MAVEN

REVIEW ARTICLE

AN INSIGHT TO THE BIOLOGICAL ASPECT OF ORAL MELANOCYTES – A BRIEF REVIEW

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ABSTRACT

The presence of the melanocytes in the oral mucosa is a well-established fact, but the physiology of the melanin initiation to the formation is not well un- derstood. The role of melanocytes in formation of melanin acts as a multitask- ing molecule from stress sensing to stress bearers to UV rays and reactive oxygen species and it plays a pivotal role in tissue homeostasis. The pathways of melanogenesis is a broad aspect of research and is still focused on. This paper will put a light on the biological aspects of melanin pigmentation in- cluding biophysiology, its role and brief advances in this area. (2017, Vol. 01; Issue 01: Page 77 - 82)

Keywords: Melanin, Melanocyte, Melanocytic markers.

INTRODUCTION

The term "pigmentations of the oral mucosa" may be applied to a wide range of entities caused by the ac- cumulations of one or more pig- ments and causing a change in col- our of the tissues (1). Human oral mucosa is not uniformly coloured. Colour reflects the clinical state of mucosa. Inflamed tissues are red, because of increase in number and dilations of blood vessels whereas normal healthy tissues are pink. The colouration is net result of many factors one of which is pig- mentation. Oral pigmentation oc- curs in all races. Light skinned per- sons rarely show any oral pigmen- tation. Intensity and distribution of racial pigmentation of oral mucosa

is also variable, not only between races but varies among individuals of same races and within different areas of oral cavity (2). Various studies have been elaborately done but no significant differences can be laid between males and females
(3). The colour of oral mucosa is mainly due to MELANIN pigment (4).

FACTORS AFFECTING COLOR OF ORAL MUCOSA:

1. The number and melanogenic ac- tivity of the melanocytes in the ba- sal layer of the epithelium.
2. Difference in the number, size and distribution of melanosomes.
3. Difference in types of melanins (Eumelanin and phaeomelanin).
4. Masking effect of heavily keratin- ized epithelium.

The tissue vascularisation and the levels of hemoglobin in blood are the determinants of melanin of oral mucosa that shows no noted signs of melanin pigmentation.
Just like skin, melanin production from oral melanocytes is genetically determined. Physiological pigmen- tation of oral mucosa is common in black persons and is more frequent in darker skinned whites (Cauca- sians) than in lighter skinned whites. The Light and darkly pig- mented individuals contains same number of melanocytes in unit area of oral mucosa or skin; but the pro- duction of melanin and its break- down into keratinocytes are chief factors for colour difference in dark or white individuals (5).

LIGHT MICROSCOPY VIEW:

In hematoxylin-eosin (H&E) stained sections, melanocytes appear as randomly dispersed cells wedged between the basal cells of the epi- dermis, having a small, dark stain- ing nucleus and a clear cytoplasm as a result of shrinkage. It is also called as low-level clear cells. The average number of melanocytes in H&E stained sections is 1 of 10 cells in the basal layer (5, 6). Because only 10 percent of the cells in the basal layer is melanocytes, each melanocyte are supplies several keratinocytes with melanin, form- ing with them an **Epidermal- Mela- nin unit or keratinocyte-melano- cyte unit** (7).

THE KERATINOCYTE-MELANOCYTE UNIT (KM UNIT):

Mature melanocytes are elongated dendritic cells that reside in the stratum basale. They contain all the proteins essentially required for bi- osynthesis of melanin and for the melanosomes to get matured,that includes tyrosinase-related pro- teins-1 (TRP-1), tryosinase (TYR) and TRP-2, gp 100, and melanoma antigen recognized by T lympho- cytes (MART-1) (8). The ratio of mel- anocytes to keratinocytes ranges from 1:10 to 1:15 in the basal layer of the epithelium. The EM unit con- sists of one melanocyte and a group of about 36 neighbouring keratino- cytes. It has been evaluated that the process of dendritic melanosome transfer is controlled by keratino- cytes, since the keratinocytes can phagocytose the melanosomes and it is influenced by the degree of ac-

tivation of the enzyme protease-activated receptor 2 (PAR-2) which is present on the surface of keratino- cytes (4). Melanocytes can also in- fluence the functional activities of keratinocytes by transferring the important biological mediators. It also appears that Langerhans cells in the epithelium and fibroblasts in the subepithelial connective tissue helps in maintaining the functional activity of the epidermal melanin unit (9).

SPECIFIC METHODS OF IDENTIFICATION:

1. Silver staining by Masson-Fon- tana method.
2. Treatment with strong oxidizing agents like hydrogen peroxide and potassium Permanganate.
3. Dihydroxyphenylalanine (DOPA) reaction.
4. Immunohistochemically by antibodies directed against S-100 and HMB-45

MELANOCYTES:

Becker first identified melanocytes in the oral epithelium in 1927; a few years later they were isolated from samples of gingival tissue by Laidlaw and Cahn. During the early intrauterine life the melanoblasts migrate from the neural crest to the epidermis and the hair follicles hence becoming dendritic cells which are differentiated. The head and neck region represents the first part of the body where melanocytes appear after approximately 10 weeks of gestation. A specialized pigment-producing cell called 'Mel- anocyte' situated in the epidermis and basal layer of the epithelium produces melanin. Melanocytes containing melanin are present even at those oral mucosal sites (5).

ORIGIN OF ORAL MELANOCYTES: (10, 11)

• Melanocytes, mealnin producing cells develop from neural crest cells. During development, melano- cyte stem cells migrate from the neural crest cells to the mucous membrane.
• Active cells are present in the stria vascularis of the cochlea, in the leptomeninges, in the substantia nigra and locus coerulus of the brain.
• Epidermal melanocytic stem cells give rises to transient amplifying melanocytes precursors and they diffrentiate into mature melanin producing melanocytes.
• Stem cell factor (SCF) and its ty- rosine C- kit signalling pathways are critical for epidermal melano- cyte development during melano- genesis.
• Notch signalling pathways are essential in the maintainence of adult melanocytes stem cells, and thus for melanocyte homeostasis.
• Endothelin-1 plays a role in differentiation of melanocyte precursors, and microopthalmia- associated transcription factor (MITF) with its cAMP response elements play a critical role in melanogenesis.

MELANIN SYNTHESIS

Melanin formation starts by hydroxylation of tyrosine to Dihydroxyphenylalanine (DOPA), which is tyrosinase dependant and then fur- ther oxidation of DOPA to DOPA- quinone occurs which is eventually gets polymerized into melanin. Mel- anin is modified and packed into as small membrane bound structures called **melanosomes**. These mela- nosomes gradually move from the cytoplasm of the melanocyte to the dendritic processes. As the content

of melanin increases in the melano- somes, the concentration of enzyme decreases.

The development of the melano- somes takes place in four stages (5, 6):

Stage I: Melanosomes are round, measuring about 0. 3mm in diame- ter and possess very intense en- zyme activity concentrated along fil- aments. They contain no melanin. **Stage II:** Melanosomes are ellipsoid in shape and measuring approxi- mately 0.5 mm in length, resem- bling the melanosomes of stage III and IV. They contain filaments lon- gitudinally arranged and also cross-links with one another. En- zyme activity is present on the membrane enveloping it as well as on the filaments.

Stage III: Melanosomes have only little tyrosinase activity, but show continued melanin deposition, par- tially through non-enzymatic polymerization.

Stage IV: Melanosomes no longer possess tyrosinase activity. Mela- nin, which is formed entirely by nonenzymatic polymerization, fills the entire organelle and obscures its internal structure.

FUNCTION OF ORAL MELANOCYTES (5, 12):

• Melanin poses antioxidant and Reactive Oxygen Species (ROS) de- pendent cytotoxic properties.

• L-DOPA inhibits the production of pro-inflammatory cytokines by T-lymphocytes and monocytes and thus down regulating inflammatory response.

• Melanosomes contain enzymes that can degrade bacteria.

• The pigment can neutralize bacte- ria-derived enzymes and toxins

• The melanosomal membrane de- grades to release of melanin 'dust' which inactivates pathogenic chem- icals, microbial toxins and other bi- ologically active molecules.

• It has been also shown that some carcinogens bind to melanin, caus- ing speculation that melanomas de- veloping at anatomical sites not ex- posed to ultraviolet light might re- sult from the carcinogenic accumu- lation in melanin containing cells.

• Play a pivotal role in innate im- mune system with a role in neutral- izing the products of superficial bacterial and fungal infective agents.

ADVANCES IN MELANOCYTIC MARKERS:

HMB 45 is identified as protein gp100 are localised in pre melano- somes and is considered as very or- ganized and specific.

Mart 1, also known as Melan A, is a small protein and serves as a tar- get for cytotoxic T Lymphocytes. It is not located in three melano- somes.

Tyrosinase, a normal protein, is the key enzyme for melanin synthe- sis. The expression is also found to be heterogeneous in case of meta- static Melanoma from its usual ho- mogenous behaviour.

Microphthalmia transcription factor is a melanocytic nuclear transcription factor usually gets ex- pressed in the embryonic stages but it also shows cross reactivity with several non melanomal cells, such as macrophages and fibro- blasts.

S100 is 21 KDA acidic calcium binding protein which was first dis- covered in glial cells. It also acts as a sensitive marker for granular cell

tumor. X Factor in melanomas s100 usually gets expressed in nucleus and cytoplasm with the sensitivity ranging to 97%.

NKI/C3 is a 25-110 KDA glycopro- tein located in on the inner mem- brane of cytoplasmic vesicles of melanocytes. It should show pe- ripheral positive staining with 86 to 100% sensitivity. It also stains neu- rothekoma medullary carcinoma of thyroid and other tumors but with a very poor sensitivity (13-17).

THE CONTROVERSIAL NEWER INSIGHTS IN MELANOGENESIS:

Despite many efforts, the regulation of pigmentation is still not fully un- derstood. The main role of tyrosi- nase plays an important role in melanogenesis in conjunction with 6BH4 dependent phenylalanine hy- droxylase (PAH) and tyrosine hy- droxylase isoform I (TH1) which provides an insight to the three member concept of pigment initia- tion. The intracellular L-Phenylala- nine uptake and turnover of L- ly- sine via PAH is important for sup- plying substrate to TH1 and tyrosi- nase. CAMP is also required for the activation of Micropathalmia asso- ciated transcription factor to induce expression of tyrosinase for the transcriptional activity of TH1 and for activation of PAH. H2O2 also in- volves in regulation of tyrosinase via p53 pathway through transcrip- tion of hepatocyte nuclear factor 1 alpha which helps in pigment for- mation (18).

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