Protein Arginine Deiminase enzymes which citrullinate epitopes for MHC II presentation are independent predictors of survival in colorectal cancer

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Introduction
- Protein Arginine Deiminases (PADs) are a family of Ca2+ dependent enzymes that are activated under cellular stress within the tumor environment.
- PADs citrullinate protein substrates to generate modified self-antigens.
- Presentation of citrullinated peptides on MHC class II stimulate CD4 T cells to mediate potent anti-tumor immunity.
- In this study we focus on the role of the PadI2 and PadI4 members in colorectal cancer.

Methods
- Using a colorectal TMA and immunohistochemistry, expression of PadI2 and PadI4 was assessed.
- Tumors were classified as a H-Score and assessed for strong, moderate, weak and negative PadI2 and PadI4 expression.
- All statistical analysis was performed using SPSS21 software.
- A study cohort (n=462) of tumor samples were analysed to determine their association with clinicopathological variables, other tumor markers and the effect on survival.

Padi2 and Padi4 Expression in Colorectal tissue

Correlation of Padi2 and Padi4 Expression with other markers

Univariate analysis indicated that Pad2 did not show any significant association with the cell cycle/survival regulators p53, BCL2, nuclear STAT1 and the immune markers MHC class I and II involved in immunosurveillance.

No significant correlation was observed with the cytokeratin 18, 19, the glycolytic enzymes Alpha Enolase (ENO-1) and the nuclear antigen Ki67 as they are citrullinated by Pad enzymes.

Conclusion

Patients with tumor that expresses either PadI2 or Cytoplasmic PadI4 have a better prognosis in colorectal cancer. After multivariate analysis both remained independent prognostic factors.

Results are consistent with the hypothesis that Pads are activated within stressed tumor cells leading to generation and presentation of citrullinated epitopes that are recognised by T cells and killed. Tumor growth is controlled by T cells and the patient has a better prognosis.