ANXA1 is involved in the acquisition of an aggressive phenotype in prostate cancer cells with acquired resistance to zoledronic acid

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The use of zoledronic acid (ZA) in the treatment of bone metastases from prostate cancer (PCa) patients and its anti-tumoral activity emphasize the appearance of resistance against this drug. In this study, we have characterized the role of ANXA1 in the acquisition and maintenance of stem-like/aggressive features in PCa cells comparing ZA-resistant DU145R80 with their parental DU145 cells. ANXA1 is over-expressed in DU145R80 cells and protein down-regulation abolishes their resistance to ZA. Moreover, ANXA1 induces DU145 and DU145R80 invasiveness acting through formyl peptide receptors (FPRs). Also, ANXA1 knockdown is able to revert DU145R80 aggressive phenotype by inhibiting the epithelial to mesenchymal transition (EMT) and reducing Focal Adhesion Kinase (FAK) and metalloproteases (MMP)-2/9 expression. DU145R80 show a cancer stem cell (CSC)-like signature with a high expression of CSC markers including CD44, CD133, NANOG, Snail, Oct4 and ALDH1A7 and CSC-related genes as STAT3. Interestingly, ANXA1 knockdown induces DU145R80 cells to revert from a putative prostate CSC to a more differentiated phenotype resembling DU145 PCa cell signature. Similar results are obtained concerning some drug resistance-related genes such as ATP Binding Cassette G2 (ABCG2) and Lung Resistant Protein (LRP). Our study provides new insights on the role of ANXA1 protein in PCa onset and progression.