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Scientists reveal how collagen's weak sacrificial bonds help protect tissue

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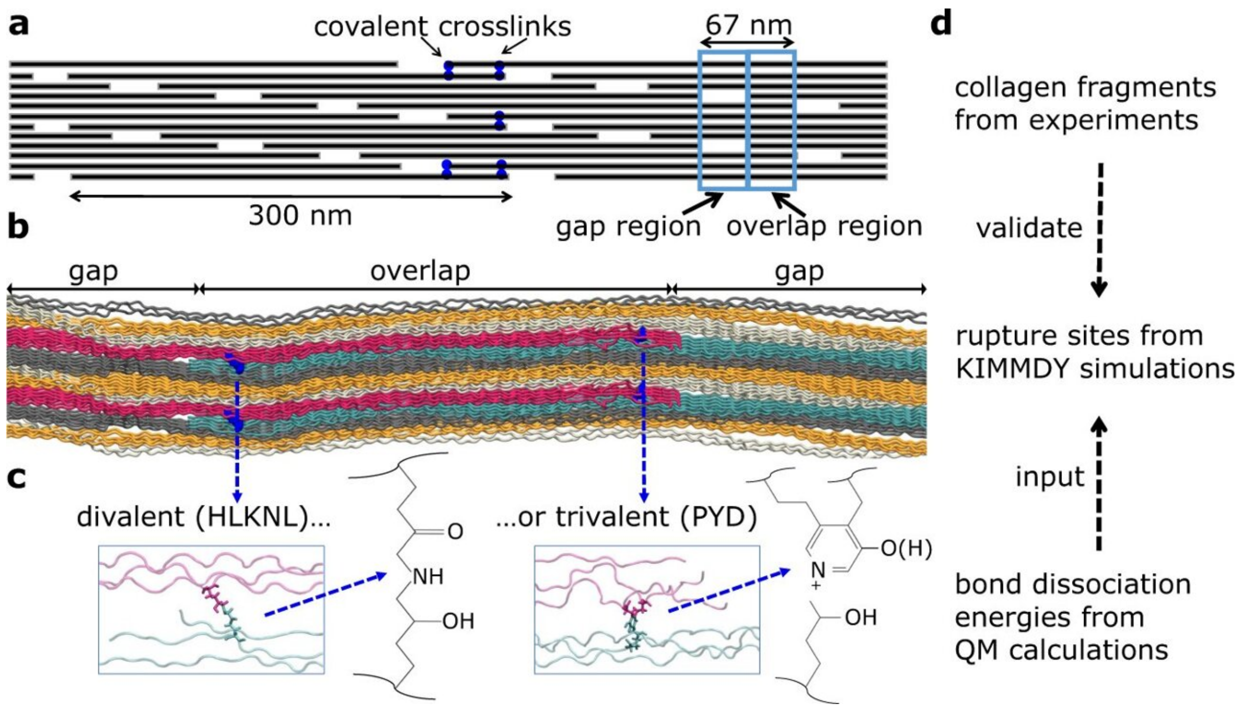

Collagen structure, spanning multiple length scales, and our corresponding methods. a) 2D projection of the staggered arrangement of collagen triple helices, each 300 nm. This results in the typical overlap and gap regions of collagen, including the 3D braiding of triple helices. b) Our atomistic model spanning one overlap (middle) and about one gap region (split into two parts) of collagen. c) Zoom in on enzymatic crosslinks connecting the triple helices. Different chemistries (divalent or trivalent) are possible at these positions, for example, Hydroxylysino-keto-norleucine (HLKNL) or Pyridinoline (PYD). d) Our workflow combines different methods as collagen spans multiple length scales. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-37726-z

One of the more unusual ways objects can increase longevity is by sacrificing a part of themselves—from dummy burial chambers used to deceive tomb raiders, to a fuse melting in an electrical circuit to safeguard appliances, to a lizard's tail breaking off to enable its escape. Sacrificial parts can also be found within collagen, the most abundant protein in our bodies.

Scientists at the Heidelberg Institute for Theoretical Studies (HITS) have revealed how the rupture of weak sacrificial bonds within collagen tissue helps to localize damage caused by excessive force, minimize negative impacts on the wider tissue, and promote recovery. Published in *Nature Communications*, the work shines light on collagen's rupture mechanisms, which is crucial for understanding tissue degradation and material aging, and may potentially advance tissue engineering techniques.

"Collagen's remarkable crosslink chemistry appears to be perfectly adapted to handling mechanical stress," says Frauke Gräter, who led the research at HITS. "By using complementary computational and experimental techniques to study collagen in rat tissue, our findings indicate that weak bonds within the crosslinks of collagen have a strong propensity to rupture before other bonds, such as those in the collagen's backbone. This serves as a protective mechanism, localizes the detrimental chemical and physical effects of radicals caused by ruptures, and likely supports molecular recovery processes."

Collagen constitutes roughly 30% of all proteins in the human body. It provides strength to bones, elasticity to skin, protection to organs, flexibility to tendons, aids in blood clotting, and supports the growth of new cells. Structurally, collagen resembles a triple-braided helix. Three chains of amino acids intertwine to form a strong and rigid backbone.

Each collagen fiber contains thousands of individual molecules that are staggered and bound to each other by crosslinks, contributing to collagen's mechanical stability. It was thought that collagen crosslinks are susceptible to rupture, however little was known about the specific sites of bond ruptures or why ruptures occur where they do.

Scientists from the Molecular Biomechanics Group at HITS aimed to unravel these puzzles using computer simulations of collagen across multiple biological scales and under different mechanical forces. They validated their findings via gel electrophoresis and mass spectrometry experiments conducted on rat tails, flexors, and Achilles tendons. By subjecting collagen to rigorous testing, the team was able to determine specific breakage points. They observed how force dissipates through the complex hierarchical structure of the tissue and how its chemical bonds bear the load.

Mature crosslinks in collagen consist of two arms, one of which is weaker than other bonds in collagen tissue. When subjected to excessive force, the weaker arm is typically first to rupture, dissipating the force and localizing detrimental effects. The scientists found that in regions of collagen tissue where weak bonds are present, other bonds—both in the crosslinks and the collagen backbone—are more likely to remain intact, thereby preserving the structural integrity of the collagen tissue.

Previous work led by HITS scientists revealed that excessive mechanical stress on collagen leads to the generation of radicals, which in turn cause damage and oxidative stress in the body. "Our latest research shows that sacrificial bonds in collagen serve a vital role in maintaining the overall integrity of the material can help to localize the impacts of this mechanical stress that could otherwise have catastrophic consequences for the tissue," explains Benedikt Rennekamp, the study's first author.

"As collagen is a major substituent of tissues in our bodies, by uncovering and understanding these rupture sites, researchers can gain valuable insights into the mechanics of collagen and potentially develop strategies to enhance its resilience and mitigate damage."

More information: Benedikt Rennekamp et al, Collagen breaks at weak sacrificial bonds taming its mechanoradicals, *Nature Communications* (2023). DOI: 10.1038/s41467-023-37726-z

Provided by Heidelberg Institute for Theoretical Studies