experience spontaneous inflammasome activation and paracrine IL-1 signalling, which is sufficient to cause symptoms, such as skin inflammation and epidermal hyperplasia.

[005] Although the function of NLR proteins in systemic inflammation is well established, less is known about their roles in organ-specific immune response and tissue homeostasis, particularly in epithelial tissues such as, for example, the skin. Apart from forming a structural barrier, human skin actively interacts with the immune system in guarding against invading pathogens and tissue damage. On the other hand, chronic unresolved skin inflammation can result in a variety of dermatological diseases and promote the development of both benign and malignant epithelial skin lesions.

[006] Thus, there is a need for methods and agents for treating or preventing skin disorders and determining cancer susceptibility.

SUMMARY OF THE INVENTION

[006a] In one aspect, the present invention refers to a method of determining the likelihood or predisposition of a subject in developing an inflammatory skin disorder and/or an autoimmune skin disorder, comprising detecting one or more mutations in the NLR family, pyrin domain containing protein 1 (NLRP1) in a sample obtained from the subject, wherein when one or more NLRP1 mutations are located at its Pyrin (PYD) and/or LRR (leucine-rich repeats) domain, the subject has increased likelihood or predisposition in developing said disorders. In another aspect, the present invention refers a method of determining whether a skin inflammation in a subject is caused by an inflammatory skin disorder and/or an autoimmune skin disorder, comprising detecting one or more mutations in the NLR family, pyrin domain containing protein 1 (NLRP1) in a sample obtained from the subject, wherein when one or more NLRP1 mutations are located at its PYD (Pyrin) and/or LRR (leucine-rich repeats) domain, the skin inflammation in the subject is caused by an inflammatory skin disorder and/or an autoimmune skin disorder. In yet another aspect, the present invention refers to the use of a therapeutically effective amount of an inhibitor capable of inhibiting the activation of NLRP1 in the manufacture of a medicament for treating a skin inflammation and/or an autoimmune skin disorder in a subject, wherein the subject has one or more NLRP1 mutations located at its Pyrin (PYD) and/or LRR (leucine-rich repeats) domain.

[007] In one example, the present disclosure refers to a method of treating or preventing an autoimmune skin disorder and/or inflammatory skin disorder in a subject in need thereof, comprising administering a therapeutically effective amount of an inhibitor capable of inhibiting the activation of inflammasome sensor NLRP1 (Nucleotide-binding domain, leucine-rich repeat containing (NLR) family, pyrin domain containing protein 1 – NLPR1).

[008] In another example, the present disclosure refers to a method of treating or preventing an autoimmune skin disorder and/or inflammatory skin disorder in a subject in need thereof, comprising administering a therapeutically effective amount of an agent that prevents the secretion of stress responsive secreted factors, known pro-inflammatory cytokines, keratinocytes differentiation markers, inflammasome-dependent cytokines, and growth factors in the skin.

[009] In yet another example, the present disclosure refers to a method of treating or preventing an autoimmune skin disorder and/or an inflammatory skin disorder in a subject in need thereof, comprising administering a therapeutically effective amount of an agent that reduces the effect of inflammasome-dependent cytokines.

[0010] In a further example, the present disclosure refers to a method of determining whether a skin inflammation in a subject is an inflammatory skin disorder and/or an autoimmune skin disorder, comprising detecting NLRP1 mutation in a sample obtained from the subject.

[0011] In another example, the present disclosure refers to a method of determining the likelihood (or predisposition) of a subject in developing an inflammatory skin disorder and/or an autoimmune skin disorder, comprising detecting NLRP1 mutation in a sample obtained from the subject.

[0012] In yet another example, the present disclosure refers to A method of treating a skin inflammation in a subject, comprising detecting NLRP1 mutation in a sample obtained from the subject; determining whether the subject has NLRP1 mutation; and wherein when the subject has NLRP1 mutation, treating the skin inflammation in the subject by administering any one of selected from the group consisting of: a therapeutically effective amount of an inhibitor capable of inhibiting the activation of inflammasome sensor NLRP1 (Nucleotide-binding domain, leucine-rich repeat containing (NLR) family, pyrin domain containing protein 1 – NLPR1); a therapeutically effective amount of an agent that prevents the secretion of stress responsive secreted factors, known pro-inflammatory cytokines, keratinocytes differentiation markers, inflammasome-dependent cytokines, and growth factors in the skin; a therapeutically effective amount of an agent that reduces the effect of inflammasome-dependent cytokines; and a therapeutically effective amount of an inflammasome sensor NLRP1 mutant into the subject in need thereof.

[0013] In a further example, the present disclosure refers to a method of treating or preventing a skin tumour in a subject in need thereof, comprising administering a therapeutically effective amount of an inflammasome sensor NLRP1 mutant into the subject in need thereof.

[0014] In another example, the present disclosure refers to an isolated polypeptide having at least 70% sequence identity to the polypeptide of mutant NLRP1, or fragment thereof.

[0015] In yet another example, the present disclosure refers to an isolated nucleic acid having at least 70% sequence identity to the nucleic acid of mutant NLRP1, or fragment thereof.

[0016] In another example, the present disclosure refers to a vector comprising the nucleic acid as disclosed herein.

[0017] In a further example, the present disclosure refers to a host cell comprising the vector as disclosed herein.

[0018] In one example, the present disclosure refers to a cell culture system comprising the host cell as disclosed herein.

[0019] In another example, the present disclosure refers to a method of treating obesity and/or metabolic disorder in a subject in need thereof, comprising administering a therapeutically effective amount of an inflammasome sensor NLRP1 mutant into the subject in need thereof.

[0020] In yet another example, the present disclosure refers to a method of treating or preventing cancer in a subject in need thereof, comprising administering a therapeutically effective amount of an activator capable of activating inflammasome sensor NLRP1.

BRIEF DESCRIPTION OF THE DRAWINGS

CLAIMS

1. A method of determining the likelihood or predisposition of a subject in developing an inflammatory skin disorder and/or an autoimmune skin disorder, comprising detecting one or more mutations in the NLR family, pyrin domain containing protein 1 (NLRP1) in a sample obtained from the subject, wherein when one or more NLRP1 mutations are located at its Pyrin (PYD) and/or LRR (leucine-rich repeats) domain, the subject has increased likelihood or predisposition in developing said disorders.

2. A method of determining whether a skin inflammation in a subject is caused by an inflammatory skin disorder and/or an autoimmune skin disorder, comprising detecting one or more mutations in the NLR family, pyrin domain containing protein 1 (NLRP1) in a sample obtained from the subject, wherein when one or more NLRP1 mutations are located at its PYD (Pyrin) and/or LRR (leucine-rich repeats) domain, the skin inflammation in the subject is caused by an inflammatory skin disorder and/or an autoimmune skin disorder.

3. The method of claim 1 or 2, wherein the one or more NLRP1 mutations are located at its PYD domain.

4. The method of any one of claims 1-3, wherein the one or more NLRP1 mutations result in at least one or two or all amino acid substitution selected from the group consisting of A54T, M77T, and A66V.

5. The method of claim 1 or 2, wherein the one or more NLRP1 mutations are located at the LRR domain.

6. The method of any one of claims 1, 2, 5, wherein one NLRP1 mutation results in the deletion of amino acid phenylalanine at position 787 to arginine at position 843 (F787 to R843 or F787_R843del).

7. The method of any of claims 1-6, wherein the method further comprises detecting increased accumulation of oligomerised ASC (Apoptosis-associated speck-like protein

containing a CARD), also known as PYCARD) in the sample derived from the patient as compared to a sample derived from an individual not carrying said NLRP1 mutations.

8. The method of claim 7, wherein the method further comprises:
   a) isolating keratinocytes from the subject and culturing them *in vitro*;
   b) obtaining cell lysate from the cell keratinocyte cell culture and applying a chemical cross-linking agent to the cell lysate;
   c) analysing the cell lysate with Western-Blot using an ASC antibody to detect oligomerisation of ASC, wherein the oligomerisation is indicated by the presence of protein bands corresponding to molecule sizes larger than that of single ASC protein.

9. Use of a therapeutically effective amount of an inhibitor capable of inhibiting the activation of NLRP1 in the manufacture of a medicament for treating a skin inflammation and/or an autoimmune skin disorder in a subject, wherein the subject has one or more NLRP1 mutations located at its Pyrin (PYD) and/or LRR (leucine-rich repeats) domain.

10. The use of claim 9, wherein the one or more NLRP1 mutations are located at its PYD domain.

11. The use of claim 9 or 10, wherein the one or more NLRP1 mutations result in at least one or two or all amino acid substitution selected from the group consisting of A54T, M77T, and A66V.

12. The use of claim 9, wherein the one or more NLRP1 mutations are located at the LRR domain.

13. The use of claim 9 or 12, wherein one of the NLRP1 mutations results in the deletion of amino acid phenylalanine at position 787 to arginine at position 843 (F787 to R843 or F787_R843del).

14. The use of any one of claims 9 to 13, wherein the use further comprises detecting increased accumulation of oligomerised ASC (Apoptosis-associated speck-like protein containing a CARD), also known as PYCARD) in the sample derived from the patient as compared to a sample derived from an individual not carrying said NLRP1 mutations.

15. The use of claim 14, wherein the accumulation of oligomerisation is detected by: a) isolating keratinocytes from the subject and culturing them in vitro; b) obtaining cell lysate from the cell keratinocyte cell culture and applying a chemical cross-linking agent to the cell lysate; c) analysing the cell lysate with Western-Blot using an ASC antibody to detect oligomerisation of ASC, wherein the oligomerisation is indicated by the presence of protein bands corresponding to molecule sizes larger than that of single ASC protein..

16. The use of any one of claims 9-15, wherein the inhibitor inhibits the activation of NLRP1 by:

1) preventing the oligomerisation of NLRP1; or
2) preventing the proteolytic cleavage of NLRP1, wherein the location of the proteolytic cleavage is within the FIIND domain of NLRP1, wherein the location of the proteolytic cleavage is between phenylalanine at position 1212 and serine at position 1213.

17. The method of any one of claims 1 to 8 or the use of any one of claims 9-16, wherein the sample is selected from the group consisting of bodily fluid, and skin.

18. The method of any one of claims 1 to 8 or the use of any one of claims 9-16, wherein the skin is selected from the group consisting of epidermis, glabrous skin, plantar skin, and epidermal appendages.

19. The method of any one of claims 1 to 8 or the use of any one of claims 9-16, wherein the skin is keratinocytes and/or fibroblast.

20. The method of any one of claims 1 to 8 or the use of any one of claims 9-16, wherein the inflammatory skin disorder and/or autoimmune skin disorder is selected from the group consisting of MSPC (multiple self-healing palmoplantar carcinoma), FKLC (familial keratosis lichenoides chronica), conjunctiva, CAPSs (cryopyrin-associated periodic syndromes), FMFs (familial Mediterranean fever syndromes), MASs (macrophage activation syndromes), KAs (Keratoacanthomas), MSEE (multiple self-healing squamous epithelioma), KLC (keratosis lichenoides chronica), Nekam's disease, psoriasis, vitiligo-related autoimmune diseases, epidermal inflammation, hyperplasia, epithelial hyperplasia, generalized vitiligo, Addison's disease, congenital toxoplamosis, keratosis pilaris, lichen planus, and skin tumour.

21. The method or the use of claim 20, wherein the MSPC is selected from the group consisting of MSPC-TN-1, MSPC-RO-1, MSPC-FR-1, and MSPC SCC.

22. The method or the use of claim 20, wherein the FKLC is FKLC-EG-1.