



## 'Third Space' Perspective on Redefining Oral Pathology: Hypothetical Considerations

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### ABSTRACT

Recent molecular analysis has shown the evidences which claims human interstitium as a new organ in the body. However, in routine hematoxylin and eosin stained sections these spaces are not evident and thus probably has not received much attention. The implications of this discovery in oral pathology, especially cancer metastasis are immense. Although the structure and components of oral mucosa differ from that of skin and gastrointestinal tract (GIT) in various aspects, if the above findings are established in the oral submucosa, various oral diseases related to fluid and fluid dynamics may perhaps be reviewed. In this editorial, we have made attempt to hypothetically consider the various possible implications of 'third space' in the field of dentistry.

**Keywords:** Interstitium, Oral cancer, Oral pathology.

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The evolution in *in-vivo* microscopy and real-time imaging is redefining the human histological structures. In a recent study, Benias et al. utilized the probe-based confocal laser endomicroscopy (pCLE) imaging

technology to assess the human tissue structure following intravenous injection of fluorescein. The authors observed the extrahepatic bile and pancreatic ducts and noted an explicit interstitial tissue architecture, which they could not correlate with any known histological structures. They observed a reticular pattern of 20  $\mu\text{m}$  wide dark branching bands, which surrounded large, fluorescein-filled polygonal spaces, in the submucosa region of the ducts. Further investigation on fascia, dermis, peribronchial, peri-arterial soft tissues, gastrointestinal tract, and urinary bladder showed all the above-mentioned structures begging the revision of micro-anatomy of human interstitial tissue, based on real-time imaging technology.<sup>1</sup>

An in-depth ultrastructural and immunohistochemical study further revealed interesting findings pertaining to this newly discovered "third space".<sup>2</sup> Detailed study revealed that the collagen bundles surrounding the fluid-filled spaces were asymmetrically lined on one side by CD 34 positive (but lacking ultrastructural features of an endothelial cell) flat cells, with scant cytoplasm, an oblong nucleus and without a basement membrane. Further analysis of the fluid, suggested the spaces to be of a pre-lymphatic nature. The frozen section evaluation of the submucosae of various tissues also confirmed the presence of these spaces. However, in routine H and E sections, these spaces were never evident. The authors proposed that the appearance of submucosa in the histopathological slides as collagen bundles represents the collapsed form of the fluid-filled polygonal spaces. The loss of fluid from these delicate spaces during the tissue processing might result in the collapse of the entire architecture.<sup>1</sup>

The implications of this discovery in oral pathology, especially cancer metastasis are immense. Although the structure and components of oral mucosa differ from that of skin and GIT in various aspects, if the

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above findings are established in the oral submucosa, various oral diseases related to fluid and fluid dynamics may perhaps be reviewed. In the oral mucosa, the junction between oral epithelium and lamina propria is obvious, the distinction between oral mucosa and underlying submucosa is often relatively less apparent. In the gingiva and parts of the hard palate, oral mucosa is attached directly to the periosteum of underlying bone, with no intervening submucosa, known as the mucoperiosteum. However, unlike GIT, submucosa of oral mucosa wherever present is not separated by a muscular layer (muscularis mucosae).<sup>3</sup> Thus, if such reticular fluid-filled prelymphatic spaces do exist in the oral submucosa, it would be easily accessible to external pathogens or cancer cells, which might explain the heightened inflammatory response of oral mucosa to any external obnoxious agent or injury.

The chief implication of the above is in the understanding of early or occult distant lymphatic metastasis in oral cancer cases with  $\leq 10$  mm depth of invasion. The presence of such spaces might provide an explanation and pathway for the involvement of the lymph nodes at early stages of oral cancer and could be of vital prognostic significance. Local spread can be due to the migration of cancer cells via these fluid-filled spaces which is in direct contact with the extracellular matrix. Thus, interstitium can be enlisted as a mode of cancer spread and metastasis. Further, the presence of remnant cancer cells in the fluid-filled spaces might result in local recurrences and failure of surgical treatment, thus supporting the significance of depth of invasion in the T1 and T2 cases.<sup>4</sup> Site-specific biological distinctness in oral cancer can be attributed to probable

morphological diversity in these fluid-filled spaces (micro-environmental heterogeneity). The variations noted in the overall survival and recurrences of oral cancer patients based on the site involved within the oral cavity might be determined by the presence or absence of these spaces in the submucosa of the oral tissues. Hence, future in-depth studies pertaining to the oral cavity are required to precisely map the architecture and dimensions of this newly discovered space, which could altogether change the management of cancer.

Secondly, these spaces might have a role in oral soft tissue edema and spread of local infection. Further, the study of the lining cells of the spaces (whether fibroblast-like or mesenchymal stem cell) could determine their role in the wound healing or collagen disorders. Active migration of various immune cells into these spaces could determine the inflammatory and immunologic diseases. Lastly, this dynamically compressible interstitial layer might serve as a cushion and shock absorber.

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