**Role of Renin in C3 Glomerulopathy**

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**Abstract**

C3 glomerulopathies (C3G) are ultra-rare kidney diseases defined by the deposition of complement proteins and their breakdown products in the renal glomerulus. These deposits reflect uncontrolled activation of the alternative pathway (AP) of the complement system. A discovery platform (SOMAscan) using multiplexed protein microarray technology to probe over 1300 analytes in plasma samples of patients with C3G (n=39) identified renin as differentially upregulated (p-value = 0.0013) when compared to controls (n=34). Renin is a peptidase of the renin-angiotensin-aldosterone system (RAAS) that has been reported to have C3 cleavage activity. Whether renin may play a contributory role in the pathogenesis of C3G is unknown. We sought to test renin cleavage of C3 using a broad range of renin concentrations coupled with immunofluorescence electrophoresis (IFE) and silver staining to detect cleavage activity. No C3 breakdown products were identified at biologically relevant concentrations of renin. These results do not support a direct role for renin in promoting further AP dysregulation in patients with C3G.

**C3 glomerulopathy**

C3 glomerulopathies (C3G) are ultra-rare complement-mediated renal diseases.

- C3 affects 2-3 persons per million – two major subtypes are recognized: dense deposit disease (DDD) and C3 glomerulonephritis (C3GN).
- Many patients with C3G have abnormal levels of complement proteins that circulate in the blood stream.
- Complement protein levels and their breakdown products can define patient-specific biomarker profiles.
- By measuring complement proteins a unique complement ‘signature’ can be determined for each person. DDD and C3GN have both commonalities and differences when a broad panel of complement proteins are compared. These biomarkers define specific profiles that are characteristic of DDD and C3GN. These tests can localize the sites of on-going complement dysregulation in C3G.

**RFOMScan technology**

RFOMScan

- More than 20,000 proteins are estimated to circulate in the human body.
- SOMAscan is a protein screening technology that tests over 1300 proteins in human plasma, serum or cell lysates.
- SOMAscan uses SOMAmer (Slow Off-rate Modified Aptamers) reagents to capture proteins.
- It is sensitive, quantifiable, reproducible and specific.
- Minute amounts of protein can be detected.
- The generated signal is proportional to the amount of target protein in the sample.

**Aptamers**

- Unique small sequence of DNA molecules
- Bind targets with high affinity and specificity
- Targets are proteins, carbohydrates & other compounds
- Affordable, easily produced
- Non-toxic
- Stable

**C3 structure & proteases**

**Proteases of Complement Component C3**

- A serine protease, BBSA—liberates kallikrein from the kininogens leading to the regulation of blood pressure and the activation of inflammation.
- Protease that directly cleaves C3 (Irmscher et al 2018).

**Renin expression & activity**

- **Silver Stain**
  - **Recombinant Renin - A**
  - **Recombinant Renin - B**
  - **Recombinant Renin - C**

**Summary / Future directions**

- The SOMAscan technology has the potential to discover new disease-specific biomarkers.
- SOMAscan results show that expression of renin is significantly elevated in C3GN and DDD in comparison to controls (non-renal phenotype).
- Recombinant renin does not cleave C3 at physiologically relevant concentrations.
- ACE1s and ARBs are common therapies for glomerulonephritis patients (including patients with C3G) to control proteinuria and blood pressure.
- Their use has been shown to increase levels of renin.

**Conclusions**

- While SOMAscan can aid in the discovery of new biomarkers up or down regulated in C3G, in vitro studies are necessary to determine if there is a biological role or simply an incidental finding.
- Clinical data should be considered when analyzing biomarkers, due to the fact that therapies can alter protein expression.
- The upregulation of renin in C3G is an incidental finding secondary to patient therapy.
- New biomarkers may be of value as diagnostic markers or as drug targets.
- New biomarkers may provide a more refined understanding of C3G.

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**References**


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