

Potentially malignant oral disorders and oral cancer - a study on immunosurveillance

Akademisk avhandling

som för avläggande av odontologie doktorsexamen vid Institutionen för Odontologi,
Sahlgrenska Akademien,
vid Göteborgs Universitet kommer att offentlig försvaras i
Föreläsningssal 3, Institutionen för Odontologi, Medicinaregatan 12D, Göteborg

Fredagen den 30 januari 2015, kl. 9.00

av

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Avhandlingen baseras på följande delarbeten:

- I. **J Gustafson**, C Eklund, M Wallström, G Zellin, B Magnusson, B Hasséus
Langerin-expressing and CD83-expressing cells in oral lichen planus lesions.
Acta Odontol Scand. 2007 Jun;65(3): 156-61
- II. **J Öhman**, B Magnusson, E Telemo, M Jontell, B Hasséus
Langerhans cells and T cells sense cell dysplasia in oral leukoplakias and oral
squamous cell carcinomas- evidence for immunosurveillance.
Scand J Immunol. 2012 Jul;76(1):39-48. doi: 10.1111/j.1365-3083.2012.02701.
- III. **J Öhman**, R Mowjood, L Larsson, A Kovács, B Magnusson, G Kjeller, M Jontell,
B Hasséus
Presence of CD3-Positive T Cells in oral premalignant leukoplakia indicates
prevention of cancer transformation.
*Accepted for publication in Anticancer Research, vol. 35, 2015 PMID not
available yet.*
- IV. **J Öhman**, H Rexius, L Mjörnstedt, H Gonzalez, E Holmberg, G Dellgren, B
Hasséus
Oral and lip cancer in solid organ transplant patients –A cohort study from a
Swedish Transplant Centre.
*Accepted for publication in Oral Oncol (2014), doi:
<http://dx.doi.org/10.1016/j.oraloncology.2014.11.007>*



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ABSTRACT

The cancer immunosurveillance hypothesis postulates that the immune system can recognize cancer cell precursors and destroy those cells before a clinical manifestation occurs. During the last decades several groups have presented evidence of the influence and role of immune activation in oral squamous cell carcinoma (OSCC) patients; however, much less is known about the role of immune activation in potentially malignant oral disorders (PMOD). OSCC may be preceded by a PMOD. Two of the most common PMODs in the Western population are oral leukoplakia (LPL), defined as a predominantly white patch in the oral mucosa that cannot be characterized as any other definable lesion, and oral lichen planus (OLP) defined as a chronic inflammation in the oral mucosa manifested as bilateral white hyperkeratotic striations with or without erythema, ulceration, bullae or plaque.

The general aim of this thesis was to characterize the immune response in PMODs and oral cancer and to relate immune response to malignant transformation. Another aim was to address whether long-term immunosuppression in a large cohort of solid organ transplant (SOT) patients predisposes for cancer in the oral cavity and lip.

In papers I–III clinical data and biopsy specimens were analysed from patients with OLP and healthy oral mucosa (I), patients with LPL with and without dysplasia and OSCC (II) and those with LPL with dysplasia with (LPL-ca) or without (LPL-dys) malignant transformation (III). Immunohistochemistry was used to detect different cell types of interest, in particular, subtypes of dendritic Langerhans cells (LCs) and T cells. In paper IV a cohort of SOT patients were correlated with the Swedish Cancer Register for prevalence of oral and lip cancer and compared with the prevalence in the Swedish population. Overall 5-year survival in SOT patients with oral and lip cancer was compared to an age- and gender-matched control group with oral and lip cancer without previous SOT.

In paper I the results showed that OLP patients had a significantly higher number of dendritic Langerhans cells (LCs) in the epithelium and the connective tissue than in healthy control patients. Also, cells with dendritic morphology and expressing the maturation marker CD83 were found in clusters with lymphocytes in the connective tissue.

In paper II the results showed that both cytotoxic T cells and dendritic Langerhans cells were significantly increased in connective tissue in LPL with dysplasia compared to LPL without dysplasia, indicating an immune response to cells with cell dysplasia. In OSCC, the influx of T cells and LCs was increased almost a thousand-fold compared to LPL. Confocal laser scanning microscopy revealed a co-localization of LCs and T cells in LPL with dysplasia and OSCC, indicating possible immune activation

In paper III quantitative analyses showed that patients with LPL displaying cell dysplasia that transformed into OSCC had lower numbers of T cells than a group of patients with LPL with dysplasia that did not transform into OSCC during the observation period.

In paper IV the results showed a standardized incidence ratio (SIR) that was increased for both oral (SIR: 6.3) and lip cancer (SIR: 43.7) in SOT patients compared to non-SOT patients. Also, the overall 5-year survival was decreased for lip cancer in SOT patients compared to non-SOT lip cancer patients.

To conclude the findings in papers I, II and III, evidence of immunosurveillance in PMOD and OSCC are presented. After long-standing immunosuppression in patients with SOT there is an increased risk for both lip and oral cancer, and the overall survival for patients with lip cancer is also negatively affected.

The concept of immunosurveillance originally proposed by Dunn *et al.* in 2004 is well in line with the findings in this thesis of PMOD and oral cancer.

Keywords: immunosurveillance, potentially malignant oral disorders, oral cancer, solid organ transplantation, immunosuppression, T cells, Langerhans cells.

ISBN: 978-91-628-9268-5