [106,120,121], with BiP being the one observed to be the most closely associated with the mutated COMP [120]. Furthermore, intracellular (ER) retention of mutant COMP is accompanied by the concurrent retention of the proteoglycans Fibromodulin and Decorin and several FACIT collagens, including Collagen types II, VI, IX, XI and XII, but not Aggrecan [106] and the possibility remains that the disturbance of the secretion patterns of ECM molecules may extend to a more generalized perturbance in the secretion of *Matrisome* components (i.e., not necessarily serving as COMP ligands). In chondrocytes of dysplastic patients, the above proteoglycans, alongside Collagen type IX and other proteoglycans else than Aggrecan, may suffer disturbances in their synthesis and post-translational processing. This may be deduced from observations on the consequences of forced expression of mutated COMP in cultivated chondrocyte-like cells where the overall levels of secretion of glycosaminoglycan-bearing molecules are significantly reduced [122].

11. Intricate mutational patterns of the COMP gene are reproduced in neoplastic conditions

The array of mutations unfolded in ectopically expressed COMP transcripts of a comprehensive set of 14 cancer types account for 245 (TCGH and cBioPortal portals [123,124]; Fig. 6). No apparent bias for a specific cancer type or a possible correlation with clinical parameters is currently known. Cancer-associated mutations also seem to strongly concentrate in the Type II (28.6 %) and Type III Ca^{2+} (17.1 %) TSP repeat domains of COMP (i.e., only 11.4 % and 4.3 % for the *C*- and *N*-terminal domains, respectively). Contrary to the genetic linkage of COMP aberrations with skeletal growth abnormalities and a definite pathological phenotype, the clinical significance of COMP mutations in cancer remains obscure. There is also no current evidence that individuals carrying inherited COMP mutations perturbing bone stability and length may develop any type of tumor and, vice versa. Among the most commonly identified mutations are frame shifts (25), stop codon alterations (10) and amino acid deletions (8). Intriguingly, splicing

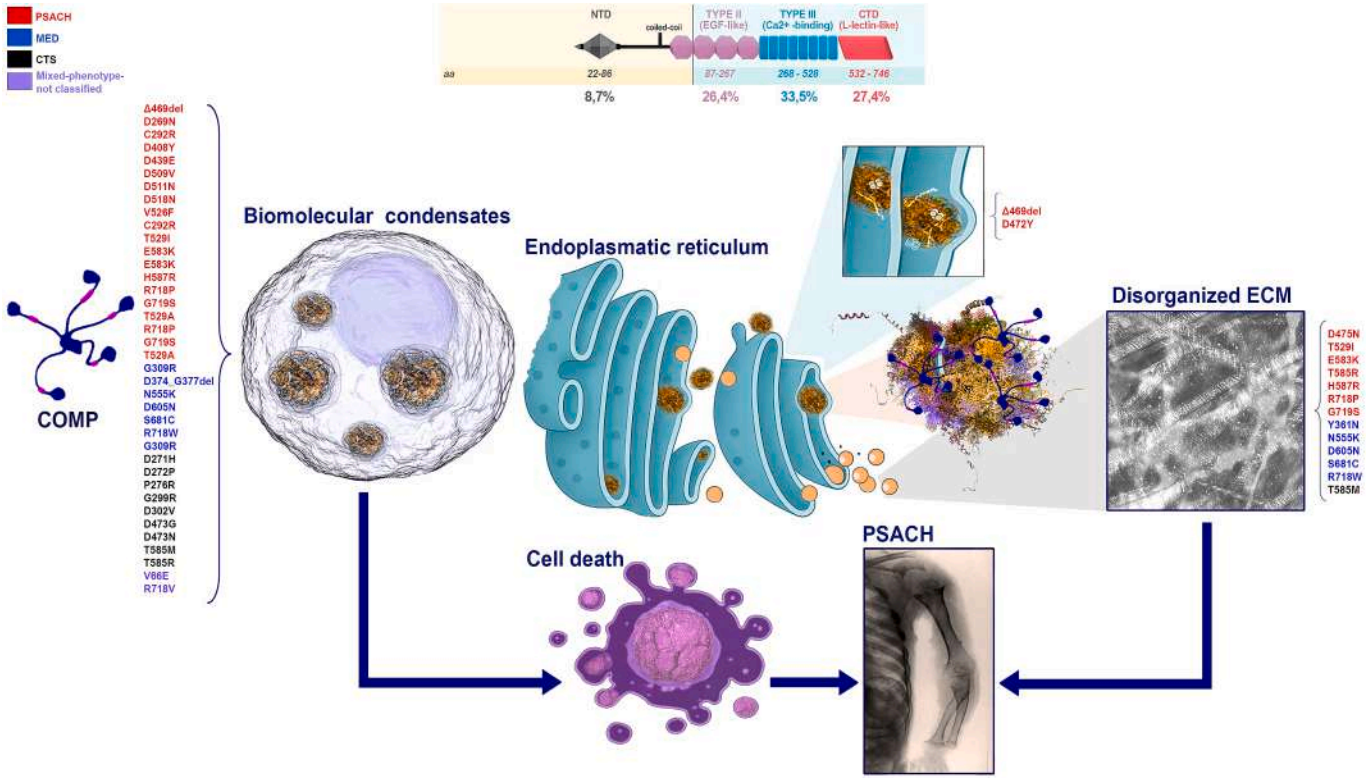

Fig. 7. Diagrammatic mechanistic overview of COMP mutations associated with skeletal malformations. The upper scheme reports the relative distribution (%) of the known mutations within each COMP domain, out of the total identified. Color coding of the individual mutations is according to the skeletal disorder with which they have been linked (a pseudochondrodysplastic condition is illustrated as reference disorder). An array of inherited mutations of the COMP gene (listed on the left) causes aberrant synthetic processing of the macromolecule within the endoplasmatic reticulum (ER), its entrapment within the organelle (ER stress) and a likely incorporation into biomolecular condensates that disrupt proteostasis, evokes unfolded protein response (UPR) and may lead to programmed cell death of chondrocytes during embryonic development and in adult individuals. Two specific mutations (i.e., Δ489del and D472Y) have been found to prevent the concurrent secretion of other *Matrisome* components that are critical for correct assembly of cartilage ECMs. Loss of COMP within such matrices caused by the array of mutations listed on the right has been demonstrated to lead to a marked disorganization of the supramolecular assembly of the cartilage and bone ECMs and concur to the evolvement of skeletal disorders. Abbreviations: PSACH, pseudochondrodysplasia; MED, multiple epiphysial dysplasia; CTS, carpal tunnel syndrome.

mutations (21) have identified solely in cancer and have left entirely covert the significance of gene alteration in neoplastic COMP. In cancer lesions, the most frequently mutated amino acids largely coincide with those of genetic diseases and unknown phenotypes (Fig. 6). Notably, in tumors the substituting residues are not covering the entire repertoire of essential amino acids as reported for mutations associated with genetic anomalies (i.e., 6 amino acids are not appearing as replacement residues in cancer).

In the context of mutations occurring in cancer conditions it is noteworthy that an intracellular entrapment of COMP recalling that observed in genetically disordered chondrocytes is frequently observed and proposed to increment their intracellular Warburg's effect [125]. This observation would further link the phenomenon to the participation of entrapped COMP to the formation of specific intracellular biomolecular condensates and their modulation of electrochemical balances within the cell [126]. Whether the molecular mechanisms underpinning intracellular retention of COMP in cancer cells are analogous to those ruling in diseased chondrocytes is currently unknown. Nonetheless, the question remains whether the mutational pattern defined in cancer-associated COMP may be the key for its ER accumulation.

A direct comparison of the mutations found in inherited genetic disorders versus cancer shows comparable COMP domain distribution ranging from 6 % in the *N*-terminal domain to 42 % for the Type III Ca^{2+} TSP repeat domain (which remains the most affected) and producing, a 28.6 % comprehensive overlap. Unfortunately, none of the genetic mutations that have been experimentally assayed for their impact on chondrocyte behavior and matrix assembly have thus far been reproduced in cancer cells to more closely explore their significance in the context of a transformed cell. Another crucial point is that, while cytosolic retention of COMP in diseased chondrocytes is deleterious for the cells as it induces programmed cell death, intracellular accumulation of COMP in breast cancer cells seems beneficial for the cells as it augments their drug resistance [127]. Similarly to the conditions documented in dysplastic chondrocytes, perturbed secretion of COMP (alongside an enhanced synthesis of the macromolecule) modulates intracellular calcium homeostasis [125]. This leads to the interference calpain activation the significantly reduced activation of the downstream apoptosis effectors, caspases-9, -7 and -3. Thus, remarkably, mutationally linked (or even mutation-independent) intracellular accumulation of COMP has diametrically opposed effects in healthy and transformed cells, acting as a promoter or inhibitor of regulated cell death.

12. COMP's involvement in homeostatic and pathophysiological phenomena implicates unorthodox molecular interactions

Implicitly, correct expression and matrix assembly of COMP is a primary requisite for proper homeostasis of cartilage and bone tissues. Correct expression and subcellular localization of the pentamer may also impact on homeostatic balances of the vascular system because of its expression in subpopulations of vascular smooth muscle cells. A defined identity of the COMP-producing smooth muscle cells has not been established and the possibility remains that COMP may preferentially be synthesized by mural cells and pericytes making thereby ambiguous the

precise source of COMP in blood vessels. Totally unexpectedly, COMP has been immunolocalized within mitochondria of cultured vascular smooth muscle cells, where it has been proposed to regulate oxidative stress and resistance to hypoxia [80,128,129]. However, the entailed intracellular trafficking modes channeling COMP inside mitochondria remains elusive. Via a direct linkage to prohibin-2, COMP seems to control the mitochondrial bioenergetics, believed to be instrumental for maintaining a contractile smooth muscle cell phenotype [128].

Sustained accessibility of COMP to pulmonary endothelial cells seems critically important in controlling blood pressure because of the putative interaction of COMP with the Piezo-1 non-selective cation channel of the endothelial cell membrane, the consequent triggering of Ca^{2+} influxes and the activations of Ca^{2+}/calmodulin-dependent kinase II and eNOS [130]. In physiological conditions it remains obscure how COMP would be able to come in apposition to endothelial cells. In atherogenic conditions, on the other hand, COMP seems capable of suppressing the oscillatory shear stress-induced activation of endothelial cells by antagonizing the binding of α5β1 integrin to fibronectin and other inflammation-promoting ECM components that may accumulate in atherosclerotic plaques. In these compartments, the primary source of COMP is likely to be the inflammatory M2-type macrophages and activated smooth muscle/mural cells, while upregulation of COMP seems to counteract the plaque calcification process [70]. In fact, when atherosclerotic conditions are experimentally induced in $ApoE^{-/-}$/$COMP^{-/-}$ double-knockout mice, plaque calcification is strongly attenuated [83,88]. Interestingly, COMP's interference with the plaque calcification phenomenon is believed to be mediated by the αvβ3 integrin, sustaining the alluring hypothesis that differentiated integrin receptor binding to atherosclerotic COMP may influence two distinct atherogenic processes.

Expression of COMP in subpopulations of vascular smooth muscle cells retards their senescence and, accordingly, COMP knockout mice exhibit vascular dysfunctions following experimental challenge of the blood flow in the abdominal aorta [131]. The precise mechanism underlying the age-protracting function of COMP is currently not understood but could be related to its putative modulation of apoptosis, as observed in cancer cells. The collective set of findings in wild type and genetically manipulated mouse models of vascular biology raises another doubt. It remains uncertain whether these aberrant patterns of COMP expression and the annexed molecular interactions are transposable and fully reproduced in human beings. As of to date, production of COMP in subsets of human vascular smooth muscle cells has not been incontrovertibly documented. Eventually, the most remarkable hemostatic function of COMP thus far proposed is that related to thrombosis/coagulation processes. A high-affinity binding of thrombin to COMP has been pinpointed to the Type II EGF TSP repeat segment spanning residues 84-261 and has been suggested to involve two separated binding sites [132]. Again, in COMP null mouse, loss of COMP causes a shortened tail-bleeding and blood clotting time and an accelerated ferric-chloride–induced thrombosis. Meanwhile, retention of COMP within platelets seems to be an evolutionary conserved phenomenon as COMP can be detected in mouse, rat and human platelets, inferring that COMP is a constitutive gene product of megakaryocytes. However, COMP secretion by platelets seems to require their activation which is accompanied by de novo synthesis of COMP [132]. Overall, these findings would suggest that COMP may act as a natural thrombin inhibitor and an endogenous governor of coagulation processes. The ubiquitous nature of this anti-coagulant activity remains to be more solidly demonstrated.

13. Conclusion and perspectives

The structural-functional relationship exhibited by COMP highlights how macromolecular entities of the *Matrisome* may deviate from their canonical structure-preserving function to assume pivotal cellular process-associated roles dictated by discrete structural traits. Inherited loss of COMP because of gene mutations markedly impacts on cartilage formation and bone growth, as a consequence of the disruption of the supramolecular organization of the cartilage ECMs, the impaired matrix-retention of pivotal growth factors and signaling molecules, the perturbed secretion of collagens, Matrilins and other COMP ligands of the *Matrisome*, and the succumbing of chondrocytes. The precise molecular mechanisms inducing regulated cell death in the chondrocytes of the diseased cartilages remains to be elucidated but it is plausible that intracellular retention of mutated COMP perturbs the cytoplasmic biomolecular condensate equilibrium which thereby activates cell death programs. Remarkably, cancer cells also pronouncedly retain COMP intracellularly, but this cytoplasmic COMP accumulation does not appear to coincide with the mutational pattern detected in the chondrocytes associated with skeletal malformation. Vice versa, intracellular COMP retention by cancer cells seems beneficial and to contribute to their malignancy. This highlights a rather complex orchestration of the mechanics by intracellular and extracellular COMP may impact on cancer cell behavior. The importance of COMP outside cartilage is still an open field to explore, especially its significance in tumor formation and progression and in inflammatory conditions.

CRediT authorship contribution statement

Erika Boiardi: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Simona Demmi:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Graziana Tittaferrante:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Mirca Lazzaretti:** Visualization. **Giorgio Malpeli:** Visualization, Formal analysis, Data curation. **Giorgia Brancolini:** Validation, Formal analysis, Data curation. **Roberto Perris:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review.

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Data availability

Data will be made available on request.

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