

# $\alpha_2$ - $\mu$ -Globulin Fragment: A Unique Protein in the Kidneys



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## Abstract

$\alpha_2$ - $\mu$ -Globulin ( $A_2$ ), an 18.6kDa protein produced in the liver, accumulates in the proximal tubule as a 15.5kDa cleavage product called " $\alpha_2$ - $\mu$ -globulin fragment" ( $A_2$ -f).  $A_2$ -f possesses several unusual properties: (i) it escapes lysosomal degradation in the proximal tubules which is the common degradative pathway for all other proteins processed at this site; (ii) it accumulates selectively in the cytosol of proximal tubule, where it may represent the most abundant protein; and (iii) it crosses a biological membrane to enter the cytosol. The structural features that mediate this unusual behavior have never been identified.

## Background and Significance

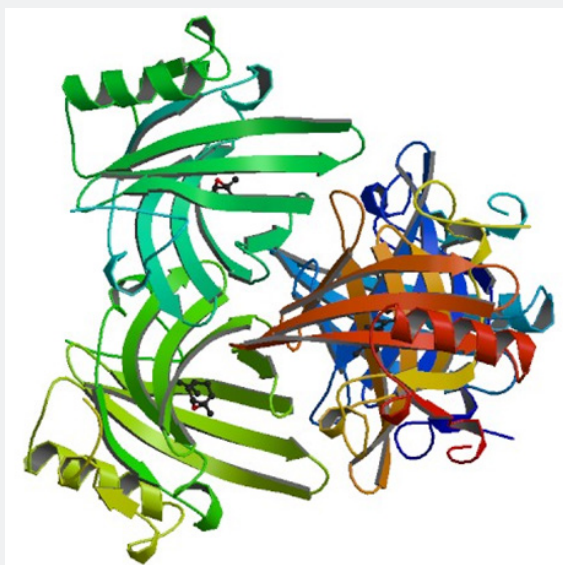
$\alpha_2$ - $\mu$ -Globulin fragment ( $A_2$ -f) represents about 5% of the total soluble protein content of the kidney [1,2]. It was initially thought to be a unique kidney fatty acid binding protein for several reasons: (a) it has a similar molecular size as all known FABPs, is found in the soluble protein fraction; and (b) it is abundant in cells with high fatty acid flux and binds long chain fatty acids *in vitro* [2,3]. Localization of  $A_2$ -f to the proximal tubule, the site with the highest fatty acid flux in the kidney, further supported the idea that the 15.5kDa protein was a unique kidney fatty acid binding protein (kFABP) [2]. The complete sequence analysis of the protein revealed it is derived from the proteolytic conversion of the precursor protein,  $A_2$ .

It is believed that unusual structural features permit  $A_2$ -f to be targeted to the proximal tubule cell, to escape lysosomal degradation and to enter the cytosol [4,5]. A study showed that  $A_2$  is synthesized in the liver but not in the kidney. RT-PCR confirmed that mRNA for  $A_2$ -f is abundant in the liver but cannot be detected in the kidney [6]. Removal of 9 amino acid residues from the C-terminus and 2-3 residues from the N-terminus of  $A_2$  (18.6kDa) produces  $A_2$ -f, a protein with an apparent molecular weight of 15.5kDa [6]. Although the proteolytic conversion of  $A_2$  to  $A_2$ -f is believed to be mediated by lysosomal cysteine proteases [7], the specific enzyme(s) responsible for converting  $A_2$  to  $A_2$ -f have never been identified. To date, successful conversion of  $A_2$  to  $A_2$ -f *in vitro* has not been reported.

$A_2$ -f binds long chain fatty acids *in vitro* with a 1:1 stoichiometry [2,3]. It is known that  $A_2$ -f displays a very high binding affinity for long chain fatty acids with a  $K_d$  that ranges from 0.1-2mM, depending upon the structure of the specific fatty acid ligand [2]. Although the structure of  $A_2$ -f has not been studied, the tertiary structure of  $A_2$  has only been determined by X-ray crystallography [8,9]. According to the published structure, each protein molecule envelopes a molecule of long chain fatty acid in its  $\beta$ -barrel cavity and transports it to mitochondria and peroxisomes where the fatty acids undergo  $\beta$ -oxidation to produce acetyl CoA and ultimately, generates ATP.

## Structural Information

The crystal structure of the precursor protein,  $A_2$  (18.6kDa) has been reported at 2.8Å resolution (Figure 1). It identifies Tyr-124 as a key residue involved in hydrogen bonding of the carboxyl group of the ligand fatty acid [8]. According to the authors, the hydroxyl group of Try-124 interacts with the ionized form of the carbonyl group of the fatty acid in the ligand binding site. Tyr-124 points towards the electron density of the bound ligand (whose electron density appears to resemble that of a pheromone). Even though some structural features of  $A_2$  and  $A_2$ -f may differ, crystallographic information from  $A_2$  is likely to be very important for beginning the sequential assignment of the NMR resonances of  $A_2$ -f in our study.



**Figure 1:** Ribbon diagram of the precursor protein  $\alpha_2\text{-}\mu$ -globulin ( $A_2$ ) shown as a trimer and based on the crystal structure solved at 2.9Å resolution [2].

### Conclusion

It has become increasingly clear over a period of time that  $A_2$ -f plays many key physiological roles in the cell, including retinol, fatty acid and pheromone transport. It may also fulfill important functions in maintenance of innate immunity, cell regulation, morphogenesis and angiogenesis. It is believed that its precursor protein,  $A_2$ , may represent an unusual example of a physiologic

protein capable of accumulating as a fragment ( $A_2$ -f) in a distant cell type.

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