

**ORAL IMMUNE CROSS-ROADS: MINI-REVIEW****Ibrahim Mohamed Saeed Shnawa\***

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Qasim, Babylon/IRAQ.**ABSTRACT**

The immune molecules (Complement, interferons), the immune receptors (TLRs, KIR, KAR, CD38), the functioning immune cells (Neutrophil, eosinophil, dendritic, langrhans, T and B cells) and glands (Salivary and Tonsils) are coexisted in the oral cavity. These elements (Except the glands) may be of local, systemic or both of local and systemic origins. Such components are the formed elements of the oral mucosal immune compartment. In this mini-review, an expression was made about each of their elements for; the structure, general function, systemic immune cross – road function and a deduction on the possible oral immune cross- road function. The immune cross-road functions means the mono or bidirectional cooperation between the

natural (Innate) and adaptive immunity. There were an evident analogy between the systemic immune cross-road functions with the possible oral immune cross-road functions. Such analogy have led to the opinion holds the position that there was a real oral immune cross-road functions covering; immune proteins, immune receptor and immune cells constitute a tripartite system. Thus, oral immune compartment is a mini-ature of the tripartite systemic immune system.

**KEYWORDS:** Cross-road, function, immune, molecule, receptor, structure.**I – Overview**

Katssikis et al, 2007<sup>[1]</sup>, have been pioneering the field of immune cross-roads which means the interest that deals with the mono or the bidirectional cooperation between natural (innate) and adaptive immunity, then the team keep their outstanding book vived through it second and third editions<sup>[2,3]</sup> Shnawa and ALAlwany, 2014<sup>[4]</sup> Published a book entitled "The dualism of Immune function "concerned with the immune cross-roads with an emphasis on complement and Papiloma virus induced mammary human cancer. In the present mini-

review attempts were made to focus onto such cooperation, so far concerned with the oral mucosal compartment. The oral mucosal compartment includes immune molecules like complement and interferons, receptors like TLRs, KIR, KAR, CD38 and immune cells like neutrophil, eosinophil, macrophages and lymphoid cells Tables 1,2&3, in addition to salivary glands and tonsils.<sup>[5]</sup> Each of these elements was expressed for the aspects of; Structure, general immune function, systemic immune cross-road functions then oral immune cross-road functions.

## II – Origins

The origins of the components of oral immune compartments(Except salivary gland and tonsils) can be traced to three possible origins;local,systemic,both local and systemic.<sup>[4]</sup>

## III - Dipartite or tripartite

Back to 1970s immunity has been divided into dipartite system as innate and adaptive or acquired. Recently,<sup>[1,2,3,4]</sup> immunity is now well documented as a tripartite system. Since there is a grey area in between the black and white areas, which is the cross – roads that are involved in the mono and the bidirectional cooperation.<sup>[4]</sup>

## IV – Linked or Separate

Three opinions are apparent to the spectacular viewer to the seen of the immune system. The first holds the position that mucosal immune system is entirely separate from the systemic immune system. The second however, hold the believe that systemic immune priming led to the mucosal as transcendent immunoglobulins from the systemic response, but mucosal didn't mount such response. Finally the third state that the mucosal somewhat linked in a way or other to the systemic immune system. The author and his co-workers have been proving in a series of research works that what so ever the nature of the vaccine application site to the rabbits, both local and systemic responses are mounted.<sup>[5]</sup> Thus, mucosal immune system is linked to systemic immune system.

## V – Immune Molecules

### V-i-: Complement

Complement system constitute a group of a plasma proteins that consist of 9 to 35 components with an inherent sensitivity to the temperature 56C so that decompementized within half an hour and are of haemolytic nature. The activated complement have main five

functions; opsonization, direct Cell lysis, attraction and activation of phagocyte, cause mast cell degranulation and promote B lymphocyte activation.

Alternative pathway take part in the innate immunity while classical pathway have a role in the adaptive immunity. Since complement shape the B lymphocyte responses. Binding of the antigen to C3b, C3dg, C3d complex to the CR2 on antigen presenting cell, Follicular dendritic cells may enhance antigen presentation to B lymphocytes.

The oral cavity salivary gland secretion do contains complement fractions that take part in immune complex formation between dental oral pathogen antigens and their own specific antibodies. Such complexes may be deposited in the oral soft supporting tissues.<sup>[7,8,9]</sup>

### **Vii: Interferons**

The interferons are of two major types. Type one consist of interferon alpha and beta while type two includes interferon gamma. Interferon alpha is single polypeptide that contain 115 to 167 amino acids. interferon beta is a glycol-proteins of 165 to 166 amino acids. While interferon gamma is a polypeptide chain of 143 amino acids with molecular mass of 17 KDA in homodimeric form.

Type I and II interferons can protect cells from viral infection and they are able to regulate expression of MHCI antigen presentation .Interferon gamma is the major immunoregulatory cytokine through promoting the inductive phase of the immune response as well as promoting enhancement of CD4 T cell responses.

Interferons affects both natural and adaptive immune responses. They played a regulatory role onto macrophage, B lymphocytes and T lymphocytes. Thus, Interferon alpha and beta take part in the innate immunity while interferon gamma take part in adaptive immune responses through regulation of B lymphocyte development and proliferation, immunoglobulin class switching.<sup>[10]</sup>

In the oral compartment, and on activation of type I helper cells will secret TNF alpha, INF gamma and IL2 and these collectively activate macrophage and cytotoxic T lymphocyte. These helper cells are involved in delayed hypersensitivity reactions.<sup>[11,12]</sup>

**Table 1: The immune molecules at the cross-roads between innate and adaptive response.**

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Natural(innate);  
 Acute Phase Protein C, Alternative complement  
 Interferon alpha and B, Natural defensine  
 Cross-Roads;  
 Opsonins  
 Interferon gamma  
 IL17  
 Adaptive;  
 Classical and lectin complement  
 Antibodies and cytokines including INF gamma and IL17.

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## **VI – Receptors**

### **VI- I; Toll-like Receptors(TLRs)**

In the early era of immunology, immunologists hold the idea that professional macrophage recognize the foreign invaders on the bases of friend or enemy latter on with the commencing of mid 1990s Towards two thousands they discovered a membrane surface associated TLRs onto miro and macrophages which may provide relative specificity in recognition of invaders that depends on the specific surface molecular patterns on the microbes.

TLRs are trans membrane surface proteins, they constitute a single membrane spanning protein macromolecules of non-catalytic receptor nature that recognize conserved molecular structures on the microbial surfaces. TLRs immune functions includes fitting the danger, protect the useful and ignore the harmless, throughout three mechanisms respectively as; a detection of unusual molecular patterns, sensing the extent of tissue damage and determine the class of immune responses.

TLRs initiate signal transduction which triggers the natural immune response genes and instruct the development of adaptive immune responses. TLRs control the natural immune host defense mechanisms against the invading pathogens and take part in the aetiogenesis of immune disorders.<sup>[13,14,15]</sup> In addition, TLR signaling pathways helpful in the advancement of cancer progression in an instance and induces anti-tumor immune responses in others.<sup>[15]</sup>

The TLR functions in the oral mucosal compartment ;The ligation of the surface TLRs of the langerhans cells lead to the synthesis and release of IL10,TGFB and forked head box protein(Foxp)3 from regulatory T lymphocytes which represents the key players in the oral mucosal tolerance.<sup>[16,17]</sup>

TLRs mediate control of adaptive immunity orchestrated by dendritic cell populations at distinct oral anatomic sites. They control multiple dendritic cell functions and activate signals that critically involved in the initiation of adaptive immune responses.<sup>[18]</sup>

#### **VI – ii; KIR and KAR**

These receptors are of trans-membrane protein nature found as surface receptors of the natural killer cells. Their extracellular domains tend to have similar molecular structures but their intracellular domains are somewhat different .The NK receptors KIR and KAR posses an antigenic function and they expresses killing activity for viral infected cells and cancer transformed cells .NK inhibits T cell through the action of dendritic cells .Such activities of NK also noted in the oral mucosal compartment.<sup>[19,20]</sup>

#### **VI –iii-, CD38**

It is an ecto-enzyme that catalyse the formation of three products CADRP,ADRP and NADP. It acts as nucleotidase and as a signaling molecule in pro-oncogenic receptor in adenoma.CD38 affects dendritic cell, neutrophil, B and T lymphocytes as well as it produces calcium mobilizing CADPR from substrate and do signaling through some chemokine receptors.

CD38 regulate the trafficking of neutrophil ,monocyte and dendritic cells in response to vaccination and infection. It is eligible for an optimal T cell dependent humoral immune responses and acts as a co-receptor for BCR during regulation of B lymphocyte activities .It initiate and regulate both of the natural and adaptive immune responses. Since it may take part in the regulation of TH2 cells during B lymphocyte triggering in an immune response.<sup>[21]</sup>

#### **VI – iv: CD28**

It is homo dimeric glycoprotein composed of disulfied bond with molecular weight of 44KDA for each of its subunits .Each monomer contains 134 extra amino acids fragments .It is expressed on the surface of T and B lymphocyte subpopulations. CD28 regulate T cell

responses to antigenic stimulation during cell contact with antigen presenting cells and is known as a co-stimulatory receptor.<sup>[21]</sup>

**Table 2: The immune receptors at the cross-roads between innate and adaptive immunity.**

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Natural (innate):

TLRs

KIR and KAR

Adhesins and selectins

MHC I & II molecules

Cross-Roads

TLRs

CD38,CD28

KIR & KAR

Adaptive:

MHC I & II molecules

BCR

TCR

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## VII – Myeloid Cells

### VII-I; Neutrophils

Mature neutrophils are seen as cells with 12 to 15 um in diameter containing nucleus with two to five lobes linked together with thin filaments of nuclear material. Cytoplasm is granulated with two types of granules. Its surface contain an array of markers like FC of IgG,C3b,C5bi,C5a and CD markers like CD16,CD52,CD49b,CD11a,CD11b and CD28.

Neutrophil displayed a number of immunologic functions like ,phagocytosis ,respiratory burst ,antibody dependent cell mediated cytotoxicity the basic of parasite extracellular killing .Among these functions ,the immune cross-road functions are the antibody assisted extracellular killing of the parasite ,and Nutrophil delivered M.tuberculosis to dendritic cells promoting tuberculus adaptive immune responses.<sup>[23]</sup>

Activated neutrophil release C5a fragment and leukotrien-B4 in the oral cavity to emigrate from the blood vessels, then macrophage liberate IL1 ,TNF which lend opportunity for

continuation of the oral inflammatory reactions. Latter on, emigration is also directed by IL8,CXCL5 and CCL2.<sup>[19,24]</sup>

### VII-ii: Eosinophils

It is the leukocyte with a characteristic intra-cytoplasmic coarse granules and bilobed nucleus. These bilobes are interconnected with filaments. They bears some surface markers such as FC of IgG and IgE,CD11a,CD11b,CD15,CD23,CD32 and CD14.Eosinophils are weak to moderate phagocytic cells ,they kills parasite through ADCC assisted extracellular killing and through respiratory burst.<sup>[25,26]</sup> They respond well to T lymphocyte chemotocitic factors.

### VIII: Mononuclear Cell system

Mononuclear cell system comprise number of cell morphotypes in different tissues have different specific tissue forms .The size of the individual cell may differ from resting to activated cell forms .Cells mostly of kidney shape nuclei with nongranular cytoplasm as in the case of blood monocyte .Cell membrane bears number of surface markers like,MHCI&II,Ia ,CR1,CR2,CD11,CD18,CD14,CD16,Cd17 and CD31.<sup>[19]</sup>

Mononuclear cell system cells performed number of immunologic functions like, phagocytosis, antigen processing ,antigen presentation ,cytokine production. Antibody activated macrophages kills helminth larvae in an antibody dependent ADCC mechanism and antibody independent mechanisms ,and recognizes foreign invading microbe through TLRs ,providing co stimulatory signals for T cells during the recognition process ,both in systemic and oral mucosal compartment.<sup>[27]</sup>

Dentritic cells(DCs) as a type of mononuclear cell system are going to be expressed within this paragraph. DCs are nonphagocytic, nonendocytic, take up and process antigens to CD4 T cells through MHC I &II ,or CD1 pathways. They provide costimulatory signals for CD4 T cells. Communication between DC and NK cells is found to be bidirectional. DC maturation stimulate to bridge the NK cells responses to T cell responses through T cell stimulation.<sup>[28,29]</sup> Professional DCs respond to environment and carry on an antigenic message to the responsive T cells instructing them either to develop tolerance state or to initiate immune response.<sup>[30]</sup>

In oral cavity the phagocytosis of the antigens is accomplished by macrophages and dendritic cells or lymphoid tissue langerhans cells. These cells process antigens internally and present their peptide fragments with MHC II molecules then briefly linked to T cells through the intracellular adhesion molecules. Recognition of these antigens promoted by the committed T cells, since T cell provides the first signal and the second signal provided by the APC.<sup>[19]</sup>

The chronic periodontitis tissue consist of CD1a langerhans cell, CD83 mature DCs infiltrating CD4 lymphoid cells in lamina propria and the activation of mature DCs by oral *Poryphoromonas gingivalis* leading to the release of cytokines as well as formation of T cell-DC foci.<sup>[29]</sup>

### – Lymphoid Cell System: IX

#### IX-i: Natural killer cells

They are large granular lymphocyte(NK).NK lacks memory, specificity and antigen binding receptors. Their KIR, KAR and immunoglobulin like receptor ILRs. NK functions through perforin action onto virus infected cells or tumor cells or the killing can be through ADCC. NK exhibits signaling with other immune cells, since they perform bidirectional activation and regulation of DCs and T cell responses.<sup>[31,19,25]</sup>

#### IX – ii; B lymphocytes

They are the bone marrow derived lymphocytes .Their ontogeny starts with lymphoid cell progenitor and developed to pre, pro, immature then mature in bone marrow. B cells have three phenotypes as B1,B2 and B10.B cells carry on their surfaces several type of markers like;CD19,CD20,CD22,B7-1,B7-2,CD5 and CD35.There are two B cell systems, the mucosal and the systemic .B cells may acts as APC or regulatory B cells in the oral compartment, presenting the antigenic peptides to the T cells, in turn the antigen primed T cell activate plasma cells to produce opsonizing antibodies usable in facilitation of phagocytosis. The IL10 and IL12 producing B cell phenotypes may take part in the cell-cell communications.<sup>[32,33,34]</sup>

#### IX – iii: T lymphocytes

This lymphocyte type is originated from the lymphoid lineage of the pluripotent stem cells in bone marrow and when it is immature migrate to the thymus for differentiation into mature T cells through the action of positive, and negative selection process with help of thymic hormones. Mature T cells are of two major phenotypes as helpers and regulators.Helpers can

be;Th0,Th1,TH2,TH3,TH9,TH17,TH22as well as natural TH2 cells.The regulator appear to be of one phenotype which is T reg.<sup>[35]</sup>

T cells helps in antibody production, cytotoxicity and regulation. TH9 plays a major role in the immune responses to parasite. It enhances T reg activity and dampen TH17 induced autoimmune gastritis. Treg are of natural and adaptive types. Oral TH3, T reg. have important roles in oral immune mechanisms.<sup>[36,37,38,39]</sup>

**Table 3: The immune cells at the cross-roads between innate and adaptive immunity.**

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Natural (innate):

Meyloid Cells,

Neutrophil

Eosinophil

Basophil

Mononuclear cell system, Lymphomeyloid

Macrophage types

Lymphoid,

NK,NKT

Natural TH2 ,natural T reg.

Cross-Roads,

Neutrophil

Macrophage types

NK,NKT

Adaptive;

Activated macrophage

B cells

T cells including helpers and regulator

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### **X-Mediators**

#### **X – i: Antibodies**

Antibodies are specific immunoglobulins(Igs), Igs are described as four chains units. Two heavy and two light chains .Each of the chain types has fixed carboxy and variable amino terminals. Specificity resides in the paratope regions of the molecule. The antibodies have

opsonizing activities. They may have enhancing phagocytic and extracellular killing potentials.

Oral existing antibodies can be of local or systemic origins. Such antibodies may have a role in opsonization of the antigens from the oral invading microbes. Or they may form immune complexes with the locally available complement proteins of the saliva. They may be involved in the extracellular killing of parasites by micro or macrophages through ADCC and take part in complement mediated bacteriolysis. Oral SIgA through immune exclusion mechanisms can inhibit the adherence of the invading bacteria to the oral mucosa.<sup>[19,39,40]</sup>

### **X- ii: Cytokines**

Cytokines are hormone-like peptides that act in a network-like way, and are produced by both immune and non-immune cells. They are classified in different classification trends, like according to; the source, immunity, haemopoiesis and regulatory potentials. Cytokines can be produced in local tissues or on the systemic levels. Interferon alpha and beta were working in the innate immune mechanisms to virus infection within the period when no antibody formed, while interferon gamma is working well in the adaptive immune responses. IL17 express an interplay in immune functions both in the innate and adaptive immune mechanisms. IL8 direct the neutrophil migration within the oral mucosa with help of IL1 and TNF.<sup>[19]</sup>

Oral TH1 cells produce cytokines that activate mainly macrophages while oral TH2 cells secrete their cytokines within the oral cavity to help in local mucosal antibody production.<sup>[12,19]</sup>

### **XI- Signalings**

Cell-Cell relations take several forms like, direct killing(CTL,NK), suppressive action(Treg.), helper effect(TH1,TH2,TH3,TH9,TH17,TH22),Competitive effect, energizing and tolerizing effects. Cell-cell communication occurs through direct contact or through cytokine action or through both mechanisms. When, lymphocyte release cytokine, the released cytokine binds to a receptor on other cell, such binding influences the function of cell bound that cytokine. Cytokine acts as intracellular messenger. Signal transduction is the molecular events that transmit signal to the cell interior and induce specific cellular responses. NK-DC cross-talk involved cell-cell contact as well as cytokine action. Cross-talk may happen between immune-immune cells, immune cell and the intracellular pathogen and between the intracellular pathogen and immune cells.<sup>[31,32,41,42]</sup>

## XII – CONCLUSION

The immune system is a tripartite system rather than dipartite system. This system may be subdivided into natural, cross-roads and adaptive responses. It can be ramified into systemic and mucosal immune compartments. The relation of mucosal to systemic is a matter of debate. The immune cross-roads was detailed to their own components. To this end, the immune cross-roads can be observed in the oral mucosal compartment, the way similar to that found in the systemic immune system. Stomium is an immune compartment that harbors the tripartite elements of the mucosal immune system which can be represented by the oral mucosa, salivary gland, tonsils are the niches that serves as an acting stage for such kinds of interplays. The functional interplays between the different immune cells are depending on the cell-cell signaling and cell-cell cross-talks. Hence, oral mucosal immune compartment may represent a mini-ature to the tripartite systemic immune system.

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