Alpha-2-macroglobulin

What is Alpha-2-Macroglobulin (A2M)

Alpha-2-Macroglobulin is a family of proteins that are multifaceted and highly conserved among metazoans (animals of metazoan division with body fully developed into tissues and organs). To make it simple for the readr, these are invertebrate animals that evolved from a single cell. The A2M proteins are also present in archaea and bacteria. Although alpha-2-macroglobulin family proteins have many functions in various biological processes, one of the most conserved activities is protease inhibition, which especially helps the body's immune system by neutralizing pathogenic proteases (enzymes involved in breakdown of proteins into simpler amino acids) [1]. **In other words, it prevents (inhibit) important proteins from bring broken down or destroyed.**

In mammals, the primary site of alpha-2-macroglobulin synthesis is the liver, and it is distributed in the blood, probably to allow better access to all regions of the body, where it majorly contributes to the the innate immune system. Apart from protease regulation, alpha-2-macroglobulin is also involved in the regulation of several other effector molecules as well as the modulation of the host's physiology, thus exert numerous effects on health and in disease progression [2]. **Therefore, A2M has an overall important role in the immune system and regular physiology of the animal.**

Mechanism of action (warning: heavy scientific language below)

Alpha-2-macroglobulin gene encodes a protease inhibitor (to prevent the breakn down of proteins) and cytokine (signalling protein) transporter protein. For inhibtion of a wide range of proteases, including trypsis, thrombin, and collagenase, alpha-2-macroglobulin uses a "**bait-and-trap**" action of amino acids. Alpha-2-macroglobulin acts by developing a tetrameric (structure with four subunits or amino acids) cage enclosing active proteolytic enzymes, ultimately inhibiting the physical interaction between proteolytic enzymes and substrate molecules. See figure one for explanation. This phenomenon can be termed as protease **'snap-trap'** or **'venus-flytrap'**. **Consequently, proteases 'imprisoned' by alpha-2-macroglobulin become unable to cleave larger substrate molecules for example, collagen**. While short degradation of short peptide like sneaking into the alpha-2-macroglobulin cage is not affected. The existence of a 'bait

region,' which is a string of amino acids and functions as an extraordinarily good substrate molecule for endopeptidases (enzymes that cleave the peptide bond of nonterminal amino acids) of all catalytic forms, helps alpha-2-macroglobulin to preferentially catch exclusively active proteolytic enzymes. Alpha-2-macroglobulin becomes 'activated' after cleavage of the bait area by a proteolytic enzyme and encounters a structural transformation, therefore 'capturing' active proteolytic enzymes within its tetrameric cage. Alpha-2-macroglobulin after activation exhibits a reactive thioester (molecule with sulfur-acyl group bond) that binds with smaller primary amines in the protease to produce covalent alpha-2-macroglobulin/protease complexes in addition to sterically trapping proteolytic enzymes [3-5].

It can also block the production of cytokines, causing inflammatory processes to be disrupted. Alpha-2-macroglobulin depletion is caused by mutations in its gene. And for its potential to boost the elimination and breakdown of A-beta, the primary component of beta-amyloid plaques, the alpha-2-macroglobulin gene has been linked to Alzheimer's disease (neurological disease) [6].

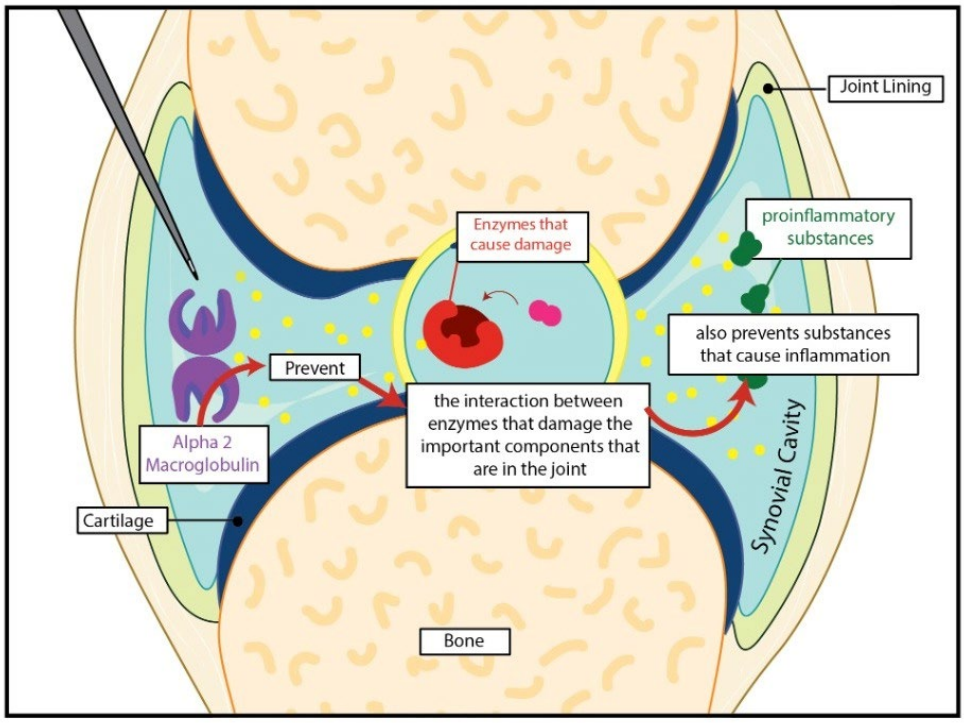

Figure: Alpha 2 M mechanism of action (Art by Daniela James).

Benefits of alpha-2-macroglobulin

To this date there is no therapeutic approach available that can cure arthritis at its root. Sigifincat progress has been done towards the slow down, halt, and even reverse joint degeneration after some long-term treatments.

Being a broad-spectrum proteinase inhibitor alpha-2-macroglobulin is commonly found in blood and synovial fluid (fluid present between joints). Its unique molecular structure comprises a bait or trap domain and four-arm configurations (as shown in figure 1), allowing it to inhibit practically all types of proteolytic enzymes. Alpha-2-macroglobulin could trap proteolytic enzymes that cause systemic inflammation. As a result, alpha-2-macroglobulin protects the human body against both endogenous and external inflammatory damages [7]. In both knee osteoarthritic patients and healthy people, however, the concentration of alpha-2-macroglobulin in synovial fluid is found to be substantially lower than that in the bloodstream. Upon this premise, a great number of research studies have looked into the therapeutic impact of intra-articular injections of alpha-2-macroglobulin on knee osteoarthritis. Alpha-2-macroglobulin administration in the knee joint has been shown to successfully postpone the articular cartilage degradation [8-10]. Furthermore, animal models have been used to assess the efficacy of alpha-2-macroglobulin, and the results have validated its protective role [11]. **For this reason, it has become so widely used in horses with inflamatioon in their joints.**

When combined, alpha-2-macroglobulin and platelet-rich plasma (PRP) therapy provide a potent treatment for osteoarthritis. This method aids in the long-term alleviation of pain related to osteoarthritis [12].

PRP in combination with alpha-2-macroglobulin therapy could provide pain management and better function, allowing patients to resume a healthy lifestyle without the ache and stiffening of osteoarthritis. This combined therapy can enable horses to regain their quality of life and even their athletic capabilities.

The injection of alpha-2-macroglobulin is a cutting-edge novel therapy for the treatment of osteoarthritis and other chronic musculoskeletal diseases. Alpha-2-macroglobulin stimulates the healing process after injecting into an osteoarthritic or sore location because it is a plasma protein molecule that naturally exists in the bloodstream.

As per Dr. Jason M. Cuéllar's study report in human patients, alpha-2-macroglobulin has been used in clinics to treat a variety of orthopedic painful conditions, including subacromial bursitis, lateral epicondylitis, and Achilles tendonitis, with satisfying and promising results. It has also been documented that alpha-2-macroglobulin has therapeutic potential for pain related to degenerative disc disease and enthesopathy (collection of problemtic constions related to rendons and ligaments), a degenerative condition related to knee osteoarthritis. Alpha-2-macroglobulin treatment involves concentrating alpha-2-macroglobulin proteins from donor serum and injecting those into the afflicted body area. To deal with a low concentration of alpha-2-macroglobulin in the synovial fluid, an alpha-2-macroglobulin-rich formulation can be injected into the knee joint of laboratory models, as described in prior studies. Alpha-2-macroglobulin concentrating is now a reality thanks to advanced technologies. A newly designed technique offers a novel approach for concentrating alpha-2-macroglobulin from serum. This concentration system's tangential flow filter technique can concentrate larger proteins such as alpha-2-macroglobulin while filtering out smaller ones. In less than 1 hour, this technique makes alpha-2-macroglobulin-rich concentrations for injection [13].

Despite the fact that a very advanced technique of alpha-2-macroglobulin concentration has already been developed, scientists are still trying to establish a more cost-effective and easy technique. Over 100 tailored variants of alpha-2-macroglobulin have been developed based on its molecular characteristics, 2 of these have the strongest inhibitory action, including CYT-98 and CYT-108 variants [9].

According to the data, the synthesized targeted alpha-2-macroglobulin variants functioned considerably better than the wild-type alpha-2-macroglobulin in protecting joint cartilage against inflammatory destruction. More clinical studies should be conducted to confirm its safety profile in the human body, as well as the large-scale production.

In conclusion, alpha-2-macroglobulin significantly plays role in;

- To prevent cartilage degeneration by halting cartilage breakdown.
- Prevention of osteoarthritis from getting worse.
- Possible joint healing and restoration.
- Reduction of the osteoarthritis associated severe pain.
- Relieving pain while improving joint function.

- Promoting tissue proliferation.

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