O18 A novel calcium-mediated epithelial-to-mesenchymal transition pathway controlled by lipids: an opportunity for prostate cancer adjuvant therapy

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Introduction & Objectives: Fatty acid (FA) content of periprostatic adipose tissue (PPAT) has been associated with prostate cancer (PCa) aggressiveness, and indolent tumors are characterized by high levels of linoleic and eicosapentaenoic acids. Moreover, cancer progression has been linked to both the epithelial-to-mesenchymal transition (EMT) process and a *deregulated calcium signaling.* Therefore, we hypothesize that FA may interfere with these mechanisms driving disease aggressiveness.

Materials & Methods: Samples from 48 pT3 PCa patients were analyzed by immunohistochemistry on tissue microarrays. In vitro and ex vivo experiments were conducted using PCa cell lines and organotypic culture of human PCa slices. Effects of FA were measured by qPCR, immunohistochemistry, migration assays, and cytosolic Ca^{2+} measurements.

Results: Markers associated with cancer aggressiveness such as the EMT transcription factor Zeb1 and the Ca^{2+}-activated K+ channel SK3, were upregulated in cancer cells infiltrating PPAT compared to intraprostatic cells. However, this increase was not observed in 30% of cases, suggesting that in these patients PPAT could contain factors able to reverse EMT. Accordingly, we demonstrated that linoleic and eicosapentaenoic acids dramatically reduced the effects of EMT inducers such as TGFb and hypoxia. These FA exert anticancer effects through a Ca^{2+}-dependent pathway involving Zeb1 and the SK3 channel. Functional assays in human PCa slices demonstrated the potential of these lipids to normalize the Ca^{2+} entry in cancer cells.

Conclusions: Lipids influence PCa progression by modulating Ca^{2+}-dependent EMT. These findings, strengthened by a functional approach using human tumors, may allow the use of FA as adjuvant for PCa treatments.