Stabilin-2 and Cancer Metastasis

Subjects: Pathology
Contributor: Edward N. Harris , Erika Baker

Stabilin-2 is a systemic clearance receptor for hyaluronic acid (HA). HA is typically enriched in the extracellular matrix of several types of cancer cells, thus, Stabilin-2 may interact with the extracellular matrix of cancer cells depending on the physiological environment of the tissue. This is especially relevant for the liver sinusoids and lymph nodes which express high levels of Stabilin-2 and also are sites of metastases for a number of cancer types.

hyaluronic acid Stabilin-2 cancer metastasis receptor

1. Introduction

In 1889, Dr. Stephen Paget's "seed and soil" theory of metastasis stated that a tumor cell (or seed) will find a home in certain compatible tissues (soil) to continue growing in a suitable environment [1]. Tissues with the highest expression of Stabilin-2 (sinusoids of liver, lymph node) are also the primary targets (soil) of metastatic cancers from breast, colon, prostate, gastrointestinal, etc. (seeds) [2]. Metastatic tumor cells often contain distinctive surface markers for enabling them to escape their indigenous tissue to travel and thrive at a distal site. One of the common markers is CD44 and its splice variants and this is why it has been of such interest in cancer research. CD44 is a HA binding molecule which is not highly endocytic and many cancers (as well as immune cells) express variants of CD44 and have abundant pericellular HA [3][4]. HA is a ubiquitous molecule and it actually helps to "cloak" or "hide" the cancer cell from immune surveillance. Metastatic cells that are not detected by the immune system often immobilize in the sinusoids of liver, lymph node and bone marrow. To investigate why this occurs, Martens et al. analyzed the scavenger receptor profile of these tissues and found a number of receptors that are pattern recognition receptors as well as specific ligand receptors. These include both Stabilin-1 and -2, DC-SIGN, mannose receptor (MR), MARCO, and LYVE-1 expressed by the endothelium and resident macrophages expressing MR, DC-SIGN, Sialoadhesin, CD163, and Thrombomodulin. These receptors represent a trapping mechanism for metastatic cells. Of these 11 receptors, only Stabilin-2 recognizes and binds with HA. It is interesting to note that the organ with the highest expression of Stabilin-2 is the spleen, though it is not a site for tumor metastasis. The spleen only expressed four of the 11 receptors listed here and so it may not have the optimal profile to immobilize metastatic cells [5]. In light of the hypothesis that Stabilin-2 may aid in the retention of metastatic cells, a study focused on the remodeling of endothelium in hepatocellular carcinoma (HCC) revealed that the loss of Stabilin-2 expression increased survival of the patients that were sampled. As normal cells become cancerous, they de-differentiate and lose many of their tissue-specific markers. Unfortunately, loss of Stabilin-2 expression in the peri-tumorous environment was the least likely to occur of all the SEC markers tested and may be a significant factor for endothelial-tumor cell adhesion and invasion [6].

The lymphatic system or “second circulatory system” is a common transportation highway for metastases and tumor lymphangiogenesis and is common among the various types of cancer. The lymph node itself highly expresses Stabilin-2 and acts as one of the entrapping receptors for metastatic tumor cells. A study in which the investigators injected PC3M-LN4 prostate cancer cells that are known to be rich in pericellular HA in mice, found that when Stabilin-2 was blocked with a blocking antibody prior to tumor injection, the number of lymph node metastases was dramatically reduced [7]. A follow-up human patient study in the evaluation of tongue cancer supports this finding in which the potential of solid tumor lymph node metastases is positively correlated with Stabilin-2 expression in lymph node [8]. Though it is known that pericellular HA increases metastatic potential, it also increases interaction with Stabilin-2 which allows for tumors to grow at distal sites.

2. Influence

Stabilin-2 is the primary scavenger receptor for HA as mentioned previously. Mice lacking Stabilin-2 expression (stab2KO) have very high HA levels in their circulating plasma, though the mice are physiologically normal in all other aspects [9]. The role of circulating HA in a metastatic model was carried out in stab2KO mice in which mice were injected with B16F10 melanoma cells and the number of metastatic nodules was assessed in the lungs. The results are that 1) the number of metastatic nodules was lower in Stab2KO than WT mice, 2) there was significantly less rolling and tethering of cells in the Stab2KO mice compared to WT, suggesting the importance of circulating HA, or rather the lack of it, promotes metastatic cellular attachment [10]. This paper demonstrates that Stabilin-2 does not need to directly interact with metastatic cells, but the levels of ligands also affect metastatic activity.

CD44 and its splice variants are enriched in a variety of cancer cells and all of these receptors bind HA [11][12]. Therefore, the use of HA as a vehicle for nanoparticles to target cancer cells may be a promising therapeutic tool. Evaluation of HA-based nanoparticles often begin and end in the cell culture stage without further assessment in a physiological model [13]. In the experimental animal, nanoparticles coated with HA often accumulate in the liver due to Stabilin-2 binding and endocytosis activities [14][15]. If HA is required for nanoparticle targeting, then it must be physically or chemically modified to optimize delivery to the target tissue while avoiding accumulation within the liver. For example, carboxymethylation of HA allowed for greater drug sequestration and overall efficacy of drug delivery within a limited time window, though the study lacked some key data for liver or renal clearance [16]. Likewise, nanoparticles coated with low molecular weight HA have higher internalization rates by tumor cells and better efficacy than nanoparticles without HA and little to no toxicity to either liver or kidney. However, other treatments, such as radiation, were required to significantly hinder growth of tumors [17]. The bottom line is that many nanoparticles have been developed for drug delivery to a variety different types of cancer and there is not yet a developed HA-based nanoparticle that contains optimal drug delivery to the target tissue without off-target effects while retaining the intrinsic properties of HA for binding to key receptors [18][19][20].

References

1. Paget, S. The Distribution of Secondary Growths in Cancer of the Breast. Lancet 1889, 133, 571–573.
2. Jiang, W.G.; Sanders, A.J.; Katoh, M.; Ungefroren, H.; Gieseler, F.; Prince, M.; Thompson, S.K.; Zollo, M.; Spano, D.; Dhawan, P.; et al. Tissue invasion and metastasis: Molecular, biological and clinical perspectives. Semin. Cancer Biol. 2015, 35, S244–S275.
3. DeGrendele, H.C.; Estess, P.; Siegelman, M.H. Requirement for CD44 in activated T cell extravasation into an inflammatory site. Science 1997, 278, 672–675.
4. Zoller, M. CD44: Can a cancer-initiating cell profit from an abundantly expressed molecule? Nat. Rev. Cancer 2011, 11, 254–267.
5. Martens, J.H.; Kzhyshkowska, J.; Falkowski-Hansen, M.; Schledzewski, K.; Gratchev, A.; Mansmann, U.; Schmuttermaier, C.; Dippel, E.; Koenen, W.; Riedel, F.; et al. Differential expression of a gene signature for scavenger/lectin receptors by endothelial cells and macrophages in human lymph node sinuses, the primary sites of regional metastasis. J. Pathol. 2006, 208, 574–589.
6. Geraud, C.; Mogler, C.; Runge, A.; Evdokimov, K.; Lu, S.; Schledzewski, K.; Arnold, B.; Hammerling, G.; Koch, P.S.; Breuhahn, K.; et al. Endothelial transdifferentiation in hepatocellular carcinoma: Loss of Stabilin-2 expression in peri-tumourous liver correlates with increased survival. Liver Int. 2013, 33, 1428–1440.
7. Simpson, M.A.; Weigel, J.A.; Weigel, P.H. Systemic blockade of the hyaluronan receptor for endocytosis prevents lymph node metastasis of prostate cancer. Int. J. Cancer 2012, 131, E836–E840.
8. Han, M.W.; Lee, J.C.; Park, S.Y.; Kim, Y.M.; Cho, K.J.; Kim, S.W.; Lee, M.; Nam, S.Y.; Kim, I.S.; Kim, S.Y. Homotypic Interaction of Stabilin-2 Plays a Critical Role in Lymph Node Metastasis of Tongue Cancer. Anticancer Res. 2016, 36, 6611–6618.
9. Schledzewski, K.; Geraud, C.; Arnold, B.; Wang, S.; Grone, H.J.; Kempf, T.; Wollert, K.C.; Straub, B.K.; Schirmacher, P.; Demory, A.; et al. Deficiency of liver sinusoidal scavenger receptors stabilin-1 and -2 in mice causes glomerulofibrotic nephropathy via impaired hepatic clearance of noxious blood factors. J. Clin. Investig. 2011, 121, 703–714.
10. Hirose, Y.; Saijou, E.; Sugano, Y.; Takeshita, F.; Nishimura, S.; Nonaka, H.; Chen, Y.R.; Sekine, K.; Kido, T.; Nakamura, T.; et al. Inhibition of Stabilin-2 elevates circulating hyaluronic acid levels and prevents tumor metastasis. Proc. Natl. Acad. Sci. USA 2012, 109, 4263–4268.
11. Chen, C.; Zhao, S.; Karnad, A.; Freeman, J.W. The biology and role of CD44 in cancer progression: Therapeutic implications. J. Hematol. Oncol. 2018, 11, 64.
12. Yan, Y.; Zuo, X.; Wei, D. Concise Review: Emerging Role of CD44 in Cancer Stem Cells: A Promising Biomarker and Therapeutic Target. Stem Cells Transl. Med. 2015, 4, 1033–1043.

13. Hayward, S.L.; Francis, D.M.; Kholmatov, P.; Kidambi, S. Targeted Delivery of MicroRNA125a-5p by Engineered Lipid Nanoparticles for the Treatment of HER2 Positive Metastatic Breast Cancer. J. Biomed. Nanotechnol. 2016, 12, 554–568.
14. Jeannot, V.; Mazzaferro, S.; Lavaud, J.; Vanwonterghem, L.; Henry, M.; Arboleas, M.; Vollaire, J.; Josserand, V.; Coll, J.L.; Lecommandoux, S.; et al. Targeting CD44 receptor-positive lung tumors using polysaccharide-based nanocarriers: Influence of nanoparticle size and administration route. Nanomedicine 2016, 12, 921–932.
15. Jeannot, V.; Gauche, C.; Mazzaferro, S.; Couvet, M.; Vanwonterghem, L.; Henry, M.; Didier, C.; Vollaire, J.; Josserand, V.; Coll, J.L.; et al. Anti-tumor efficacy of hyaluronan-based nanoparticles for the co-delivery of drugs in lung cancer. J. Control. Release 2018, 275, 117–128.
16. Woodman, J.L.; Suh, M.S.; Zhang, J.; Kondaveeti, Y.; Burgess, D.J.; White, B.A.; Prestwich, G.D.; Kuhn, L.T. Carboxymethyl Hyaluronan-Stabilized Nanoparticles for Anticancer Drug Delivery. Int. J. Cell Biol. 2015, 2015, 249573.
17. Rosch, J.G.; Landry, M.R.; Thomas, C.R., Jr.; Sun, C. Enhancing chemoradiation of colorectal cancer through targeted delivery of raltitrexed by hyaluronic acid coated nanoparticles. Nanoscale 2019, 11, 13947–13960.
18. Rao, N.V.; Yoon, H.Y.; Han, H.S.; Ko, H.; Son, S.; Lee, M.; Lee, H.; Jo, D.G.; Kang, Y.M.; Park, J.H. Recent developments in hyaluronic acid-based nanomedicine for targeted cancer treatment. Expert Opin. Drug Deliv. 2016, 13, 239–252.
19. Ossipov, D.A. Nanostructured hyaluronic acid-based materials for active delivery to cancer. Expert Opin. Drug Deliv. 2010, 7, 681–703.
20. Oh, E.J.; Park, K.; Kim, K.S.; Kim, J.; Yang, J.A.; Kong, J.H.; Lee, M.Y.; Hoffman, A.S.; Hahn, S.K. Target specific and long-acting delivery of protein, peptide, and nucleotide therapeutics using hyaluronic acid derivatives. J. Control. Release 2010, 141, 2–12.