

Kallikrein in Human Saliva

Occasionally I ponder the process of product development, more specifically why some ideas don't even make it to the point of demonstrating failure while other product development processes go through so many Gantt charts and leadership changes at the top of the organization and eventually need to be taken out into the back alley and beaten with a rubber mallet. Other than job security for the project evangelists, I can find no reason for the latter; for the former, dullness (e.g. lacking the excitement of recombinant DNA or microRNAs), lack of intellectual property protection, failure fit into an existing corporate framework, and lack of a satisfactory evangelist). This is a story of a research observation which fits into the latter category.

Some thirty-plus years ago I was a faculty member at the University of North Carolina at Chapel Hill, a faculty member from the University of North Carolina at Greensboro contacted me regarding xerostomia secondary to cancer chemotherapy. I had given a lecture on saliva to one of her neighbors who was in a graduate dental program. I contacted a colleague in the School of Dentistry and we looked at various factors such as lysozyme and salivary IgA. At the same time I was doing some work in collaboration with a colleague on the processing of EGF in rat submaxillary gland. Assay of glandular kallikrein was part of this project. We had run out of ideas on the xerostomia project and one afternoon I decided to assay the saliva samples (control and cancer chemotherapy patients) for glandular kallikrein. To our great surprise, glandular kallikrein activity was markedly elevated in mixed saliva samples from patients with solid tumors distant from the oral cavity. These patients had breast cancer, colon cancer, and other tumors; no tumors in the oral cavity or salivary glands. We published several more papers (2- 4) to convince ourselves that the observation was real. In one unpublished study with a small number of colon cancer patients, we observed that salivary kallikrein was a prognostic biomarker in that levels of salivary kallikrein decreased in patients who were improving and increasing patients who were getting worse. A couple of factors frustrated further and the project was dropped. In the intervening years, there has been marked increase in work on glandular kallikrein and cancer (5-7).

I periodically try to "sell" this project but have no takers. I use the term "sell" advisedly as there is nothing but an observation. Perhaps in the current climate, there might have been interest in securing intellectual property but thirty years ago was a different landscape in academia. So, no intellectual property. Second, while the concept would be use in large-population screening, it is not clear as to where the data would lead in terms of next steps. Screening is useful if there is a pathway to use the information. Since the elevation of salivary kallikrein is not tumor-specific, next steps are not clear. If my comments in the second step seem rambling, it is a reflection of the third issue which is a total lack of understanding of the mechanism. We never got far in this aspect but are reasonably confident it is not derived from blood; levels of kallikrein high enough to pass from plasma into saliva (most likely through gingival crevicular fluid) should, in principle, result in marked hypotension as seen in carcinoid syndrome (8) . While much needs to be understood, salivary kallikrein is as promising a biomarker as most listed in my recent book (9).

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