Abstract Number: 4835
Presentation Title: Involvement of human kallikreins in a proteolytic cascade pathway in the prostate
Presentation Start/End Time: Tuesday, Apr 19, 2005, 1:00 PM - 5:00 PM
Board Number: Board #16
Author Block: Iacovos P. Michael, Georgios Pampalakis, Stephen D. Mikolajczyk, Johan Malm, Georgia Sotiropoulou, Eleftherios P. Diamandis. Department of Laboratory Medicine and Pathobiology, University of Toronto & Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada, Department of Pharmacy, School of Health Sciences, University of Patras, Rion, Greece, Beckman Coulter Inc., San Diego, CA, Section for Clinical Chemistry, Department of Laboratory Medicine, Lund University, University Hospital Malmö, Malmö, Sweden

Human kallikreins (hKs) are a family of 15 serine proteases, which are secreted as proenzymes and activated by proteolytic cleavage of the propeptide. Previous studies have shown that hK2, 3, 4, 5, 8, 11, 14 and 15 are expressed in the prostate and present in the seminal plasma. Experimental evidence suggests that crosstalk between hKs may exist in the prostate (e.g. hK2, 4 and 15 can activate prohK3) and that these enzymes may have role in normal prostate physiology and prostate cancer progression. Several hKs appear to be promising serum biomarkers for prostate cancer while hK3/PSA (prostate specific antigen) is an established biomarker presently used for prostate cancer diagnosis and monitoring.

In this study we examine the potential involvement of hKs in a proteolytic cascade pathway in the prostate, focusing primarily on the role of human kallikrein 5 (hK5; encoded by the KLK5 gene). hK5 is expressed in various tissues of the male reproductive system (i.e. testis, epididymis, seminal vesicles, prostate) and is present in seminal plasma.

In order to determine if hK5 could activate other prohKs, we first examined its ability to cleave synthetic heptapeptides containing prohK activation sites. We found that hK5 cleaves prohK2 and prohK3 heptapeptides most efficiently. We further verified that hK5 can activate recombinant prohK3 and prohK2, in vitro and, subsequently, inactivate these two enzymes by cleavage of hK3 at the internal peptide bonds R85-F86 and K182-S183 and of hK2 at R145-F146. These hK3 fragments are known to exist in seminal plasma but we also detected them in prostate tissue extracts, indicating that the proteolytic cascade pathway is initiated in the prostate rather than in seminal plasma.

Serine proteinase inhibitors (serpins) and Zn$^{2+}$ can inhibit hK2 and hK3 activities in prostate tissue and seminal plasma. We found that Zn$^{2+}$ and the serpins antithrombin, a$_2$-antiplasmin and protein C inhibitor are also able to efficiently inhibit hK5 activity. Finally, we showed that hK5 is able to digest semenogelins (Sgs) I and II (putative substrates for hK2 and hK3) and fibronectin; suggesting that hK5 may also have a role in seminal clot liquefaction.

The results of this study point to the existence of a kallikrein enzyme proteolytic cascade pathway in the prostate. Under physiological conditions, hKs are activated in the prostate but are "silenced" by an allosteric reversible inhibition by Zn$^{2+}$. After ejaculation hKs are reactivated, due to Zn$^{2+}$ redistribution to Sgs, and liquefy the seminal clot, which leads to the release of motile spermatozoa. On the other hand, during metastatic prostate cancer, it is known that Zn$^{2+}$ levels are decreased in prostate. This may result in increased hK activity and enhanced degradation of extracellular matrix components (e.g. by hK5) and insulin-like growth factor binding proteins (e.g. by hK2 and hK3). These events may enhance the progression and metastasis of prostate cancer.