A targeted data mining approach to identify molecular determinants of cervical cancer progression and recurrence

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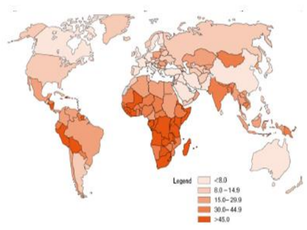
Background and Objectives

Human Papilloma Virus (HPV): Causal agent of Cervical Carcinoma

- Cervical cancer is the second most common cancer among women in the developing countries like India, only after breast cancer.
- Cervical cancer is associated with infection of high risk varieties of Human Papilloma Virus (HPV) in more than 99% of the cases, with HPV 16 and 18 being most predominant.
- Understanding cervical cancer biology is thus of great importance as it poses a high disease-burden in the developing countries.

Figure 1: Global burden of cervical cancer: Age standardized incidence rate (per 100.000 women)



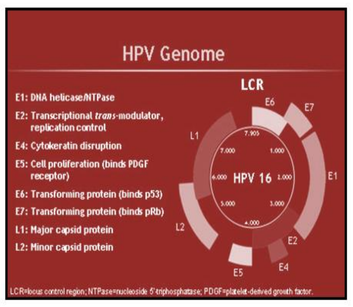
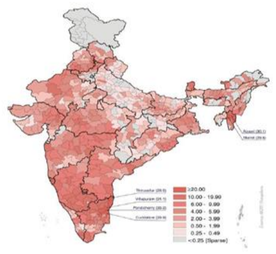
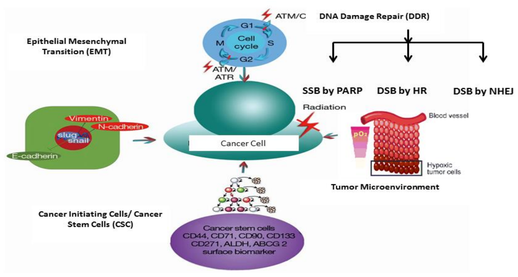


Figure 2: District-wise comparison of age-adjusted incidence of cervical cancer (per 100,000 population)



Mechanisms of development of radioresistance in cervical cancer patients



Adapted from Chen et al. Journal of Thoracic Disease (2017)

Mode of action of HPV leading to causation of Cervical Cancer

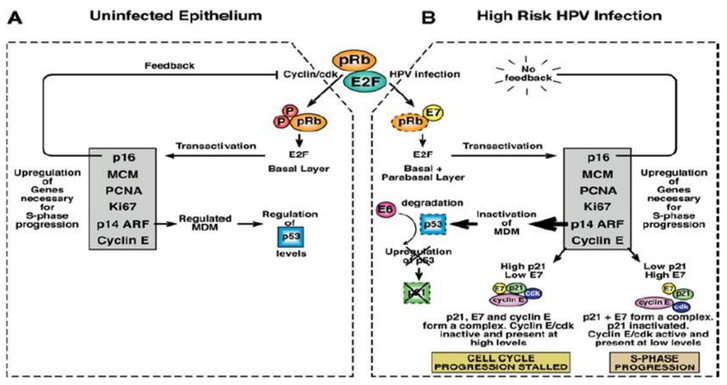


Figure 3 Stimulation of cell-cycle progression by high-risk HPV types

Doorbar et. al., Clinical Science, 2006

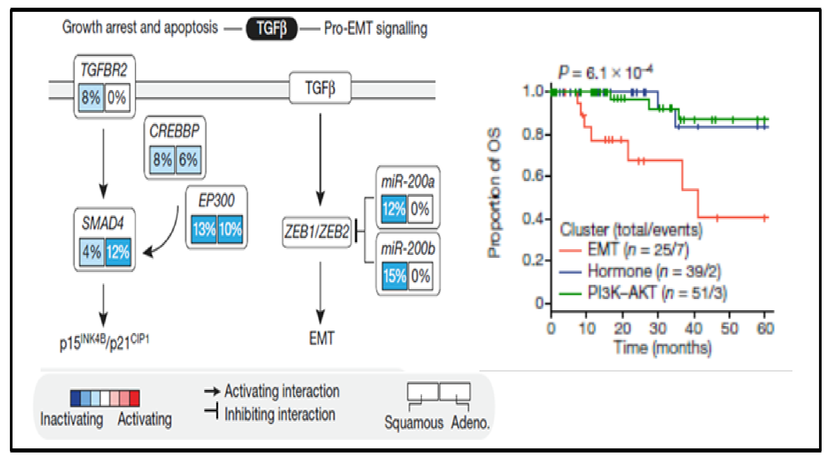
The E6 and E7 proteins of high-risk HPV types lead to cellular transformation by interacting with the PDZ domain cellular proteins and Rb, contributing to neoplastic progression, while the E6-mediated p53 degradation prevents the repair of chance mutations occurring in the genome and hence disrupting normal cellular homeostasis, ultimately leading to development of cancer in HPV infected cervix.

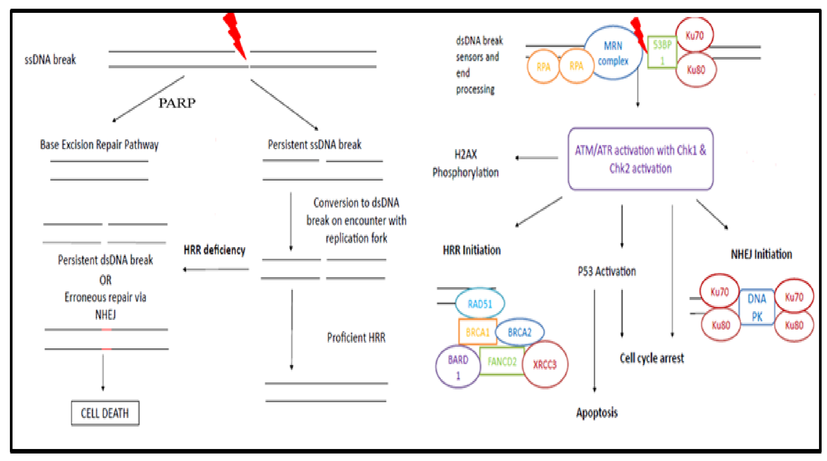
Objectives

To analyze the expression profiles of genes associated with DNA Damage Response (DDR) and Epithelial Mesenchymal Transition (EMT) in The Cancer Genome Atlas (TCGA) data on cervical squamous cell carcinoma based on:

1. **Early (I-IIA) or Late stage (IIB and above) of disease**
2. **Recurred or non-recurred post therapy**

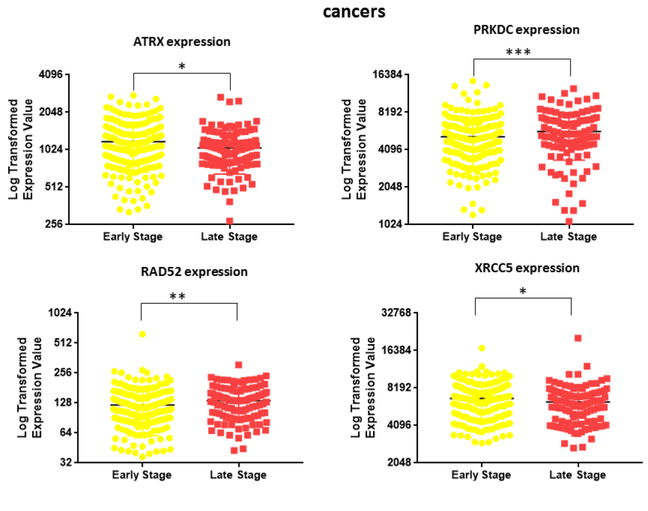
Status of EMT and DNA damage response in cervical cancer



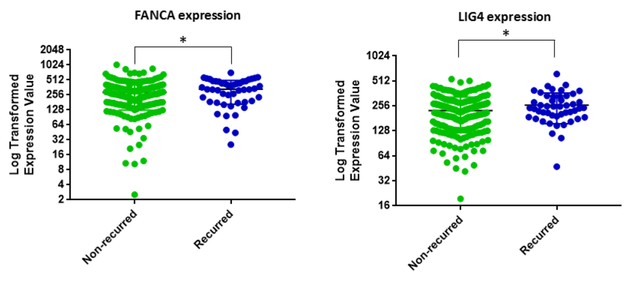


Results and Conclusions

Significantly altered genes in the DDR pathway between early and late stage cervical cancers



Significantly altered genes in the DDR pathway between non-recurred and recurred cervical cancer cases



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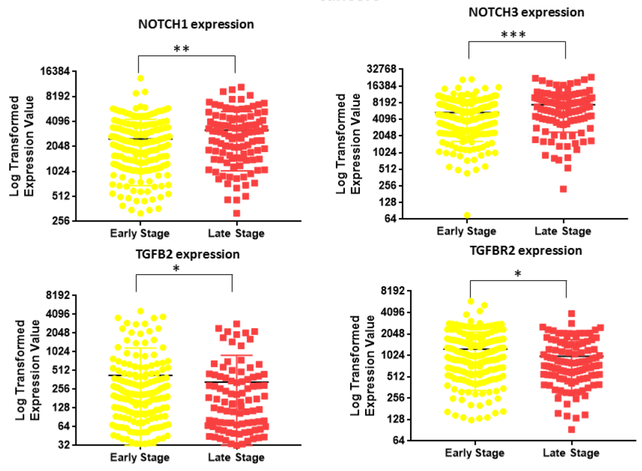

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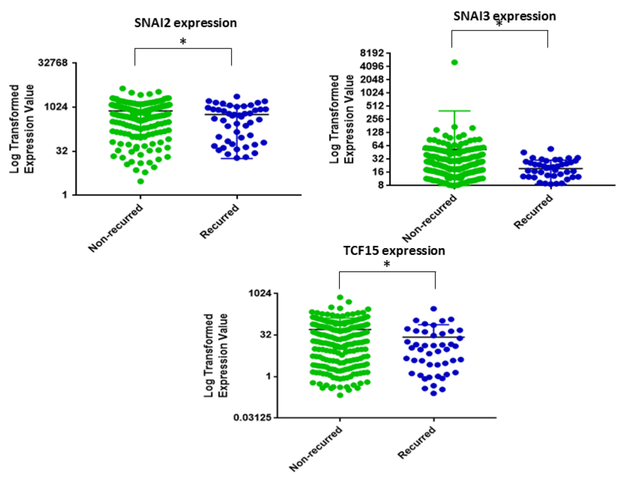

Conclusions

- DDR genes regulating both the Homologous Recombination Repair and Non-homologous End Joining were found to be altered between Early and Late stage cervical cancers as well as comparison of recurred and non-recurred cervical cancers
- Several EMT regulating transcription factors were found to be altered between Early and Late stage cervical cancers as well as comparison of recurred and non-recurred cervical cancers
- Future studies are needed to identify interplay between DDR and EMT in driving cervical cancer progression and therapy resistance

Acknowldgements

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