Original Article

# Evaluation of PD-L1 and PD-1 expression in aggressive eyelid sebaceous gland carcinoma and its clinical significance

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**Purpose:** Eyelid sebaceous gland carcinoma (SGC) is an aggressive but rare malignancy of ocular region. Over-expression of PD-L1 and PD-1 has been demonstrated in a variety of solid tumors including conjunctival melanoma. PD-L1 is an immunoinhibitory molecule that suppresses the effective T cells response against tumor antigen leading to the progression of tumors. Inhibitors of the interaction of PD-L1 and PD-1 are associated with good clinical response various carcinomas. The prognostic value of the PD-1/PD-L1 axis in SGC remains unexplored. The purpose of this study was to evaluate expressions of PD-1 and its ligand PD-L1 in SGC and correlate its expression with clinicopathological features and patients survival. **Methods:** The immunohistochemical expression of PD-L1 and PD-1 was evaluated in 30 SGC cases. **Results:** PD-L1 immunopositivity was detected in 41.9% of the SGC cases. PD-1 expression in tumor infiltrative lymphocytes (TILs) was observed in 53.3% samples. Tumor PD-L1 positivity, PD-1 expression in TILs and tumor size (>10 mm) was associated with reduced disease-free survival. On multivariate analysis only tumor size (>10 mm) and a combined positivity of PD-L1 in tumor cells and PD-1 in TILs with an odds ratio of 5.212 (95% confidence interval 1.449-18.737) continued to be significantly associated with SGC recurrence. **Conclusion:** PD-L1 is overexpressed in 50% of SGC cases. The combined tumor PD-L1 positivity and TILs showing PD-1 expression within the same SGC patient's samples predict high-risk SGC, suggesting that the up-regulation of PD-L1 in tumor cells and PD-1 positivity within the same SGC patient may aggravate tumor recurrence.

**Key words:** Eyelid, PD-1, PD-L1, sebaceous gland carcinoma

**Access this article online**
**Website:** www.ijo.in
**DOI:** 10.4103/ijo.IJO_2056_18
**Quick Response Code:**

Sebaceous gland carcinoma (SGC) of the eyelid arises from sebaceous glands of ocular adnexa.[1] Its significance among eyelid malignancies is due to its multifocal origin and pagetoid spread.[2,3] SGC is also considered to be one of the most aggressive eyelid tumor. It accounts for 1%-5.5% of all eyelid malignancies and is the most common eyelid malignancy with the reported rate of 31.2% in Indian population after basal and squamous cell carcinoma.[4] Incidence of SGC varies from 0.5% to 5% of all lid carcinomas in the USA and 28% in China.[1-5] The risk of metastasis and recurrence is approximately 10%-15% and the mortality rate is found to be 10%-40%. Treatment of SGC includes excision with clear margins. Radical surgical procedures like exenteration are reserved for the most advanced stages.[6-8]

Cancer escapes the immune responses by various mechanisms such as immune check point inhibition. One such check point of a particular interest is the interaction between programmed cell death ligand 1 (PD-L1) and its interaction with its receptor, programmed cell death receptor (PD-1).[9]

PD-L1 is a 40-kDa trans-membrane protein encoded by the CD74 gene on chromosome 9. It is expressed on natural killer cells, macrophages, myeloid dendritic cells, B cells, resting T-cells, epithelial cells and tumor cells.[10] PD-1 is a type of trans-membrane, inhibitory receptor for PD-L1 which belongs to the CD28/CTLA-4 subfamily of immunoglobulin superfamily which is expressed on T cells, B cells, monocytes, natural killer cells, dendritic cells and many tumor-infiltrating lymphocytes (TILs) and regulates autoimmunity and tolerance.[10]

In response to the immune attack, cancer cells overexpress PD-L1 which binds to a PD-1 receptor on T cells, inhibiting the activation of T-cells and induces the production of cytokine (such as IFN-γ and IL-2) thereby suppressing effective T-cell response against a tumor antigen.[11] Various studies have shown that blocking the interaction between PD-L1 and PD-1 pathway by many approved drugs such as nivolumab and pembrolizumab enhances the endogenous anti-tumor responses in non-small cell lung carcinoma and melanoma.[12,13] These drugs have shown therapeutic success in different malignancies including BCC and cutaneous melanoma.[14-16] Overexpression of PD-L1 has been reported in various types of tumor such as ovarian cancer, colorectal adenocarcinoma,

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Received: 13-Dec-2018 Revision: 25-Apr-2019
Accepted: 04-Jun-2019 Published: 22-Nov-2019



**Cite this article as:** Jayaraj P, Sen S. Evaluation of PD-L1 and PD-1 expression in aggressive eyelid sebaceous gland carcinoma and its clinical significance. Indian J Ophthalmol 2019;67:1983-7.

South Asian J Exp Biol; 11 (3): 260-265; 2021 [DOI: 10.38150/sajeb.11(3).p260-265]

South Asian Journal of Experimental Biology

ISSN: 2230-9799 Vol. 11, Issue 3 Page 260-265 http://www.sajeb.org

REGULAR ARTICLE

# A cost-effective set-up to demonstrate embryonic limb development in Aseel (*Gallus gallus domesticus*)

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ARTICLE INFO

*Article History:*
Received: 21 Feb 2021
Revised: 17 Apr 2021
Accepted: 20 Apr 2021

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*Keywords:* Apoptosis, Embryonic development, Fertilised egg incubation set-up, *Gallus gallus domesticus,* Limb development, Osteogenesis, Window-making

ABSTRACT

Limb development during embryogenesis is a classical model used to study pattern formation. Experiments with biological model systems currently require expensive equipment to maintain optimal conditions, an impractical option for low-scale studies. Currently popular ex-vivo methods lead to stunted embryonic limb development, a high infection and fatality rate. As an alternative, the presented paper uses a novel, cost-effective set up to study the developing chick embryo as a biological model in order to visualize Chondrogenesis alongwith formation of ossification centers and apoptotic events occurring in the limb bud of the developing embryo.This cup-in-cup model constructed using polystyrene cups is instrumental in observing the developing embryos and correlating them to Hamilton-Hamburger (HH) developmental stages without exposing them to the outside environment and approaching a near perfect embryo survival rate. Anatomical events during skeleton development such as chondrogenesis, osteogenesis, and apoptosis are studied using Alcian Blue, Alizarin Red and Nile Blue Sulphate staining protocols revealing successful formation and progression of ossification centers and apoptotic regions in the limb bud. The chick embryo system is an excellent model that aids in understanding osteogenesis at both basic and clinical science level and enhance our knowledge about embryological development. The cup-in-cup system presented in this study proves to be a realistic addition to the subject of embryology and an ideal, sustainable experimental medium for low-scale research studies.

## 1. Introduction

The chick embryo is an efficient and cost-effective biological model to study the process of embryogenesis. Apart from its similarity to the human embryo, its wide-spread applications are also related to ethical acceptability, large size, year-around accessibility and ease of conducting genetic manipulations (Seabra&Bhogal,2010). For these reasons, chick embryos have played a vital role in anatomical, embryological and developmental biology research (Harvey, 1928; Lee et al., 2011; Smith et al., 2016). Limb development studies in the chick embryo are instrumental in understanding the related events of limb bud formation, chondrogenesis, osteogenesis and apoptosis.