Extracellular interaction networks: from structure to functions

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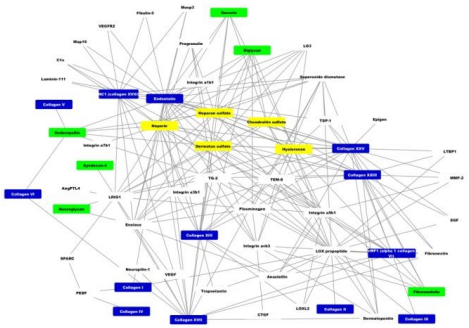
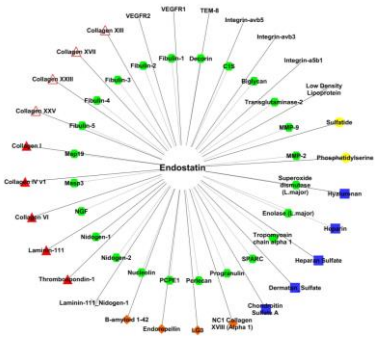


MatrixDB

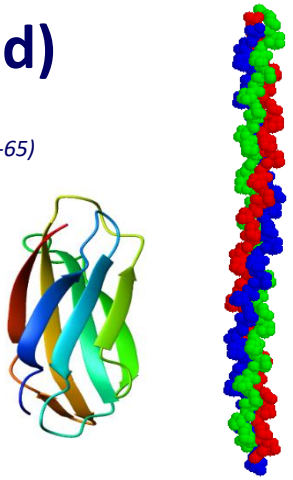
http://matrixdb.univ-lyon1.fr/



The extracellular matrix (ECM): a small proteome

1100 proteins (matrisome and matrisome-asociated)

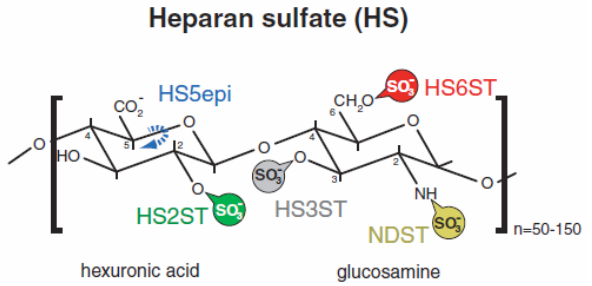
- Intrinsically disordered sequences *(Peysselon et al. 2011 Mol Biosyst. 7:3353-65)*
- Multi-domain proteins
- Multimers and supramolecular assemblies



6 polysaccharides (glycosaminolycans, GAGs)

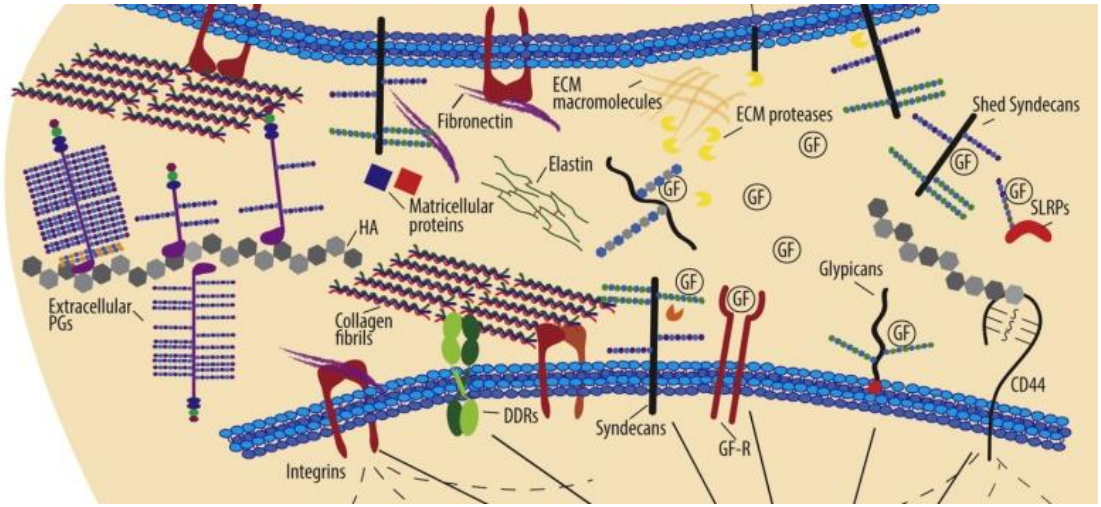
- Hyaluronan
- Heparin, heparan, chondroitin, dermatan, and keratan sulfate
- Structural heterogeneity

Bioactive fragments (matricryptins) released upon remodeling *(Ricard-Blum and Vallet, Matrix Biol. 2017 Nov 11. pii: S0945-053X(17)30277-9)*



(Bülow, Hobert Ann Rev Cell Dev Biol 2006 22:375–407)

The ECM is a network of protein and GAG interactions



(Theocharis et al. 2016 Adv Drug Deliv Rev. 97:4-27)

Why building the ECM network *in vitro*?

- To identify new functions of ECM proteins
- To decipher the molecular mechanisms underlying ECM assembly and functions
- To determine how the ECM network is rewired in diseases
- To build 3D models of tissue-specific ECM

The ECM network is context-dependent

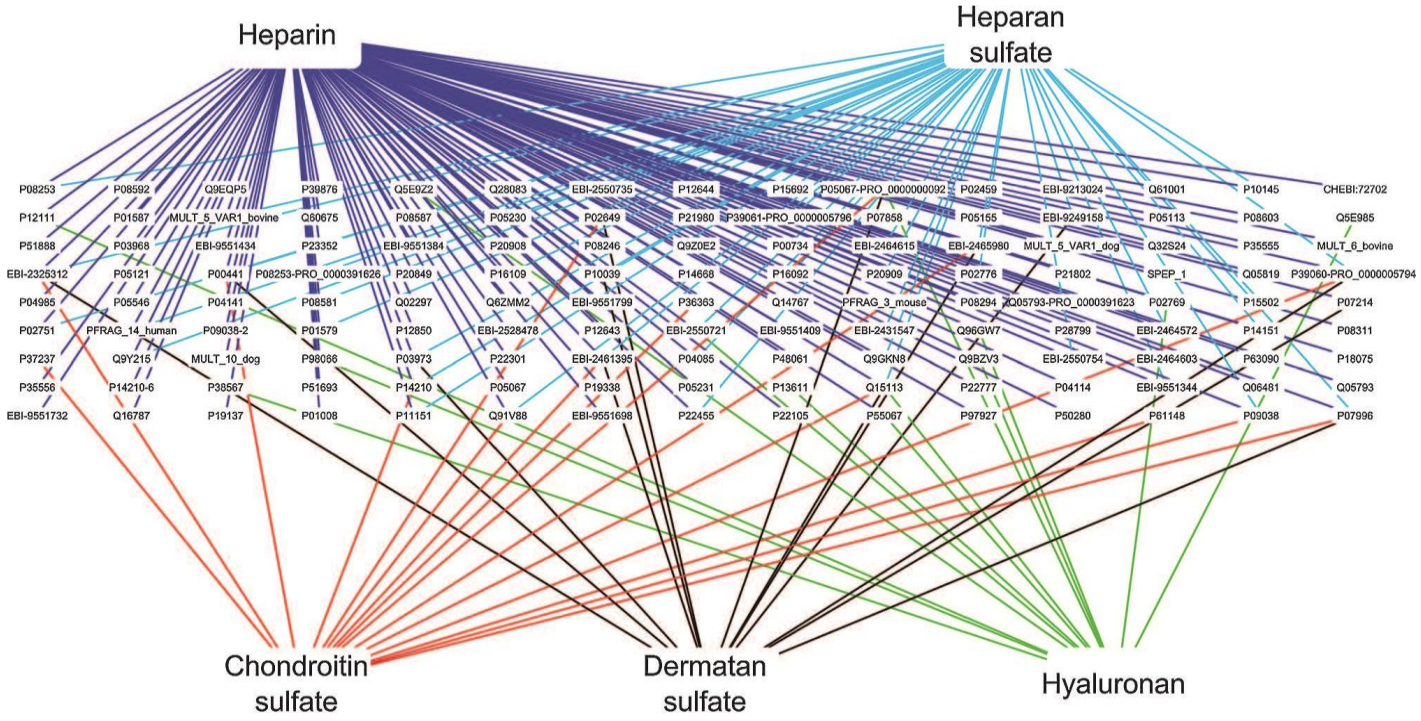
- **Flavors:** tissue, molecular function, biological process
- **Regulators**: mutations, splicing, post-translational modifications, growth factors, proteinases, **intrinsic disorder**
- **Prioritizers**: **kinetics** and **affinity**

Molecular and biological contexts promote/abolishe **interactions** leading to **network rewiring** (loss/gain of functions)

Human ECM interaction network 2.0

- **200** new interactions connecting **60** ECM proteins/GAGs identified by SPRi, SPR, and BLI

- **5600** interactions connecting **850** ECM proteins/GAGs in databases

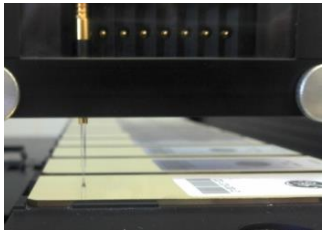


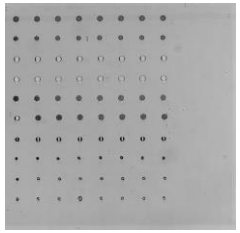
Heparin/Heparan sulfate network

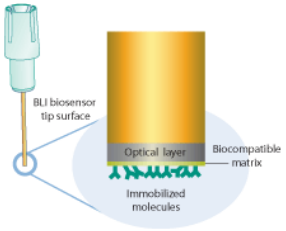
(Vallet et al. 2017, Handbook of SPR, 2nd edition)

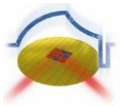
1. Identification of interactions

Experimental data







SPR  **SPRi** **BLI**

Surface **P**lasmon **R**esonance

Bio-**L**ayer **I**nterferometry

Literature curation

PubMed

MatrixDB

IntAct

IMEx

matrixdb.univ-lyon1.fr

Launay et al. Nucleic Acids Res 2015 43: D321-327

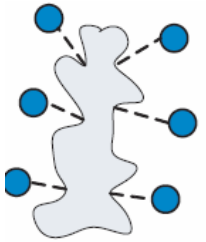
Predictions of protein-protein interactions

- Domain-domain interactions 3did
- Integrated Interactions Database *(ophid.utoronto.ca/iid/)*

2. Characterization of interactions: binding sites

Binding interface
3D structure of binary/ternary complexes

Competitive
interactions



Non-competitive
interactions

- X-ray, NMR
- SAXS, cryo-EM
- Molecular modeling
- Molecular dynamics

Intrinsic disorder

Acknowledgements

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