Commentary
Volume 6:2, 2022

Journal of Hepatology and Pancreatic Science

ISSN: 2573-4563 Open Access

The Pathophysiology of Liver Disease with TAM Receptors

Montserrat Tutusaus*

Department of Cell Death and Proliferation, IIBB-CSIC, IDIBAPS, 08036 Barcelona, Spain

Description

One of the 20 families of receptor tyrosine kinases are TAM receptors. They are made up of the structurally related Tyro-3, Axl, and MerTK receptors. TAM receptors have been widely examined, and they are expressed in a wide range of tissues across the body. In a nutshell, Axl is expressed in populations of cells in the liver, kidney, heart, skeletal muscle, testis, and cerebellum, as well as in blood-circulating cells like monocytes and activated platelets. Additionally, endothelial cells express Axl and its ligand Gas6. Tyro3 is mostly expressed in the central nervous system, where it is found in the cerebral cortex, cerebellum, olfactory bulbs, amygdala, platelets, and other tissues. MerTK is expressed in populations of cells in the ovaries, testes, liver, lung, kidney, cerebral cortex, and retina, as well as in blood-circulating cells such monocytes, platelets, and natural killer cells [1].

The extracellular domain (EC) of TAM receptors is composed of two tandem N-terminal immunoglobulin-like (Ig-like) domains that facilitate interactions between the receptor and ligand, as well as two fibronectin type III (FNIII) domains. Transmembrane domain (TM) and intracellular C-terminus tyrosine kinase domain come after the extracellular domain (EC) (TKD). The binding of the EC domain by its ligands is necessary for the activation of TAM receptors. The two most well-known ligands, Gas6 and Protein S (also known as Pros1), have a significant degree of structural similarity. Although more TAM receptor ligands have been discovered, such as galectin-3 and tubby-like protein 1 (Tulp-1), their physiological functions are still mostly unclear.

TAM receptors are crucial for controlling the innate immune response. They particularly stimulate tissue healing and serve as an inhibitor of inflammatory reactions. First, these receptors control efferocytosis, a critical step in the recovery of immunological and tissue homeostasis, which involves the phagocytosis of apoptotic cells. Phosphatidyl-serine (PtdSer), which is exposed on the membrane surface of dying cells, can bind to TAM receptors and start the uptake process mechanically. Additionally, PtdSer binds to the G1a domain of either Gas6 or Protein S in the presence of Ca^{2+} ions, increasing the absorption of apoptotic materials by macrophages and other phagocytes. Triple TAM knockout (KO) mice were created to demonstrate the critical function of TAM receptors in tissue homeostasis. These mice were sterile by 3 weeks of age as a result of defective testis development [2].

The fact that Sertoli cells express all three TAM receptors led to the buildup of apoptotic spermatogenic cells in these mice. Second, TAM receptors act as a negative feedback loop for the innate immune response by inhibiting Toll-like receptor (TLR) signalling. In more detail, these receptors interact with the type I interferon receptor (IFNAR)/STAT1 complex after ligand-mediated auto-phosphorylation, which at first increases the inflammatory response. However, this association causes functional changes in IFNAR/STAT towards an anti-inflammatory molecule, which in turn induces transcription of the suppressors of cytokine signalling 1 and 3 (SOCS1 and 3) proteins. These proteins ultimately prevent pro-inflammatory signalling from TLR and cytokine receptors. Additionally, TAM receptors might be involved in the interaction between the virus and the host during SARS-CoV2 infection, which was recently the subject of a thorough investigation [3,4].

The liver must operate as an immunological barrier while simultaneously preserving immune tolerance because it is constantly exposed to germs from the gut and microbial compounds from the portal circulation. The first study to look into TAM receptor function in the liver found that these receptors are essential for preserving liver immunological tolerance. In fact, Axl/Mertk/Tyro3 triple KO mice experienced spontaneous inflammation that persisted and eventually became chronic. Axl and MerTK are infrequently co-expressed in mice, according to research on the differentiating expression of TAM receptors. Instead, in vitro-cultured macrophages and dendritic cells originating from bone marrow primarily expressed MerTK or Axl, respectively. *In vivo* tests on mouse macrophages and dendritic cells from the spleen and lung validated these findings. Although Tyro3 expression was lacking in KC, murine liver-resident macrophages defied this norm and showed co-expression of Axl and MerTK. MerTK is also known to be present in all mouse tissue-resident macrophages, including liver-resident macrophages, but not Axl. have examined the function of TAM receptors in hepatic homeostasis in Cx3cr1-specific double KO mice (Axl/Mertk). Apoptotic cells accumulated in the liver with ageing in mice lacking Axl and MerTK. These mice also had inflammatory infiltrates in their livers, which were accompanied by elevated levels of the pro-inflammatory cytokines and chemokines in their liver mRNA as well as blood levels of the indicators for liver injury. As a result, Axl and Mer increased efferocytosis and reduced excessive immunological activation in the liver, in line with the recognised roles of TAM receptors. However, further research is required to fully understand the function of TAM receptors in the liver's tolerogenic barrier defence [4,5].

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Linger, Rachel M.A., Amy K. Keating, H. Shelton Earp, and Douglas K. Graham. "TAM receptor tyrosine kinases: Biologic functions, signaling, and potential therapeutic targeting in human cancer." *Adv Cancer Res* 100 (2008):35-83.
2. Angelillo-Scherrer, Anne, Laurent Burnier, Nathalie Flores, and Pierre Savi, et al. "Role of Gas6 receptors in platelet signaling during thrombus stabilization and implications for antithrombotic therapy." *J Clin Investig* 115 (2005): 237-246.
3. Nomura, Koji, Anna Vilalta, David H. Allendorf, and Tamara C. Hornik, et al. "Activated microglia desialylate and phagocytose cells *via* neuraminidase, galectin-3, and Mer Tyrosine Kinase." *J Immunol* 198 (2017): 4792-4801.
4. Wang, Zhao-Yang, Pei-Gang Wang, and Jing An. "The multifaceted roles of tam receptors during viral infection." *Virol Sin* 36 (2020): 1-12.
5. Tutusaus, Anna, Montserrat Marí, José T. Ortiz-Pérez, Gerry AF Nicolaes, et al. "Role of vitamin K-dependent factors protein S and GAS6 and TAM receptors in SARS-CoV-2 infection and COVID-19-associated [immunothrombosis." *Cells* 9 (2020): 2186.

***Address for Correspondence:** Montserrat Tutusaus, Department of Cell Death and Proliferation, IIBB-CSIC, IDIBAPS, 08036 Barcelona, Spain; E-mail: tutusaus.Mont@gmial.com*

Received: 01-Mar-2022, Manuscript No. hps-22-69524; **Editor assigned:** 03-Mar-2022, Pre QC No. P-69524; **Reviewed:** 17-Mar-2022, QC No. Q-69524; **Revised:** 21-Mar-2022, Manuscript No. R-69524; **Published:** 29-Mar-2022, DOI: 10.37421/2573-4563.2022.6.185

***How to cite this article:** Tutusaus, Montserrat. "The Pathophysiology of Liver Disease with TAM Receptors." Hepatol Pancreat Sci 6 (2022): 185.*