UMONS Université de Mons

Faculté de Médecine et de Pharmacie

Molecular Mechanism

Direct Interaction of DUX4 / DUX4c with the Multifunctional Protein C1QBP

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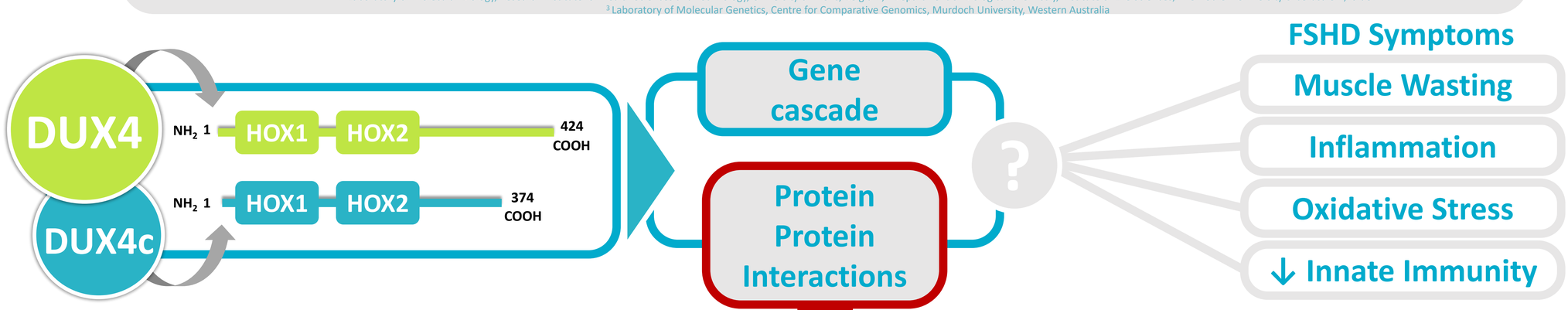


C1QBP MULTIFUNCTIONAL & MULTICOMPARTMENTAL PROTEIN

C1QBP DUX4 DUX4c

Alternative names :Hyaluronan-binding protein 1 (HAPB1) , ASF/SF2-associated protein p32 (SF2p32), Mitochondrial matrix protein p32, gC1q-R protein p32 and also p33. C1QBP has many functions :

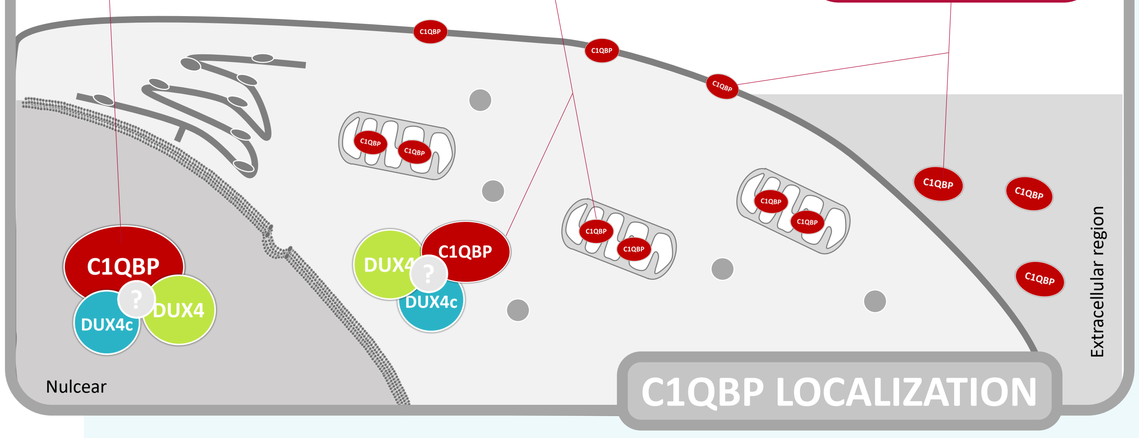
NUCLEUS
- Transcription
- Pre-mRNA splicing
- Nucleolar ribogenesis (?)

Petersen-Marth et al., 1999; Huang et al., 2008; Yoshikawa et al., 2011

CYTOPLASM/ MITOCHONDRIA
- Mitoribogenesis/Translation
- Cell migration/Proliferation
- Protects against
  - Oxidative Stress
  - Cell death/Apoptosis

Westman et al., 2013; McGee and Baines, 20011; McGee et al., 2011

MEMBRANE EXTRACELLULAR
- Receptor (C1q,…)
- Bind Hyaluronan ,…
- Modulate Immune Innate Response



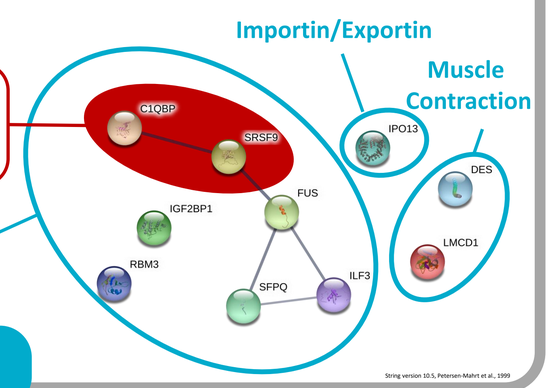
C1QBP LOCALIZATION

VALIDATED DUX4/DUX4c PARTNERS

In Ansseau et al., 2016

Could be involved in RNA-protein-nucleo-cytoplasmic shuttling

RNA Binding Proteins
- DUX4 Homeodomains are suffisant
- DNA not essential for interact



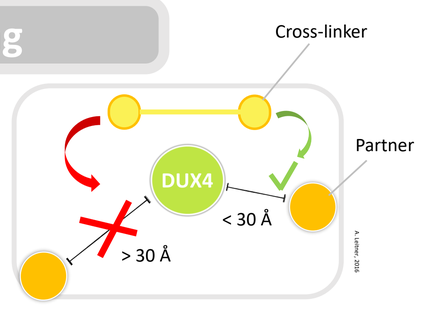
String version 10.5, Petersen-Mahrt et al., 1999

AIM : Specific interactions

METHOD

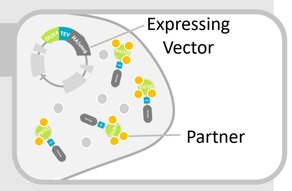
Cross-linking

- Covalent Bonds between
  - 2 groups inside 1 protein
  - 2 proteins
- Different levels of Spatial information
  - Evidence of spatial proximity
  - Localization of contact sites
  - Distance restrain

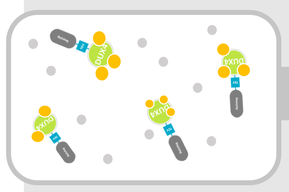


PURIFICATION OF PROTEIN COMPLEX

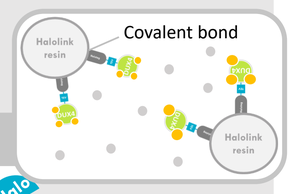
① DUX4/DUX4c - Halotag Expression



② Cellular lysis

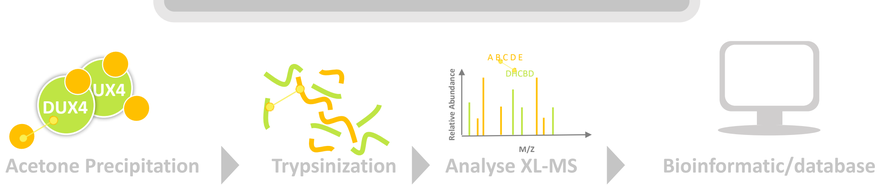


③ Purification



Covalent Capture | WASH | ELUTION — Halo TEV

Protein Identification

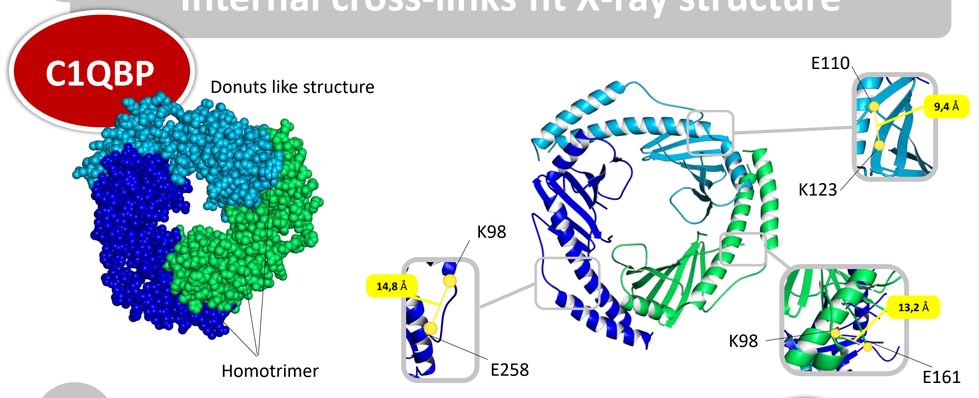


RESULTS

① Confirmed previous interactions (Ansseau et al., 2016)

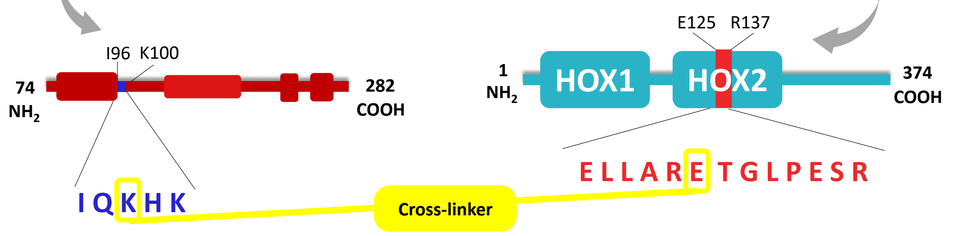
Improve cross-linking detection

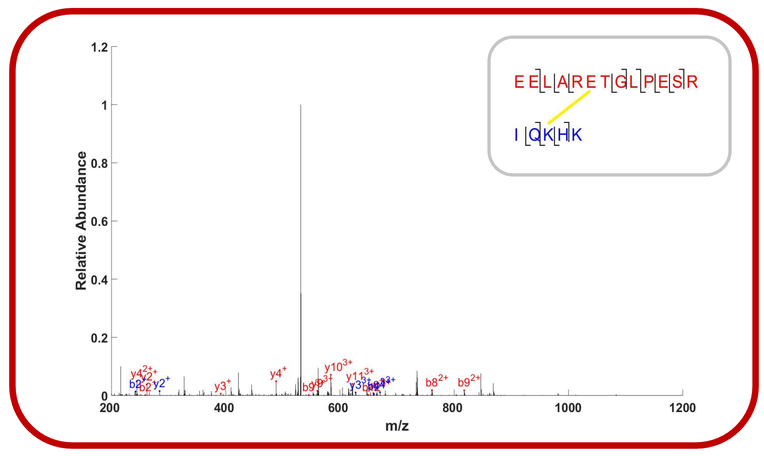
② Internal cross-links fit X-ray structure



Protein Data Bank Japan

③ C1QBP Interacts directly with DUX4c





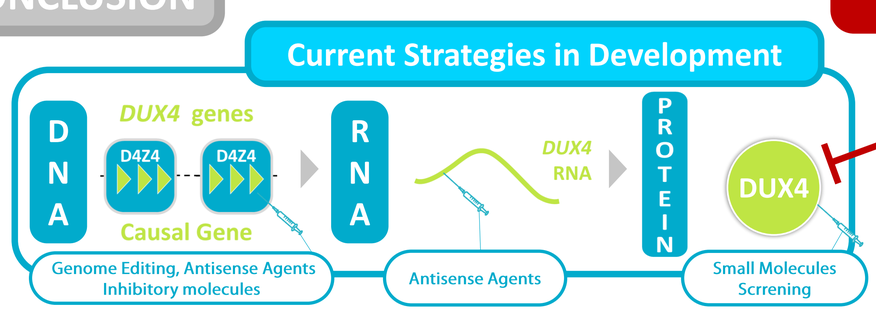
Link with FSHD

Defect in RNA splicing, transport and cell migration, innate immunity, oxidative stress and mitochondrial dysfunction

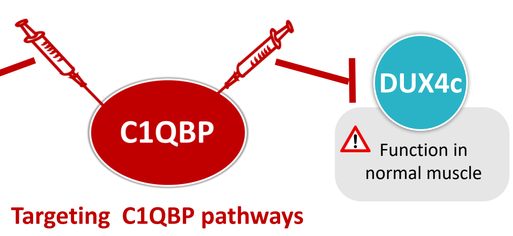
Rickard et al.,2015; Winokur et al.,2003; Turki et al., 2012

CONCLUSION

Current Strategies in Development



COMBINED THERAPIES



Targeting C1QBP pathways

PERSPECTIVES

① To identify subcellular DUX4/DUX4c and C1QBP interactions

② To identify altered C1QBP pathways following DUX4 misexpression

③ To mutate interaction sites and to analyze C1QBP pathway impacts

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