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Georgia Kontostathi, PhD student

Supervisor: Dr. Ieronymos Zoidakis

Biomedical Research Foundation, Academy of Athens,
Department of Biotechnology, Soranou Efessiou 4,
11527 Athens, Greece

Proteomic analysis of the secretome from normal and malignant cervical cell lines

Cervical cancer is one of the leading causes of mortality in women despite the recent introduction of a vaccine that protects from HPV infection. It is the second most common malignancy in women worldwide with 493,243 incidents and almost 273,505 deaths every year [1]. Cervical cancer incidence is tightly linked to HPV infection. HPV strains 16 and 18 cause the majority of cases of Cervical Intraepithelial Neoplasia (CIN) [2].

Highly malignant transformation is attributed to the constitutive expression of viral oncoproteins E6 and E7. However, the eventual steps leading to carcinogenesis and particularly the role of interleukins remain to be elucidated. The cell secretome represents the collection of the entire macromolecules secreted by a cell, and constitutes a vital aspect of cell-cell communication. Alterted secretomes of cancer cells probably contribute to individual stages of carcinogenesis.

The aim of our study is the systematic evaluation of the secretome of four cell lines in order to discover putative biomarkers and reveal pharmaceutical targets. Secreted proteins of normal keratinocytes HCK1T (Human Cervical Keratinocytes) and representative cervical cancer cell lines [C33-A (HPV^-), SiHa ($HPV16^+$), HeLa ($HPV18^+$)] are compared.

HPV is very efficient in terms of evading recognition. The virus can globally downregulate keratinocyte innate immune sensors and suppress the type I interferon response, which is critical for the control of viral infection. As a result, keratinocytes do not induce pro-inflammatory cytokines and there is no activation of Langerhans cells and/or stromal cells. Thus, there is no stimulus for dendritic cell activation, migration, antigen protein and presentation [3].

Specific alleles of Interleukin-4 (IL-4) and IL-10, cytokines with anti-inflammatory properties, increase the risk of cervical cancer [4]. IL-6 is known to be synthesized in human papilloma virus (HPV)-transformed cervical carcinoma cell lines (like SiHa and HeLa) and contributes to immunosuppression [5]. High levels of IL-8 in cervical tumors promote angiogenesis, a critical process for tumor growth [6]. Moreover, low IL-12p40 expression by cervical cancer cells is associated with poor survival of cervical cancer

patients [7]. TNFa has a functional link to IL-6 but his role in cervical cancer remains elusive.

We intend to determine the levels of IL-4, IL-10, IL-8, IL-6, IL-12p40 and TNFa in the secretome of normal and cancer cervical cell lines, as well as in clinical samples: LSIL (Low grade Squamous Intraepithelial Lesion) and HSIL (High grade Squamous Intraepithelial Lesion). Any difference detected between controls and cancer samples for these important regulators of immune response will offer novel insights in their role in cervical cancer. Therefore, we consider that the ELISA sets for IL-4, IL-6, IL-10, IL-12p40 and TNFa will be valuable tools in elucidating carcinogenesis in the cervix.

References

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