Relationship between ferritin heavy chain and epithelial to mesenchymal transition phenomenon

Ilenia Aversa*

EDITORIAL

The Epithelial-to-Mesenchymal Transition (EMT) is a complex process that occur during embryogenesis and during wound repair. In recent years, a growing interest in EMT phenomenon in the field of oncology has been observed. This is certainly useful to better understand the importance of EMT phenomenon in human diseases.

EMT process is a highly regulated trans-differentiation cellular program that allows the cell to lose the epithelial features and to acquire mesenchymal ones. To this, a well described set of gene modifications and morphological changes lead the cell to acquire the expression of mesenchymal markers, altered cell polarity, migratory and invasive capacities and to loss cell-cell adhesion molecules.

Many studies have focused on the molecular basis of EMT process; among others, the regulation of intracellular redox metabolism and altered Reactive Oxygen Species (ROS) play a key role in this noteworthily phenomenon.

Ferritin is an important protein involved in iron homeostasis. It is composed by 24 subunits of Ferritin Heavy Chain (FHC) and Ferritin Light Chain (FLC). In particular, the heavy subunit is provided of ferroxidase activity, as a matter of fact, FHC protects the cell from oxidative damage by preventing ROS generation produced by Fenton reaction. In addition to its function closely related to iron homeostasis, FHC is involved in a multitude of biochemical routes as well as in different pathways leading to neoplastic transformation, apoptosis, chemoresistance, oncomiRNAs regulation and EMT process.

In 2009, Zhang et al. showed how in AML-12 and A549 cells there was a dramatic decrease in the FHC expression after TGF-β1 stimulation. This reduction brought to an increase in intracellular Labile Iron Pool (LIP) and, in turn, to an increase in ROS production. These findings demonstrated that FHC, as an important factor in iron homeostasis, can lead tumoral cells to undergo EMT through TGF-β1 induction [1]. Eight years later, a Swedish group coordinated by Sioutas A., showed that the loss of FHC after TGF- β1 stimulation of the same cells, was due to an oxidative damage of FHC resulted in its increased degradation inside lysosomes. Moreover, the combined treatment of TGF- β1 and TNF- α, resulted in increased expression of the EMT markers ZO-1, Vimentin and N-cadherin. Overall the above data underly the potential capacity of FHC in modulating the EMT phenomenon mediated by oxidative reactions. Intriguingly, the treatment of these cells with the antioxidant molecule N-Acetyl-L-Cysteine (NAC) was able to prevent the TGF-β1-mediated loss of FHC and thus also EMT process [2].

Lobello et al. found that upon the stable and transient knock-down of FHC in SKOV3 cells, some well-known EMT markers, ZEB1 and Vimentin, were strongly increased at both mRNA and protein levels accompanied by a decrease in the main epithelial marker E-cadherin expression [3].

One year later, in 2017, it was found that knock-down of FHC allowed MCF-7 and H460 cells to acquire a mesenchymal phenotype, along with increased migratory and proliferative

Department of experimental and clinical medicine, Magna Graecia University, Catanzaro, Italy

**Author for correspondence: ilenia.aversa@unicz.it*

capacity. Noteworthily, MCF-7-silenced cells showed a dramatic morphological change that led the cells passing from a cobblestone-like morphology to a spindle-shaped and fusiform features. At these regards the authors proposed that these phenomena were attributed either to an increase in cytosolic ROS production or to a dysregulation in CXCL12/CXCR4 axis. Supporting the oxidative stress involvement, both NAC treatment and transiently FHC-reconstitution can revert EMT markers and proliferative capacity [4].

Taken all together these findings highlight that many of the FHC activities in tumour progression, and in EMT, are directly linked to the maintenance of iron homeostasis.

Iron is an essential element for physiological cellular functions: as cofactor for key enzymes, it is involved in DNA duplication and repair thus representing an important element for cell replication, metabolism and growth; but iron can also be toxic, indeed, iron overload induces free radical formation, lipid peroxidation, DNA and protein damages, leading to carcinogenesis or ferroptosis. For all these reasons, iron is considered a highly interesting element in cancer research so that an altered iron homeostasis could be, to some extent, a hallmark of cancer and FHC, as controller of iron levels, play a fundamental role in its homeostasis.

Many studies are still needed to better understand the molecular mechanism underlying the FHC power of action, but surely there is a growing body of evidences that iron metabolism and its controllers, as FHC, play a key role in cancer biology.

References

1. Zhang KH, Tian HY, Gao X, *et al.* Ferritin heavy chain-mediated iron homeostasis and subsequent increased reactive oxygen species production are essential for epithelial-mesenchymal transition. *Cancer. Res.* 69(13), 5340-5348 (2009).
2. Sioutas A, Vainikka LK, Kentson M, *et al.* Oxidant-induced autophagy and ferritin degradation contribute to epithelial-mesenchymal transition through lysosomal iron. *J. Inflamm. Res.* 10, 29-39 (2017).
3. Lobello N, Biamonte F, Pisanu ME, *et al.* Ferritin heavy chain is a negative regulator of ovarian cancer stem cell expansion and epithelial to mesenchymal transition. *Oncotarget.* 7(38), 62019-62033 (2016).
4. Aversa I, Zolea F, Ieranò C, *et al.* Epithelial-to-mesenchymal transition in FHC-silenced cells: the role of CXCR4/CXCL12 axis. *J. Exp. Clin. Cancer. Res.* 36(1), 104 (2017).