

In Defense of the Oral Cavity: The Protective Role of the Salivary Secretions

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Abstract

Saliva performs important protective roles in the oral cavity. Debate in the 1970s over the “specific” or “non-specific” action of salivary components has given way to current attempts to identify the full complement of all proteins in saliva that are now considered to act in concert. At the same time, more fundamental protective qualities of saliva*water and pH control*are receiving less attention. These qualities may be among saliva’s most important. This presentation will review recent advances in the genomics and proteomics of saliva, as well as saliva’s roles in tissue coating, alimentation, and regulation of the oral flora. (Pediatr Dent 2006;28:110-117)

KEYWORDS: SALIVA, MUCINS, SALIVARY PROTEINS, CARIES, STATHERIN

Introduction

This is the third version of “In defense of the oral cavity.” The original was written by Mandel¹ and remains the definitive review of work conducted during the 1960s and 1970s related to the protective roles of saliva. The second version was published in 1995 and focused largely on the role played by salivary mucins.² In this concise review, I will attempt to place recent findings related to major salivary functions into a historical context, highlight several salivary functions that have received less attention than others, and point out some of the most significant remaining gaps in our knowledge. The intent is not to provide an exhaustive bibliography, but rather to compliment several recent reviews³⁻⁷ and to cite selected recent references, providing the reader with the option of referring to the references cited therein.

The secret is in the whole

The 1970s were marked by a passionate scientific debate that raged as to whether salivary components acted in “specific” or “non-specific” ways.⁸⁻¹⁰ The “purists” won out and extreme focus was placed on identifying and purifying the individual components of human saliva to homogeneity using combinations of biochemical separation techniques. Each month a new salivary protein was identified and “paternity” determined, initially by apparent size and chemical composition and later by either direct determination of amino acid sequence using Edman degradation or via con-

ceptual translation of cDNA sequence (see below). Using these criteria, most salivary proteins were assigned to 1 of several salivary protein families (Table 1). Soon, the field was awash in many “rich” (but curiously not impoverished) salivary protein families.

Armed with purified molecules and an array of clever *in vitro* assays, oral biologists began to make first predictions on the role played by each individual molecule. These pioneering efforts were summarized at a workshop on Saliva and Dental Caries, sponsored by the (then) National Institutes of Dental Research.¹¹ This approach dominated the field for the next 2 decades, fueled largely by the widespread adoption of molecular cloning techniques. Unless your protein was “cloned”, no one seemed to believe your result; an expressed (cDNA) clone was seen as the ultimate rite of purification and took on an almost religious fervor.

All the while, a small group of oral biologists held fast to the view that the secret of saliva was “in the whole.” Using the functional assays employed by the “purists”, they began to classify groups of proteins by their (in vitro) functions. Proteins were termed:

- 1) adhesions, if they supported bacterial attachment to hydroxyapatite;¹²
- 2) agglutinins,^{12, 13} if they could clump bacteria or viruses (lysozyme¹⁴, mucins² and salivary agglutinin, subsequently identified as lung scavenger receptor cysteine-rich protein gp-340);^{15,16}
- 3) antimicrobial, if they could slow or put a stop to bacterial growth (histatins¹⁷, lactoferrin, peroxidase, lysozyme,¹⁸ among others);
- 4) pH modulating, if they could raise plaque pH.¹⁹

Those who believed in the value of the whole quietly pointed out that no patients, save for a rare number of

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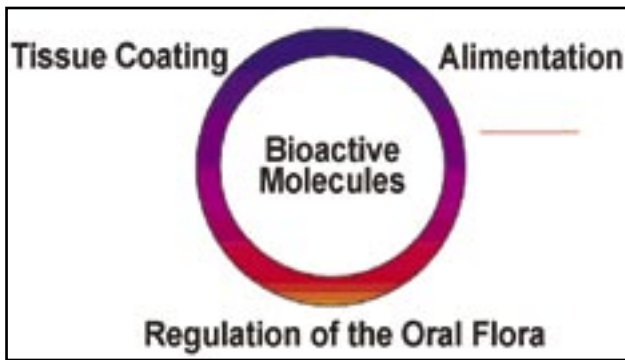


Figure 1. The functions of saliva.



Figure 2. Presentation of a “dry tongue” in a patient with salivary hypofunction.

infants lacking secretory IgA, had been identified with single- protein deficiencies of saliva associated with any disease.²⁰ Rather, the only salivary-associated pathologies were observed in those patients with catastrophic loss of all salivary function (eg, treated with radiation for head and neck cancers),²¹ Sjögren's syndrome,²² or congenital absence of salivary glands.²³ Examples of redundant functionality among salivary components became increasingly apparent.²⁴ Cautiously, the view that the salivary sum was greater than the individual component parts^{25, 26, 27, 13} began to be adopted. Indeed, salivary function began to be likened to a symphony – with the component parts working together “in concert.”

Recent advances in protein identification methods and bioinformatics have re-energized the goal of identifying the full complement of all proteins in saliva. The general discipline, now termed proteomics, has its antecedents in the pioneering efforts of those early explorers who

identified salivary components utilizing all forms of electrophoresis (paper²⁸, disc gel^{29, 30, 31}, and two-dimensional gels^{32, 33}). Work from our laboratory employed Edman degradation to identify low molecular peptides in human saliva.^{34, 35} Subsequently, a number of preliminary reports of the salivary proteome have appeared exploiting advances in mass spectrometry.³⁶⁻⁴¹ No doubt this approach will add to the already large number of salivary proteins that have been previously identified as having biological activities.⁴² Other approaches are being employed to delineate protein-protein complexes (“heterotypic complexes”²⁵) that occur in saliva.^{43 - 48}

The exciting advances of genomics and proteomics has had the unfortunate effect of luring attention away from some of the more fundamental, and perhaps more important, protective qualities of the salivary secretions – water and pH control. Indeed, when Englander et al⁴⁹ studied the role of saliva on plaque pH in caries-active subjects following a sucrose rinse, they found that when saliva access was prevented, the pH drop was greater. The observation can be attributed to the combination of reduced sugar/acid clearance and diminished neutralization of the acids formed.^{50, 51} The latter relates to buffering capacity contributed largely by bicarbonate in stimulated secretions and peptides and amino acids in “resting” or un-stimulated saliva.⁵² In studies carried out over 6 decades, it has been shown repeatedly that in the presence of saliva, dental plaque derived from “caries free” individuals (ie, those who have never experienced dental decay) exhibits 1) a higher fasting pH, 2) a less rapid and severe pH fall when subjected to a sucrose challenge, and 3) a more rapid return to resting pH levels than plaque derived from individuals who have experienced caries. If salivary contact with the plaque is blocked experimentally, the difference in plaque acidogenesis is lost.⁵³ Several studies have demonstrated differences in the levels of basic amino acids

Table 1: Salivary Protein Families

Salivary Protein Family	References
Acidic proline-rich proteins	Inzitari et al 2005 ⁹⁴
Amylases	Ramasubbu et al 1996 ⁹⁵ ; Hirtz et al 2005
Basic proline-rich proteins	Ayad et al 2000 ³⁵ ; Beeley 2001 ⁹⁷ ; Messana et al 2004 ⁹⁸
Carbonic anhydrases V8, VI (gustin)	Fujikawa-Adachi et al 1999 ⁹⁹ ; Karhumaa et al 2001 ¹⁰⁰
Cystatins	Dickinsen 2002 ¹⁰¹ ; Lupi et al 2003 ¹⁰²
Histatins	Kavanagh and Dowd 2004 ¹⁷ ; Ahmad et al 2004 ¹⁰³ ; Castagnola et al 2004 ¹⁰⁴
Lactoferrin	Tenovuo 2002 ¹⁸ ; Rudney 1989 ¹⁰⁵
Lysozyme	Pollock 1976 ¹⁴
Mucins	Tabak 1995 ² ; Offner and Troxler 2000 ⁵⁶ ; Nielsen et al 1997 ⁵⁸ ; Liu et al 1998 ⁵⁹ ; Piludu et al 2003 ¹⁰⁶ ; Chen et al 2004 ⁶⁰ ; Culp et al 2004 ¹⁰⁷
Salivary peroxidase	Mansson-Rahemtulla et al 1988 ¹⁰⁸
Statherins	Li et al 2004 ⁷⁵

and peptides when saliva derived from caries free and “caries susceptible” (ie, individuals who have experienced dental decay) subjects are compared.^{34,35} However, these observations have not been followed up and the functional role of these basic amino acids and peptides remains speculative.

A current view of salivary function is depicted in Figure 1. The functional elements are portrayed as a continuous circle to emphasize the continuity, overlap, and synergy among different components and functions.

Saliva is good for you

Bertram²² noted that the first written description of dry mouth as a patient’s chief complaint was published in 1868.³⁴ Among the features described were “dryness and soreness of the tongue” (Figure 2), a “mucous membrane (that) is perfectly dry like pink satin” (Figure 3), and “the teeth are all gone” (Figure 4). Also captured was the fact that the “patient sips cold tea to relieve the feeling of dryness and the clinging together of gums, cheeks, and tongue.” It is through experiments of nature such as this that we have gained a true appreciation of salivary function. Clearly, secretions play a significant tissue coating function (Figure 1). The physical properties of the saliva endow it with the ability to lubricate and hydrate the soft tissues of the mouth (Figures 2 and 3). In large part these attributes, termed rheological properties (high elasticity, low solubility, high adhesiveness), are derived from mucin-glycoprotein content. Based on electrophoretic mobility, 2 species were noted and purified from human saliva: mucin-glycoprotein 1 (MG1) and mucin-glycoprotein 2 (MG2).^{2,55,56} MG2 is the gene product of MUC7⁵⁷ whereas MG1 appears to be a mixture of the gene products MUC5B,⁵⁸ MUC4,⁵⁹ and MUC19.⁶⁰ Each polypeptide backbone is decorated with an almost bewildering array of carbohydrate side-chains, termed oligosaccharides. These oligosaccharides impart much of the unique physical properties of this class of macromolecule.

Less evident from these images is the role of saliva in alimentation (Figure 1), including the formation and swallowing of the food bolus. Some data suggest that in persons with compromised salivary flow, their choices of food changes, thereby putting their nutrition at risk.⁶¹ A recent study using a mouse model in which salivary flow is markedly reduced through ablation of the water channel (aquaporin 5) demonstrated that mice fed hard food pellets consumed less, leading to a reduced growth rate; when fed a liquid diet, no change in growth was observed.⁶² The integrity of the food bolus is maintained by the adhesiveness of the salivary secretions. While chewing is a voluntary response, available evidence indicates that the number of chews is optimized by food type – too few and the food bolus will not stick together, too many and it may fall apart.⁶³ What remains unexplored is whether differences in the intrinsic qualities of saliva vary among persons who display different eating habits. For example, if one’s saliva allows for the formation of a food bolus with minimal mastication, does that dampen satiation leading to greater



Figure 3. Presentation of a “dry mucosa” in a patient with salivary hypofunction.



Figure 4. Rampant decay in a patient with salivary hypofunction.

food intake? Given the epidemic of obesity in the nation,⁶⁴ this may be an area ripe for study.

The dramatic buildup of dental plaque observed (Figure 4) in hyposalivatory patients underscores the remarkable combination of antimicrobial activities and microbial disposal afforded by the salivary secretions, leading to the regulation of the oral flora (Figure 1). While we have enjoyed huge success in cataloguing many *in vitro* activities of salivary components, there is still a significant gap in demonstrating function *in vivo*. For example, in contrast to the considerable progress that has been made in delineating the functional roles of various ion channels and transporters in regulating salivary fluid secretion⁶⁵ through the use of gene ablation studies in mice, few such studies have been employed to date to evaluate the functional roles of specific salivary proteins. A recent paper by Culp and colleagues underscores this.⁶⁶ In their work, they studied caries in mice in which the water channel (aquaporin 5) was genetically ablated. Previous work had shown that this results in a 60%-65% reduction in the total volume of cholinergically stimulated saliva.^{62,67} A significant increase in caries susceptibility, primarily on the buccal and sulcal surfaces was observed. However, the caries observed was nowhere near the catastrophic level observed in experimentally desalivated animals, underscoring the protective effect afforded by the

remaining organic components of the salivary secretion.⁶⁶ In addition, there have been very few studies that have identified null (or dysfunctional) mutations in salivary proteins that associate with clear phenotypes. With the continuing refinement of the human HapMap,⁶⁸ genome-wide scans on patient populations with defined phenotypes will become more feasible to perform at lower cost.

The observed rampant decay illustrates how effective salivary secretions are at eliminating and/or buffering microbial acids and prompting remineralization of the tooth. A number of salivary molecules display this property, but a tyrosine-rich acidic peptide, subsequently named “statherin” (from the Greek, *statheropio*, “to stabilize”) was the first to be well characterized.⁶⁹⁻⁷⁷

Just as physicians are not likely to look proximal to the tonsils, dentists rarely peer beyond the soft palate. However, there is emerging literature suggesting saliva’s protective effects extend distal to the oral cavity. Helm et al⁷⁷ first reported that saliva could play a significant role in neutralizing esophageal acid. A series of salivary flow rate studies have been conducted in response to esophageal acid challenge without uncovering a clear relationship between salivary flow and esophagitis.⁷⁸ However, none of these studies has considered variation in the buffering capacity of saliva.⁷⁹ It is well established that bicarbonate concentration increases with flow rate.⁸⁰ At rest (“unstimulated” flow), non-bicarbonate buffering capacity is thought to derive from free basic amino acids and low molecular weight peptides containing histidine, lysine, and arginine.^{28, 34, 35, 52} Two recent provocative papers have suggested that saliva could have a deleterious effect in the etiology of oropharyngeal and upper gastrointestinal cancers by serving as a free radical source.^{81, 82}

A little goes a long way

Ship et al⁸³ pointed out the wide natural variation observed for stimulated flow rates of the major salivary glands in healthy adults. A major conceptual advance in our understanding of salivary function was made by Dawes and colleagues with the demonstration that saliva coats the hard and soft tissues of the mouth as a “thin-film” that has varied velocities in different locations of the mouth.^{84, 85} When salivary flow is stimulated, the velocity of the thin film increases 1 or 2 to 40 times depending on the location. The capacity of saliva to form a “thin film” relates to the various rheological properties of mucin-glycoproteins described earlier.

Saliva in children

Relatively few studies have been conducted to ascertain the ontogeny of salivary protein expression in humans. Studies conducted over the past 5 decades have documented that at birth, IgA is not detectable in saliva, but levels begin to rise rapidly by 4-8 weeks of age. Initially the IgA1 subclass dominates in concentration, but over 20 weeks the proportion of IgA2 (lacking a hinge region that is susceptible to degradation by certain organisms that elaborate the IgA1 protease) increases to adult levels.^{86, 87}

Non-immunoglobulin anti-microbial factors, such as lysozyme and salivary peroxidase (now considered part of the innate immune system), reach adult levels in early childhood.⁸⁸ Ruhl et al⁸⁹ demonstrated that MUC5B (part of mucin MG1) was remarkably constant in expression level from ages 1 month through 1 year. In contrast, the levels of MUC7 (mucin MG2), which is initially greater than MUC5B, steadily decrease to such a degree that by 1 year MUC5B dominates. Alpha-amylase levels rise steadily throughout the first year of life. Tao et al⁹⁰ recently reported on the expression of several antimicrobial peptides, including beta-defensin-3, cathelicidin LL37, and alpha-defensins 1, 2, and 3. Concentrations of these peptides were variable among the subjects studied, but HNP1 through 3 were similar to adult levels. These workers noted that the concentration of HNP1-3 is significantly greater in cavity-free children than those who have experienced dental decay.

Salivary film thickness was examined in 5-year-old children by Watanabe and Dawes who reported it to be similar to that observed in adults.⁹¹ This suggests that the basic rheological properties (“Tissue Coating”- Figure 1) of the saliva is similar in children and adults.

Clearly, much more work is needed to understand the development of the innate immune system of the oral cavity. Compelling evidence suggests that the acquisition of the commensal flora plays a key role in the gastrointestinal track,^{92, 93} but in the mouth all bacteria, commensal or not, are coated with saliva. The extent to which the salivary coat plays a role is unexplored. The accessibility of the oral cavity makes it an ideal model to study this and other related questions.

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Abstract of the Scientific Literature



Canceling General Anesthesia Because of an Upper Respiratory Infection

One of the most controversial issues in pediatric anesthesia concerns the decision to proceed with anesthesia and surgery for the child who presents with an upper respiratory tract infection (URI). In the past, doctrine dictated that children with URIs have their surgery postponed until the child is symptom free. This practice was based on the empirically supported premise that anesthesia increased the risk of serious complications and complicated the child's postoperative course. Although recent clinical data confirm that some children with URIs are at increased risk of perioperative complications, these complications can, for the most part, be anticipated, recognized, and treated. Although the child with a URI still presents a challenge, anesthesiologists are now in a better position to make informed decisions regarding the assessment and management of these children. Consequently, blanket cancellation has now become a thing of the past.

Comments: If your anesthesiologist continues to insist on canceling patients with URIs whom you have booked for dental treatment under general anesthesia, consider giving them a copy of this paper and advising them to "get up to date." Often, dental surgery is wrongly considered elective. Children who are unable eat or sleep properly because of dental pain hardly require elective surgery. Their surgery is rightly classified as urgent. Cancellation because of a URI in an otherwise healthy child will hopefully become a thing of the past. **ARM**

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51 references