Introduction and aim of the essay

Toll Like Receptors (TLRs) are a family of receptors on phagocytic cells homologues to the Drosophila receptor called Toll. TLRs function as pathogen recognition receptors (PRRs), which have an essential function in innate immunity ***(Vora et al., 2004).***

These receptors, which help the immune system to recognize pathogen associated molecular patterns (PAMPs), consist of 13 members with at least 10 human TLRs ***(Tabeta et al., 2004) .***

TLRs play an essential role in the recognition of microbial components. Dendritic cells (DC) within the epithelium express TLRs and play a sentinel role at the front line of defense ***(Hornung et al., 2002).*** Interestingly, different dendritic cell subsets express distinct sets of TLRs, and this leads to them having particular functions in innate responses and the generation of distinct T-cell subsets ***(Lebre et al., 2007).***

TLRs are members of the superfamily of Toll/Interleukin-1 receptors (TIR) with two important domains: leucine rich repeats (LRRs) and TIR domain. The intracellular TIR domain, which contains 200 amino acids, has an important role in downstream signaling while the extracellular leucine-rich repeats, which contains 24–29 amino acids repeats, has an important role in ligand recognition.TLRs have a wide range of activity in recognition of pathogen associated molecular pattern (PAMPs) ***(Rezaei et al.,2006).***

Binding of PAMPs to TLRs reflects early infection with activation of cellular signalling pathways. The common downstream signaling pathway of activated TLRs leads to activation of nuclear factor kappa B (NFkB) via myeloid differentiation protein (MyD88); Interleukin-1-

receptor-associated kinase (IRAK) and tumour necrosis factor receptor-associated factor 6 (TRAF6) signal cascade, ultimately triggering the transcription of chemokines, proinflammatory cytokines and antimicrobial substances and upregulation of cell surface molecules involved in the initiation of adaptive immune responses to pathogen and antimicrobial peptides (AMPs) ***(Amanda and Richard, 2007).***

TLR3, in contrast, activates NFkB without the MyD88 pathway, and TLR4 is only partially dependent on MyD88 for signaling ***(Amanda and Richard, 2007).***

In human skin TLRs are expressed in both DC and keratinocytes (KCs). Human keratinocytes constitutively express mRNA of TLR 1, 2, 3, 4, 5, 6, 9 and 10**.** Langerhans cells (LC) were also shown to expressTLR 1, 2, 3, 5, 6, and 10 ***(Flacher et al., 2006).***

TLRs not only sense microbial invasion but also can be activated by endogenous molecules as well as low molecular weight synthetic compounds. Given the role of innate immune machinery to provoke inflammation in host, TLRs signaling may be involved in many acute and chronic inflammatory processes in sterile and post-infection conditions such as leprosy, lung airway hyperactivity in allergic asthma, and in sepsis. By the same token, TLRs can also be associated with autoimmune diseases such as systemic lupus erythematosus or other immune unresponsive diseases like cancer. In addition, synthetic organic compounds which enhance the function of TLRs can also be useful as potential adjuvants to improve conventional vaccination strategy ***(Rabindra and Akira, 2005).***

Imidazoquinolones, such as imiquimod have been introduced into dermatologic pactice for viral warts and most recently for the treatment of epidermal skin cancers and precancerous lesions. Because the

imidazoquinolones signal through TLR7 and most probably also through TLR8, their activation profile strongly resembles that of activators of the endosomally located TLRs, with high induction of type I IFNs (IFN alpha and IFN beta) and good induction of cellular immune responses against virally infected cells ***(Hemmi et al., 2002).***

The major biologic effects of imiquimod are mediated through agonistic activity towards TLR 7and 8 and consecutively, activation of NFkB .The result of this activity is the induction of pro-inflammatory cytokines and chemokines leading to activation of antigen-presenting cells (APCs) and other components of innate immunity and eventually the mounting of a profound T-helper (Th1) weighted antitumoral cellular immune response ***(Schön, 2007).***

Aim of the essay

The aim of this essay was to throw the light on Toll like receptors and their role in normal skin, in the pathogenesis of skin diseases and the possibility of being a therapeutic tool.