pharmacologic inhibitors, the authors show that HFE binding to ALK3 diminishes polyubiquitination of ALK3 and thus its degradation via the proteasome. Consistent with this finding in cultured cells, ALK3 protein levels are reduced in mice lacking HFE, whereas ALK3 mRNA levels are not altered. The authors further analyze how the 2 most common polymorphisms in the HFE gene (C282Y and H63D) affect BMP/SMAD signaling. Indeed, both HFE variants are able to interact with ALK3 but failed to increase ALK3 protein levels on the cell surface of hepatocytes. However, the underlying mechanisms differ: although the H63D variant failed to inhibit ALK3 ubiquitination, the HFE C282Y mutant protected ALK3 from ubiquitination, similar to wild-type HFE. The authors speculate that the HFE C282Y mutant protein that does not reach the cell membrane sequesters ALK3 inside cells, thereby preventing ALK3 from trafficking to the cell surface.

Future work will need to address the mechanism of how HFE inhibits ALK3 ubiquitination and whether it interferes with a complex formed between the Smad ubiquitin regulatory factor (Smurfl), BMP type I receptors, and the inhibitory Smads 6 and 7 (ISMADs). In addition, the impact of TIR2 in BMP/SMAD signaling, as well as the dynamics of complex formation involved in the sensing of systemic iron levels needs to be unraveled. Nevertheless, the present paper represents a milestone in the understanding of iron regulation and might even have an impact on drug development to treat HH by pharmacologically regulating ubiquitination of ALK3.

Conflict-of-interest disclosure: M.U.M. received consulting fees from Novartis.

REFERENCES


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Comment on Myneni et al, page 1344

Factor XIII and adipocyte biology

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In this issue of Blood, Myneni et al demonstrate a role for the A (transglutaminase) subunit of factor XIII (FXIII-A) in cell culture models of differentiation of preadipocytes to adipocytes.1 This finding is potentially of great importance in light of recent genome-wide association and adipose tissue transcriptomic studies that implicated F13A1 in human obesity.2 Although the sources of circulating A2 have not been explored thoroughly, megakaryocyte/platelets and monocyte/macrophages likely are major players. Message for the A subunit, however, is found in a variety of cell types, raising the possibility that the A subunit may have cell type-specific functions independent of its role in blood coagulation. Myneni et al now describe a function for the A subunit synthesized during adipocyte differentiation.3 The authors demonstrate that the A subunit forms an active transglutaminase that translocates to the cell surface and promotes assembly of fibronectin into extracellular matrix, which in turn causes the differentiating cells to proliferate more in response to insulin, a key differentiation agent, while slowing down differentiation and accumulation of lipid. Two experimental paradigms implicate the A subunit in these events: inhibition by a small molecule called NC9 that incorporates irreversibly into transglutaminases and a comparative study of fibroblasts cultured from mice in which the A subunit had been knocked out. Conditioning surfaces of culture tissues with adsorbed fibronectin has long been known to dampen adipocytic differentiation.4 The present paper focuses on a more physiologically
relevant form of insolubilized fibronectin, i.e., fibronectin that is assembled into extracellular fibrils. These fibrils are elaborated by many types of cells and in a variety of experimental setups allow cells to proliferate and differentiate in response to various cues. The figure depicts the fibronectin matrix as a temporary working matrix that is the precursor to the different types of definitive matrix laid down once cells are fully differentiated. One may also think of it as a replacement for the emergency matrix of fibrin formed when thrombin is activated. As with the fibrin matrix, the fibronectin matrix and various definitive matrices are adorned with other proteins.

Fibronectin assembles at specific sites on the surfaces of cells. These sites are regulated and engage fibronectin via its N-terminal type I repeats and more C-terminal internative-binding sequences. The sites are linked to cytoplasmic motor proteins, allowing stretching of fibronectin and exposure of cryptic self-association sites. Fibronectin is cross-linked efficiently to binding partners by FXIII-A, which attacks glutamines near the fibronectin N terminus. However, cross-linking is not required for assembly. My laboratory found that increases in the rate of fibronectin deposition in response to exogenously added FXIII-A varied depending on the cell being studied: twofold for cultured HT-1080 fibrosarcoma cells. In the present paper, endogenous A subunit was deduced to cause an approximate twofold increase in fibronectin deposition by fibroblasts and >10-fold for HT-1080 fibrosarcoma cells. In the present paper, endogenous A subunit was deduced to cause an approximate twofold increase in fibronectin deposition by fibroblasts differentiating toward adipocytes. It should be noted that a second transglutaminase, transglutaminase-2 (TG2), was present in preadipocytes. Although TG2 also attacks the N-terminal glutamines of fibronectin, it seemed to play no part in modulation of fibronectin assembly and adipocyte differentiation.

The hematological community has always welcomed the chance to think more deeply about FXIII. Many questions are raised by the present paper and the genetic studies in which 7 different single nucleotide polymorphisms implicate F13A1 in obesity. What are the limits of the F13A1 transcriptional unit? Comparing preadipocytes to other cell types such as megakaryocytes and monocytes, how is transcription regulated, what controls translation, and how is the A subunit processed and secreted? How does the A subunit associate with the preadipocyte cell surface? How is it activated? What proteins are cross-linked? Can any or all of the polymorphisms that implicate F13A1 as an obesity gene be tied to modulation of fibronectin assembly by the preadipocyte? Answers to these questions could help fight the current obesity epidemic while at the same time shedding light on enigmas about the A subunit that persist 70 years after the discovery of its action on clot solubility.

Conflict-of-interest disclosure: The author declares no competing financial interest.

REFERENCES


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