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SnapShot: FABP Functions

Cell

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FABPs in health and disease

Brain-FABP (B-FABP, FABP7)
Brain development and neurogenesis
Overexpression in Down's syndrome and Schizophrenia

Heart-FABP (H-FABP, FABP3)
Muscle lipid uptake and oxidation
Biomarker for acute myocardial infarction

Adipose-FABP (A-FABP, FABP4)
Lipid storage, lipolysis, and metabolism
Metabolic diseases (e.g. atherosclerosis, insulin resistance, type 2 diabetes), cardiovascular diseases, asthma, cancer

Liver-FABP (L-FABP, FABP1)
Lipid assimilation, biosynthesis, and cellular antioxidant.
High saturated fat diet-induced hepatic steatosis

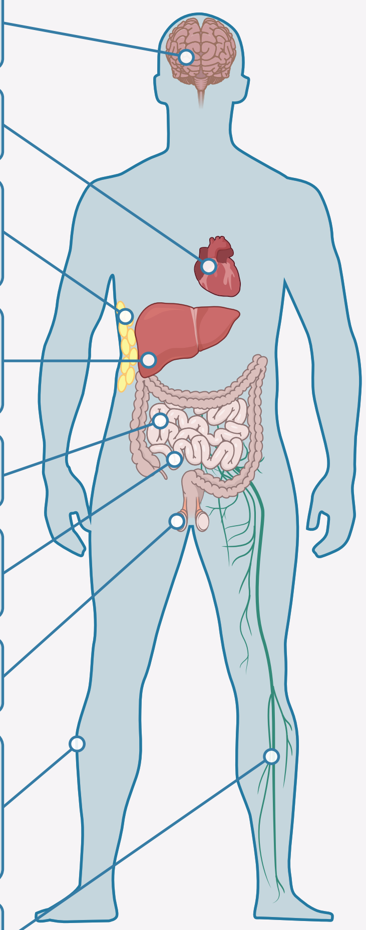
Intestine-FABP (I-FABP, FABP2)
Dietary lipid absorption
Metabolic syndromes

Ileal-FABP (IL-FABP, FABP6)
Intestine bile acid homeostasis
Bile acid-associated gut diseases and type 2 diabetes

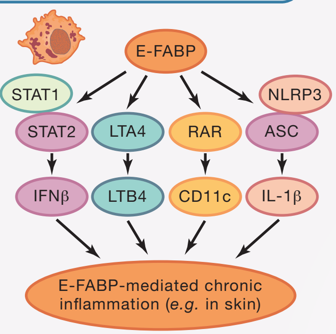
Testis-FABP (T-FABP, FABP9)
Spermatogenesis and fertilization
Sperm head abnormalities

Epidermal-FABP (E-FABP, FABP5)
FA binding and oxidation, transportation of other signaling molecules (e.g. endocannabinoids)
Inflammatory skin diseases (e.g. psoriasis, dermatitis), cancer, atherosclerosis, autoimmune diseases

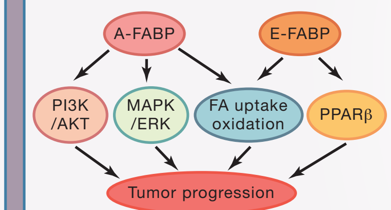
Myelin-FABP (M-FABP, FABP8)
Myelin membrane biogenesis
Guillain-Barre syndrome



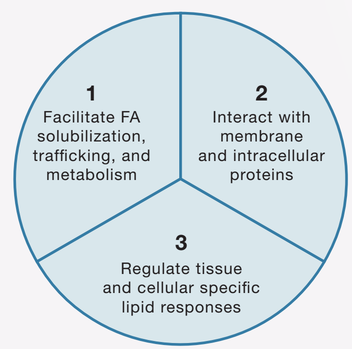
E-FABP+ macrophages
(e.g., in epidermis, dermis)

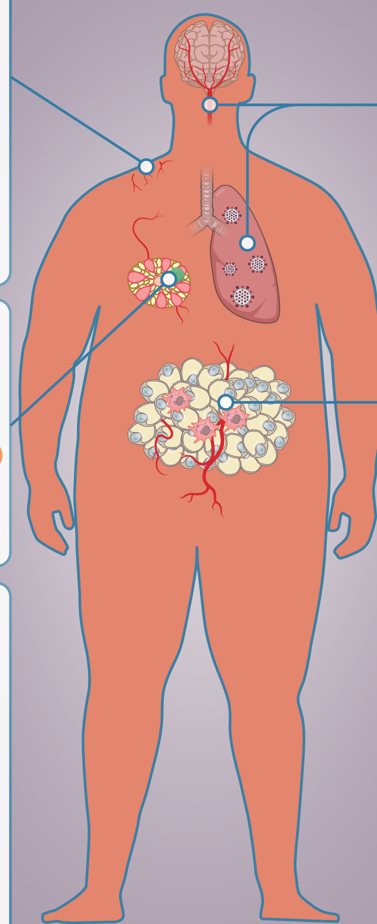


Tumor cells

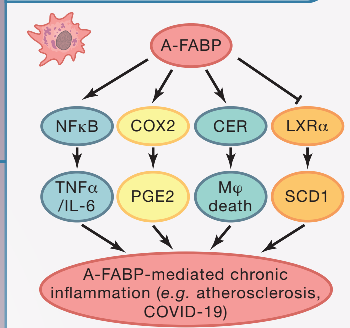


General FABP functions

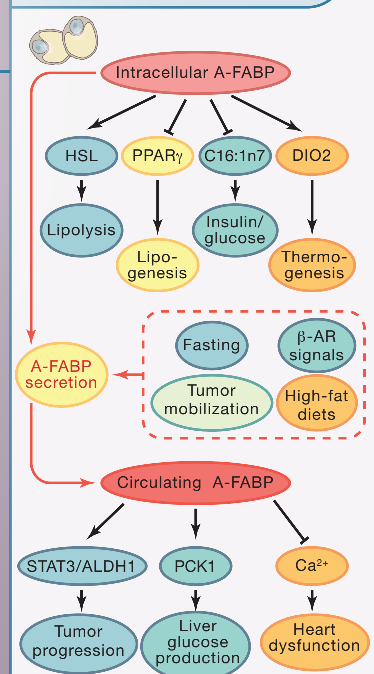




A-FABP+ macrophages
(e.g., in vessel, alveolus)



Adipocytes



Abbreviations: FABPs, fatty acid binding proteins; NFκB: nuclear factor kappa B; COX2, cyclooxygenase-2; CER, ceramide; LXR, liver X receptor; PGE2, prostaglandin E2; SCD1, stearoyl-CoA desaturase 1; STAT, signal transducer and activator of transcription; LTA4, leukotriene A4; RAR, retinoic acid receptor; NLRP3, nucleotide-binding domain leucine-rich repeat and pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a caspase-recruitment domain; IFNβ, interferon β; LTB4, leukotriene B4; HSL, hormone sensitive lipase; PPAR, peroxisome proliferator-activated receptors; DIO2, deiodinase type 2; β-AR, β-adrenergic receptor; ALDH1, aldehyde dehydrogenase isoform 1; PCK1, phosphoenolpyruvate carboxykinase 1. PI3K, phosphatidylinositol-3-kinases; MAPK, mitogen-activated protein kinase; ERK, extracellular regulated kinase

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FABPs in Health and Disease

As evolutionarily conservative proteins, fatty acid binding proteins (FABPs) play a central role in coordinating lipid transport, metabolism, and responses in various tissues and organs across species (Storch and Corsico, 2008). FABPs were named according to the tissue where they were originally identified. For example, the FABP predominantly expressed in the liver was named L-FABP (also known as FABP1), whereas the FABP mainly found in the heart was named H-FABP (also known as FABP3). The FABP family is composed of at least nine homologous proteins with similar tertiary structures and specific tissue distribution patterns (left side). All FABP members are able to bind hydrophobic lipid ligands in the cavity of the β barrel structure, which is made of 10 anti-parallel β stands and capped by a helix-turn-helix motif. Because of differences in their amino-acid sequences, FABP family members possess different lipid ligand-binding specificity and affinity. Moreover, individual FABP members exhibit unique functionality that reflects the unique environments of the tissues and organs where they are expressed. Generally, FABPs function as cytoplasmic lipid chaperones to (1) facilitate fatty acid solubilization, trafficking, and metabolism; (2) interact with various membrane and intracellular proteins (e.g., peroxisome proliferator-activated receptors [PPARs], hormone sensitive lipase [HSL]); and (3) regulate tissue and cellular specific lipid responses (middle wheel panel). In doing so, FABPs carry out pleiotropic functions to maintain tissue homeostasis in health and to participate in disease pathogenesis (left side).

FABPs in Obesity, Chronic Inflammation, and Cancer

With the prevalence of obesity, adipose-FABP (A-FABP) and epidermal-FABP (E-FABP) have become the two most studied FABP family members because of their remarkable functions in obesity-associated diseases in both animal and human studies (Hotamisligil and Bernlohr, 2015). Obesity is associated with expanded adipose tissue composed of inflammatory adipocytes and macrophages, both of which express A-FABP and E-FABP. Adipocytes predominantly express A-FABP, but E-FABP can be compensatorily upregulated during A-FABP deficiency, indicating a functional overlap between A-FABP and E-FABP in adipocytes. Studies using A-FABP and E-FABP double-knockout mice demonstrate that A-FABP and E-FABP are essential in high-fat-diet (HFD)-induced obesity, insulin resistance, and type 2 diabetes, as well as in modulating systemic lipid and glucose metabolism. Interestingly, A-FABP and E-FABP are also expressed in macrophages, but neither compensates for the other in A-FABP- or E-FABP-deficient mice, suggesting unique functions of the two FABPs in macrophages. Emerging studies demonstrate that A-FABP has a distinct expression profile than E-FABP among different macrophage subsets; thus, A-FABP and E-FABP exhibit unique functionality in different macrophages (Hao et al., 2018a; Zhang et al., 2014). These findings not only explain the uncompensated regulation of A-FABP and E-FABP in macrophages but suggest them as new markers in defining the functional heterogeneity of macrophage subsets.

Indeed, A-FABP and E-FABP regulate different signaling pathways in macrophages. Although E-FABP expression promotes the activation of STAT1/2/IFNβ, LTA4/LTB4, RAR/CD11c, or NLRP3/IL-1β pathways (top left of the right panel), A-FABP expression mainly activates NFκB/IL-6, COX2/PGE2, CER/cell death, or LXR/SCD1 in macrophages (top right of the right panel). For example, in HFD-induced obese mouse models, expression of E-FABP, but not A-FABP, in skin macrophages is essential to the induction of interleukin 1 (IL-1)β-mediated skin inflammation (Zhang et al., 2015). By contrast, A-FABP deficiency protects mice against atherosclerosis development, mainly because of its ability to reduce lipid-induced endoplasmic reticulum stress in macrophages (Erbay et al., 2009). Moreover, A-FABP is highly expressed in alveolar macrophages in COVID-19 patients, which could contribute to obesity-associated severity of COVID-19 (Liao et al., 2020; Richardson et al., 2020). In tumors, A-FABP expression in macrophages promotes tumor growth and metastasis through inducing tumor-promoting IL-6 signaling, whereas E-FABP expression in macrophages enhances type I interferon β (IFNβ) responses to inhibit tumor progression (Zhang et al., 2014; Hao et al., 2018a). Thus, A-FABP and E-FABP regulate different inflammatory and metabolic pathways, representing functional markers that demonstrate heterogeneous features of tissue macrophages.

It is worth noting that FABPs are traditionally considered as cytoplasmic proteins that coordinate lipid responses inside cells. For instance, intracellular A-FABP in adipocytes accounts for up to 5% of total cytosolic proteins and is critical in the maintenance of dynamic lipid balance by regulating HSL-mediated lipolysis and PPARγ-mediated lipogenesis. Recent studies demonstrate that external factors (e.g., HFD, β-AR signaling) are able to induce A-FABP secretion from adipocytes. Circulating A-FABP functions as a new adipokine linking obesity-associated diseases, such as enhancing obesity-associated breast cancer development and liver glucose production in diabetes (Hao et al., 2018b; Cao et al., 2013) (bottom right of the right panel). In addition, mutated tumor cells (e.g., some breast or ovarian cancer cells) ectopically upregulate the expression of A-FABP and/or E-FABP, which in turn promote tumor cell proliferation and metastasis by activating different oncogenic signaling pathways (middle left of the right panel).

In summary, accumulating evidence has demonstrated that FABP members not only exert overlapping functions in lipid binding and transport but exhibit unique characteristics in specific cells and tissues as well. Further understanding as to how different FABPs are specifically regulated in different cells and tissues (e.g., immune cell subsets), as well as the mechanisms regulating cell metabolism and function, will provide insights into the actions of FABPs and facilitate their clinical applications in obesity-associated diseases.

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REFERENCES

Cao, H., Sekiya, M., Ertunc, M.E., Burak, M.F., Mayers, J.R., White, A., Inouye, K., Rickey, L.M., Ercal, B.C., Furuhashi, M., et al. (2013). Adipocyte lipid chaperone AP2 is a secreted adipokine regulating hepatic glucose production. Cell Metab. *17*, 768–778.

Erbay, E., Babaev, V.R., Mayers, J.R., Makowski, L., Charles, K.N., Snitow, M.E., Fazio, S., Wiest, M.M., Watkins, S.M., Linton, M.F., and Hotamisligil, G.S. (2009). Reducing endoplasmic reticulum stress through a macrophage lipid chaperone alleviates atherosclerosis. Nat. Med. *15*, 1383–1391.

Hao, J., Yan, F., Zhang, Y., Triplett, A., Zhang, Y., Schultz, D.A., Sun, Y., Zeng, J., Silverstein, K.A.T., Zheng, Q., et al. (2018a). Expression of Adipocyte/Macrophage Fatty Acid-Binding Protein in Tumor-Associated Macrophages Promotes Breast Cancer Progression. Cancer Res. *78*, 2343–2355.

Hao, J., Zhang, Y., Yan, X., Yan, F., Sun, Y., Zeng, J., Waigel, S., Yin, Y., Fraig, M.M., Egilmez, N.K., et al. (2018b). Circulating Adipose Fatty Acid Binding Protein Is a New Link Underlying Obesity-Associated Breast/Mammary Tumor Development. Cell Metab. *28*, 689–705.e5.

Hotamisligil, G.S., and Bernlohr, D.A. (2015). Metabolic functions of FABPs--mechanisms and therapeutic implications. Nat. Rev. Endocrinol. *11*, 592–605.

Liao, M., Liu, Y., Yuan, J., Wen, Y., Xu, G., Zhao, J., Cheng, L., Li, J., Wang, X., Wang, F., et al. (2020). Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat. Med. *26*, 842–844.

Richardson, S., Hirsch, J.S., Narasimhan, M., Crawford, J.M., McGinn, T., Davidson, K.W., Barnaby, D.P., Becker, L.B., Chelico, J.D., Cohen, S.L., et al.; and the Northwell COVID-19 Research Consortium (2020). Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA *323*, 2052–2059.

Storch, J., and Corsico, B. (2008). The emerging functions and mechanisms of mammalian fatty acid-binding proteins. Annu. Rev. Nutr. *28*, 73–95.

Zhang, Y., Sun, Y., Rao, E., Yan, F., Li, Q., Zhang, Y., Silverstein, K.A., Liu, S., Sauter, E., Cleary, M.P., and Li, B. (2014). Fatty acid-binding protein E-FABP restricts tumor growth by promoting IFN-β responses in tumor-associated macrophages. Cancer Res. *74*, 2986–2998.

Zhang, Y., Li, Q., Rao, E., Sun, Y., Grossmann, M.E., Morris, R.J., Cleary, M.P., and Li, B. (2015). Epidermal Fatty Acid binding protein promotes skin inflammation induced by high-fat diet. Immunity *42*, 953–964.

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