Differentiation 94 (2017) 21–26

Contents lists available at ScienceDirect

Differentiation

journal homepage: www.elsevier.com/locate/diff

Review article

Focus on the role of Caveolin and Cavin protein families in liposarcoma

Silvia Codenotti[1], Marika Vezzoli[1], Eugenio Monti, Alessandro Fanzani*

Department of Molecular and Translational Medicine, University of Brescia, Viale Europa 11, 25123 Brescia, Italy

ARTICLE INFO

Keywords:
Liposarcoma
Caveolae
Caveolins
Cavins
Metabolism
Adipocytes

ABSTRACT

The identification of ancillary biomarkers useful to improve diagnosis is a major challenge for adipocytic liposarcoma (LPS), the most common type among soft tissue sarcomas affecting adulthood. Recent findings have reported the expression of some proteins belonging to Caveolin and Cavin families as a critical hallmark distinctive of the least aggressive, well-differentiated LPS tumors. These proteins are involved in the biogenesis, morphology and function of caveolae, minute bulb-shaped domains of the plasma membrane that play a crucial role in the adipose tissue by controlling hormone-dependent uptake of nutrients and contributing to the maintenance of tissue integrity. In light of this, in this paper we covered different topics, including metabolism, hypoxia and cell mechanoprotection, to outline the rationale for considering a deeper investigation of Caveolin and Cavin protein members in LPS neoplasms as an opportunity to identify pro-differentiating mechanisms that could counteract tumor growth.

1. Liposarcoma

Soft Tissue Sarcomas (STS) represent about 1% of all adult cancers and approximately 20% of childhood and adolescence tumors, according to the latest World Health Organization classification (Fletcher et al., 2013). These rare but aggressive neoplasms can originate in virtually all body tissues from mesenchymal cell precursors committed to differentiate along a number of tissue lineages, such as adipose, muscle, fibrous and cartilage. The histological heterogeneity of STS mirrors the complex molecular landscape of their genetic aberrations. The molecular classification currently recognizes two main groups: genetically complex, having a high mutational burden and a complex karyotype, or genetically simple, bearing a specific recurrent translocation, mutation, or amplification (Bridge, 2014; Dancsok et al., 2016). Over the past 10 years, the availability of new techniques, such as the whole genome sequencing, along with the development of engineered mouse and zebrafish models were useful to gain further insights into the genetic signatures and molecular mechanisms underlying sarcomagenesis (Dodd et al., 2010).

In adult age, the most common STS are undifferentiated pleomorphic sarcoma (formerly known as malignant fibrous histiocytoma), leiomyosarcoma and liposarcoma (LPS), the latter accounting for about 20% of all STS. LPS tumors exhibit morphological features and biochemical traits typically recognized in fat cells at different stages of differentiation (Matushansky et al., 2008). Four main categories are recognized, namely well-differentiated, dedifferentiated, myxoid and pleomorphic, arising in specific body districts with a prevalence on the extremity (24%) and retroperitoneum (45%) (Dei Tos, 2014). Depending on different parameters, including the specific subtype, location of primary tumor and especially the presence of dedifferentiated cell components (this being associated with an unfavorable outcome), the life expectancy of LPS patients can be highly variable (Dalal et al., 2006). The most common clinically observed LPS histologies are well-differentiated and dedifferentiated (Crago and Singer, 2011), both sharing a selective amplification in the 12q13–15 region causative of MDM2 and CDK4 overexpression (Bill et al., 2016). Well-differentiated LPS (also known as atypical lipomatous tumor) is categorized as a low-grade tumor, despite showing a high rate of local recurrence (Crago and Singer, 2011). In contrast, dedifferentiated LPS is classified as an intermediate-to high-grade lesion, having 30% 5-year overall survival compared with 90% for well-differentiated LPS (Ghadimi et al., 2011; Thway et al., 2016). Dedifferentiated LPS can present as a primary lesion (90% of cases) or as recurrence of a prior well-differentiated LPS (10% of cases, i.e., secondary dedifferentiated LPS) (Fabre-Guillevin et al., 2006; Lahat et al., 2008) undertaking a dedifferentiation process mediated by epigenetic mechanisms (Keung et al., 2015; Renner et al., 2013; Shimoji et al., 2004; Taylor et al., 2011; Ugras et al., 2011; Zhang et al., 2012). The myxoid and pleomorphic variants, frequently affecting the pediatric age group, have a striking predilection for the limbs and show a tendency to metastasize in about 30% of patients (Alaggio et al., 2009; Dadone et al., 2015; Huh et al., 2011; Stanelle et al., 2012). In most cases,

* Corresponding author.
E-mail address: alessandro.fanzani@unibs.it (A. Fanzani).
[1] These authors contributed equally to this paper.

http://dx.doi.org/10.1016/j.diff.2016.11.007
Received 5 September 2016; Received in revised form 15 November 2016; Accepted 22 November 2016
Available online 08 December 2016

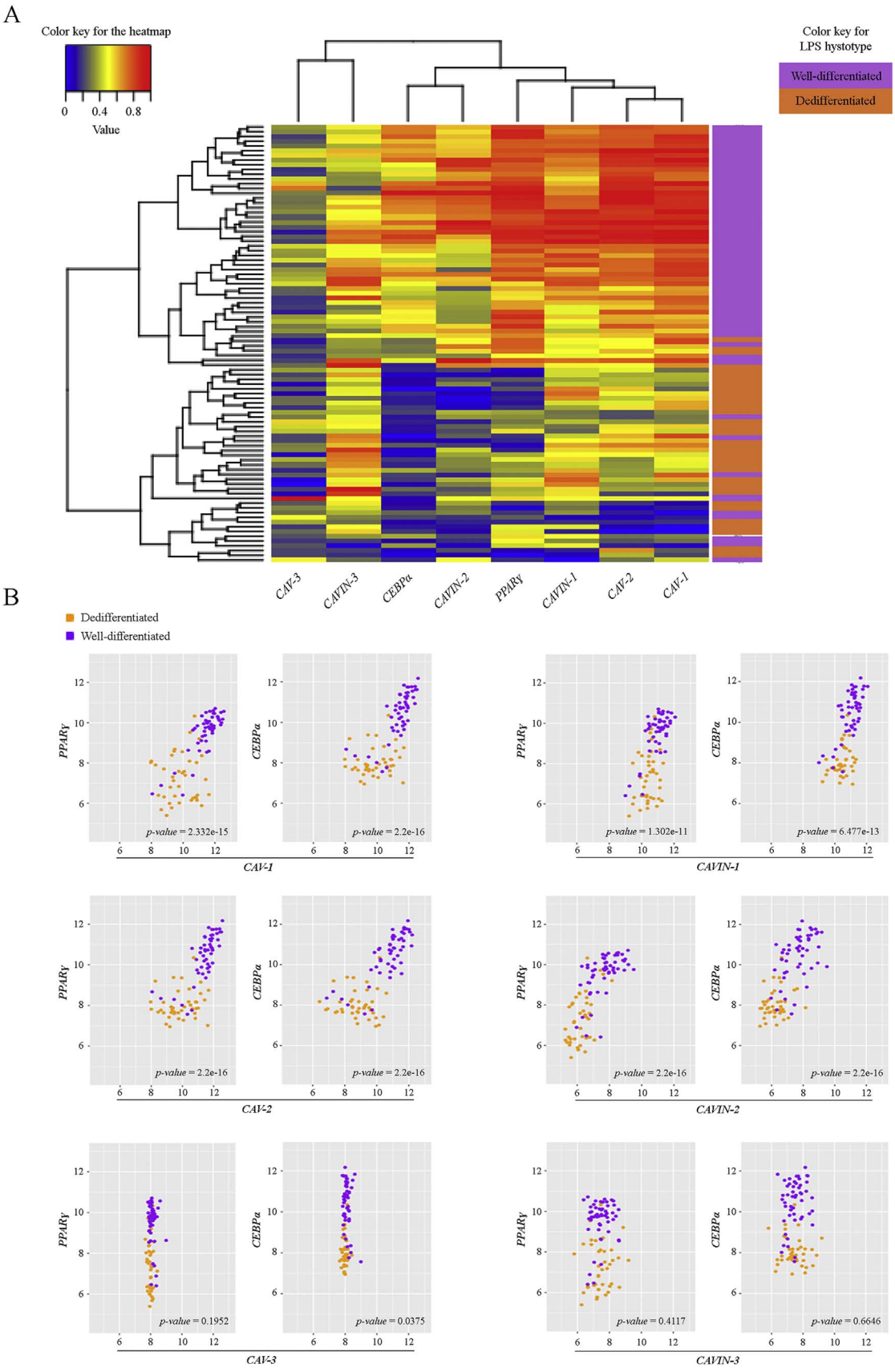

Fig. 1. *In silico* analysis of Caveolins and Cavins expression in well-differentiated versus dedifferentiated LPS. A) Heat map analysis showing the expression levels of the indicated genes relative to well-differentiated (n=52) and dedifferentiated (n=40) tumors. Low values of the gene expression (near to 0) are colored in blue, mean values (near to 0.5) are colored in yellow while high values (near to 1) are represented in red. B) The correlation between each gene and *PPARγ* or *CEBPα* in LPS tumors was computed using the Pearson correlation coefficient ρ (with corresponding *p-values* < 0.05). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)