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Shielding a healing signal: Protecting CXCL12 unlocks its regenerative power



Stromal cell-derived factor 1 (SDF-1/CXCL12) is a key regulator of tissue repair, promoting progenitor cell recruitment, angiogenesis and immune cell coordination through CXCR4 signalling. Despite its significant therapeutic potential, clinical application of CXCL12 has been limited by its rapid degradation in inflamed and wounded tissues, where proteases are highly abundant.

In a recent study, Pereira et al. describe a novel strategy to overcome this challenge using chlorite-oxidised oxyamylose (COAM), a negatively charged polysaccharide that protects CXCL12 from proteolytic degradation while fully preserving its biological activity. By extending CXCL12 stability within protease-rich environments, this approach significantly enhances wound healing and offers a promising new platform for chemokine-based regenerative therapies.

COAM was shown to protect CXCL12 from cleavage by multiple inflammation-associated proteases, including:

- MMP-9
- CD26/DPPIV
- Complex mixtures of neutrophil-derived proteases

Importantly, this protection is achieved without inhibiting the catalytic activity of the enzymes themselves.
The protective effect arises from charge-dependent electrostatic interactions between COAM and CXCL12.

By binding to the chemokine, COAM effectively shields vulnerable proteolytic cleavage sites, preventing degradation while allowing the molecule to retain its biological function and continue to support:

- Intracellular calcium mobilisation
- ERK1/2 phosphorylation
- CXCR4 internalisation
- CXCR4-dependent chemotaxis

The therapeutic potential of this strategy was demonstrated in a mouse full-thickness skin wound model. A single local administration of CXCL12 and COAM delivered within a physiological fibrin hydrogel significantly accelerated wound closure compared with CXCL12 alone, COAM alone or vehicle control.

This enhanced efficacy is attributed to prolonged local bioavailability of CXCL12 within the protease-rich wound environment, enabling sustained biological signalling from a single administration. In contrast, traditional approaches to maintaining CXCL12 activity often rely on repeated dosing, gene therapy or complex biomaterial systems to compensate for rapid degradation.

In this study a different strategy has been presented, protecting the chemokine itself rather than increasing dose or delivery frequency providing:

- Physical localisation through a fibrin hydrogel
- Chemical immobilisation via the COAM-CXCL12 complex
- Active protection against proteolytic degradation

Beyond wound healing, the COAM-CXCL12 platform may have wider applications in:

- Regenerative medicine
- Ischaemic tissue repair
- Stem and progenitor cell recruitment
- Other protease-sensitive chemokine therapies

In summary, by protecting the therapeutic signal rather than overwhelming the biological system with higher doses, the approach presented by Pereira et al. may represent a key step towards unlocking the full regenerative potential of CXCL12 and related chemokines.

References
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