Reviewer's report

Title: Toll-Like receptor 2 activation and comedogenesis: implications for the pathogenesis of acne

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Reviewer: Christos Zouboulis

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This is an interesting work confirming previous data of the direct involvement of IL-1β in comedogenesis. Despite the straightforward experimental design the authors use much space in their introduction to discuss on the current knowledge on TLR and provide a weak discussion of their data.

Abstract: The abstract has to be rewritten accordingly (s. below).

Introduction: The TLR description part has to be reduced markedly.


Page 4, lines 5-7: "We have previously speculated on the source of infundibular IL-1β in acne, which could be released either by keratinocytes [11, 12] or by the cells of the immune system [13, 14].": None of the authors was involved in any of the references [11-14], therefore, this sentence has to be rewritten.

Page 8, lines 15-17: "The expression of TLRs in both interfollicular and infundibular human keratinocytes is consistent with an innate role for these cells in the sensing of and response to bacterial pathogens." The authors have to add the term "The expression of functional TLRs..." and refer the first relevant publication: Song PI et al. J Invest Dermatol 119:424-32, 2002 Page 8, lines 22-25, page 9, lines 1-12: "There exists conflicting data on the compartmental expression of TLR2. Our observation of predominantly basal localisation in a range of human skin samples agrees with the reports of Baker et al [17] and Curry et al [18]. However, both Pivarcsi et al [19] and Jugeau et al [16] reported suprabasal TLR2 expression, which may be as a consequence of variation in detection techniques (or differences in donor sites). Alternatively, it may reflect real variation in TLR2 expression between individuals, particularly as Baker et al [17] reported variation in TLR1, TLR3 and TLR4 expression profiles. Such variation in TLR expression may be as a consequence of genetic differences in innate immunity, or result from environmental challenges as TLRs are exquisitely sensitive to induction [20]. The variation in TLR expression between individuals, and localization within different epidermal compartments, may contribute to the stochastic occurrence of acne in that a subset of infundibula may be “primed” to respond to changes in skin flora. It has been demonstrated that viable
stationary-phase P. acnes is able to directly activate NHEK via TLR2, stimulating IL-1# release [21]. " Neither conflicting data exist nor is the differential epidermal level expression of TLR2 a consequence of variation in detection techniques. Baker and Curry reported TLR2 expression in psoriatic epidermis, which is per definition hyperproliferative and exhibits a proinflammatory status. Therefore, the data of Pivarcsi et al [19] and Jugeau et al [16] are relevant for acne and the authors of the current manuscript have to further explain their inconsistent observation of predominantly basal localisation of TLR2 and look for the origin of their "range of human skin samples", which are not reported in the Materials and Methods" chapter. In addition, these data, which are only commented in the discussion have to be added in the Results section. The further discussion on "individual variations" and "stochastic occurrence of acne" has to be omitted, since no data of the authors support any of these speculative points.

Page 9, lines 13-16: These proposals have already been confirmed and published by Song PI et al. J Invest Dermatol 119:424-32, 2002 and Pivarcsi et al [19] in reference to acne, whereas the reference [22] has nothing to do with this disease.

Page 9, lines 17-19: " We found that the treatment of primary cultures of keratinocytes with TLR2 agonists provoked the release of IL-1#, confirming our hypothesis that the IL-1#responsible for infundibular cornification in acne could originate from lesional keratinocytes." The authors have to report that they confirm previously published data such as by Song PI et al. J Invest Dermatol 119:424-32, 2002 and Pivarcsi et al [19] and many others.

Page 9, lines 22-25: " Furthermore, normal morphology was maintained when PAMP activity was neutralized with specific TLR blocking antibodies, suggesting that TLR activation is indeed a potential initiating step for cornification in both infundibular keratinocytes and sebocytes." In the experiments of the authors PAMP activity was reduced but neutralized with specific TLR blocking antibodies. Therefore, a definitive conclusion is still not possible. On the other hand, sebocyte cornification is a wider matter of lineage instability or change, the authors could read unter: Selleri S et al J Invest Dermatol 126:711-20, 2006 and Ju Q et al. Exp Dermatol 20:320-5, 2011.


**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests