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(54) **HOMOGENEOUS PREPARATIONS OF IL-31**

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(57) **ABSTRACT**

Homogeneous preparations of human and murine IL-31 have been produced by mutating one or more of the cysteine residues in the polynucleotide sequences encoding the mature proteins. The cysteine mutant proteins can be shown to either bind to their cognate receptor or exhibit biological activity.

HOMOGENEOUS PREPARATIONS OF IL-31

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 60/648,189, filed Jan. 28, 2005, which is herein incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] The increased availability and identification of genes from human and other genomes has led to an increased need for efficient expression and purification of recombinant proteins. The expression of proteins in bacteria is by far the most widely used approach for the production of cloned genes. For many reasons, expression in bacteria is preferred to expression in eukaryotic cells. For example, bacteria are much easier to grow than eukaryotic cells. More specifically, the availability of a wealth of sophisticated molecular genetic tools and thousands of mutants make *E. coli,* as an expression host, extremely useful for protein production. However, the high-level production of functional proteins in *E. coli.,* especially those from eukaryotic sources has often been difficult.

[0003] IL-31 is a recently discovered protein having the structure of a four-helical-bundle cytokine. This new cytokine is fully described in co-owned PCT application WO 03/060090 and Dillon, et al., *Nautre Immunol.* 5:752-760, 2004; both incorporated by reference herein. IL-31 is a ligand with high specificity for the receptor IL-31RA and at least one additional subunit comprising OncostatinM receptor beta. IL-31 was isolated from a cDNA library generated from activated human peripheral blood cells (hPBCs), which were selected for CD3. CD3 is a cell surface marker unique to cells of lymphoid origin, particularly T cells.

[0004] Both the murine and human forms of IL-31 are known to have an odd number of cysteines. (PCT application WO 03/060090 and Dillon, et al., supra.) Expression of recombinant IL-31 can result in a heterologous mixture of proteins composed of intramolecular disulfide binding in multiple conformations. The separation of these forms can be difficult and laborious. It is therefore desirable to provide IL-31 molecules having a single intramolecular disulfide bonding pattern upon expression and methods for refolding and purifying these preparations to maintain homogeneity. Thus, the present invention provides for compositions and methods to produce homogeneous preparations of IL-31.

[0005] Despite advances in the expression of recombinant proteins in bacterial hosts, there exists a need for improved methods for producing biologically active and purified recombinant IL-31 proteins in prokaryotic systems which result in higher yields for protein production. These and other aspects of the invention will become evident upon reference to the following detailed description. In addition, various references are identified below and are incorporated by reference in their entirety.

[0006] The present invention provides such polypeptides for these and other uses that should be apparent to those skilled in the art from the teachings herein.

SUMMARY OF THE INVENTION

selected from the group consisting of SEQ ID NOs: 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30.

[0008] Within another aspect, the invention provides an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30; and a transcription terminator.

[0009] Within another aspect, the invention provides a cultured cell into which has been introduced an expression vector comprising a DNA segment encoding a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30, wherein the cell expresses the polypeptide encoded by the DNA segment. Within an embodiment the cultured cell is a prokaryotic cell. Within another embodiment the cell is a gram negative cell. Within another embodiment the cell is *E. coli.* Within another embodiment, the *E. coli* cell is *E. coli* strain W3110.

[0010] Within another aspect, the invention provides a process for producing a polypeptide comprising:

[0011] culturing a cell into which has been introduced an expression vector comprising a DNA segment encoding a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30, wherein the cell expresses the polypeptide encoded by the DNA segment; and recovering the expressed polypeptide.

[0012] Within another aspect, the invention provides an antibody or antibody fragment that specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30. Within an embodiment the antibody is selected from the group consisting of a polyclonal antibody, a murine monoclonal antibody, a humanized antibody derived from a murine monoclonal antibody, an antibody fragment, neutralizing antibody, and a human monoclonal antibody. Within another embodiment the antibody fragment is selected from the group consisting of F(ab'), F(ab), Fab', Fab, Fv, scFv, and minimal recognition unit.

[0013] Within another aspect is provided an anti-idiotype antibody comprising an anti-idiotype antibody that specifically binds to the antibody.

[0014] Within another aspect the invention provides an isolated polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30.

[0015] Within another aspect is provided a formulation comprising:

[0016] an isolated polypeptide selected from the group consisting of SEQ ID NOs: 4, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30; and

[0017] a pharmaceutically acceptable vehicle. Within an embodiment, formulation is provide in a kit.

of SEQ ID NOs: 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30 is proinflammatory.

[0019] Within another aspect the invention provides an isolated polypeptide comprising the amino acid sequence from residue 2 to residue 133 of SEQ ID NO: 23.

DETAILED DESCRIPTION OF THE INVENTION

[0020] Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms:

[0021] The term "affinity tag" is used herein to denote a polypeptide segment that can be attached to a second polypeptide to provide for purification or detection of the second polypeptide or provide sites for attachment of the second polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-histidine tract, protein A (Nilsson et al., EMBO J. 4:1075, 1985; Nilsson et al., Methods Enzymol. 198:3, 1991), glutathione S transferase (Smith and Johnson, Gene 67:31, 1988), Glu-Glu affinity tag (Grussenmeyer et al., Proc. Natl. Acad. Sci. USA 82:79524, 1985), substance P, Flag™ peptide (Hopp et al., Biotechnology 6:1204-10, 1988), streptavidin binding peptide, or other antigenic epitope or binding domain. See, in general, Ford et al., Protein Expression and Purification 2: 95-107, 1991. DNAs encoding affinity tags are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, N.J.).

[0022] The term "allelic variant" is used herein to denote any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequence. The term allelic variant is also used herein to denote a protein encoded by an allelic variant of a gene.

[0023] The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete polypeptide.

[0024] The term "complement/anti-complement pair" denotes non-identical moieties that form a noncovalently associated, stable pair under appropriate conditions. For instance, biotin and avidin (or streptavidin) are prototypical members of a complement/anti-complement pair. Other exemplary complement/anti-complement pairs include receptor/ligand pairs, antibody/antigen (or hapten or epitope) pairs, sense/antisense polynucleotide pairs, and the like. Where subsequent dissociation of the complement/anti-complement pair is desirable, the complement/anti-complement pair preferably has a binding affinity of <109 M-1.

mentary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

[0026] The term "contig" denotes a polynucleotide that has a contiguous stretch of identical or complementary sequence to another polynucleotide. Contiguous sequences are said to "overlap" a given stretch of polynucleotide sequence either in their entirety or along a partial stretch of the polynucleotide. For example, representative contigs to the polynucleotide sequence 5'-ATGGCTTAGCTT-3' are 5'-TAGCTTgagtct-3' and 3'-gtcgacTACCGA-5'.

[0027] The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons contain different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

[0028] The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

[0029] The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, Nature 316:774-78, 1985).

[0030] An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide is substantially free of other polypeptides, particularly other polypeptides of animal origin. It is preferred to provide the polypeptides in a highly purified form, i.e., greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

[0031] The term "neoplastic", when referring to cells, indicates cells undergoing new and abnormal proliferation, particularly in a tissue where in the proliferation is uncontrolled and progressive, resulting in a neoplasm. The neoplastic cells can be either malignant, i.e., invasive-and metastatic, or benign.

that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator.

[0033] The term "ortholog" denotes a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

[0034] "Paralogs" are distinct but structurally related proteins made by an organism. Paralogs are believed to arise through gene duplication. For example, α-globin, β-globin, and myoglobin are paralogs of each other.

[0035] A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized in vitro, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired.

[0036] A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10 amino acid residues are commonly referred to as "peptides".

[0037] The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

[0038] A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

[0039] The term "receptor" denotes a cell-associated protein that binds to a bioactive molecule (i.e., a ligand) and mediates the effect of the ligand on the cell. Membrane-bound receptors are characterized by a multi-peptide structure comprising an extracellular ligand-binding domain and an intracellular effector domain that is typically involved in signal transduction. Binding of ligand to receptor results in a conformational change in the receptor that causes an interaction between the effector domain and other molecule(s) in the cell. This interaction in turn leads to an alteration in the metabolism of the cell. Metabolic events

transcription, phosphorylation, dephosphorylation, increases in cyclic AMP production, mobilization of cellular calcium, mobilization of membrane lipids, cell adhesion, hydrolysis of inositol lipids and hydrolysis of phospholipids. In general, receptors can be membrane bound, cytosolic or nuclear; monomeric (e.g., thyroid stimulating hormone receptor, beta-adrenergic receptor) or multimeric (e.g., PDGF receptor, growth hormone receptor, IL-3 receptor, GM-CSF receptor, G-CSF receptor, erythropoietin receptor and IL-6 receptor).

[0040] The term "secretory signal sequence" denotes a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

[0041] The term "splice variant" is used herein to denote alternative forms of RNA transcribed from a gene. Splice variation arises naturally through use of alternative splicing sites within a transcribed RNA molecule, or less commonly between separately transcribed RNA molecules, and may result in several mRNAs transcribed from the same gene. Splice variants may encode polypeptides having altered amino acid sequence. The term splice variant is also used herein to denote a protein encoded by a splice variant of an mRNA transcribed from a gene.

[0042] Molecular weights and lengths of polymers determined by imprecise analytical methods (e.g., gel electrophoresis) will be understood to be approximate values. When such a value is expressed as "about" X or "approximately" X, the stated value of X will be understood to be accurate to ±10%.

[0043] All references cited herein are incorporated by reference in their entirety.

[0044] The present invention provides expression vectors and methods for producing recombinant IL-31 protein from a prokaryotic host and is based in part upon the discovery of compositions and methods to produce homogeneous preparations of IL-31. IL-31 is a recently discovered protein having the structure of a four-helical-bundle cytokine. This cytokine was previously identified as IL-31 and is fully described in co-assigned U.S. patent application Ser. No. 10/352,554, filed Jan. 21, 2003. See published U.S. Patent Application No. 2003-0224487, and PCT application WO 03/060090, both herein incorporated by reference. See also, Dillon, et al., *Nautre Immunol.* 5:752-760, 2004. IL-31 is a ligand with high specificity for the receptor IL-31RA and at least one additional subunit comprising OncostatinM receptor beta (OSMRbeta). The native polynucleotide and polypeptide sequences for human IL-31 are shown in SEQ ID NOs: 1 and 2, respectively. SEQ ID NO:3 shows the degenerate polynucleotide for the polypeptide having the amino acid sequence as shown in SEQ ID NO:2. The native polynucleotide and polypeptide sequences for mouse IL-31 are shown in SEQ ID NOs: 4 and 5, respectively. SEQ ID NO:6 shows the degenerate polynucleotide for the polypeptide having the amino acid sequence as shown in SEQ ID NO:5. The native polynucleotide and polypeptide sequences for human IL-31RA are shown in SEQ ID NOs: 7 and 8,

9 and 10, respectively. The native polynucleotide and polypeptide sequences for human OSMRbeta are shown in SEQ ID NOs: 11 and 12, respectively.

[0045] Both the murine and human forms of IL-31 are known to have an odd number of cysteines. (PCT application WO 03/060090 and Dillon, et al., supra.) Expression of recombinant IL-31 can result in a heterologous mixture of proteins composed of intramolecular disulfide binding in multiple conformations. The separation of these forms can be difficult and laborious. It is therefore desirable to provide IL-31 molecules having a single intramolecular disulfide bonding pattern upon expression and methods for refolding and purifying these preparations to maintain homogeneity.

[0046] In particular, the expression vectors and methods of the present invention comprise an *E. coli* expression system. Using the expression vectors described herein significantly improved the yield of recombinant protein recovered from the bacteria.

[0047] The present invention provides polynucleotide molecules, including DNA and RNA molecules, that encode Cysteine mutants of IL-31 that result in expression of a recombinant IL-31 preparation that is a homogeneous preparation. For the purposes of this invention, a homogeneous preparation of IL-31 is a preparation which comprises at least 98% of a single intramolecular disulfide bonding pattern in the purified polypeptide. In other embodiments, the single disulfide conformation in a preparation of purified polypeptide is at 99% homogeneous. In general, these Cysteine mutants will maintain some biological activity of the wildtype IL-31, as described herein. For example, the molecules of the present invention can bind to the IL-31 receptor with some specificity. Generally, a ligand binding to its cognate receptor is specific when the KD falls within the range of 100 nM to 100 pM. Specific binding in the range of 100 mM to 10 nM KD is low affinity binding. Specific binding in the range of 2.5 pM to 100 pM KD is high affinity binding. In another example, biological activity of IL-31 Cysteine mutants is present when the molecules are capable of some level of activity associated with wildtype IL-31 as described in detail herein.

[0048] When referring to native IL-31, the term shall mean IL-31 and zcytor17lig. When referring to IL-31RA, the term shall mean IL-31RA and zcytor17.

[0049] The present invention also provides methods for recovering recombinant IL-31 protein from a prokaryotic host when the IL-31 protein is expressed by the host and found within the host cell as an unglycosylated, insoluble inclusion body. When the prokaryotic cell is lysed to isolate the inclusion bodies (also called refractile bodies), the inclusion bodies are aggregates of IL-31. Therefore, the inclusion bodies must be disassociated and dissolved to isolate the IL-31 protein, and generally this requires the use of a denaturing chaotropic solvent, resulting in recovering a polypeptide that must be refolded to have significant biological activity. Once the IL-31 protein is refolded, the protein must be captured and purified. Thus, the present invention provides for methods for isolating insoluble IL-31 protein from prokaryotic cells, dissolving the insoluble IL-31 protein material in a chaotropic solvent, diluting the chaotropic solvent in such a manner that the IL-31 protein is refold buffer using cation exchange chromatography, and purifying the refolded IL-31 protein using hydrophobic interaction chromatography. Further purification is achieved using anion exchange in binding assays using an IL-31 receptor and the like.

[0050] The present invention provides mutations in the IL-31 wildtype sequences as shown in SEQ ID NOs: 1, 2, 3, 4, 5, and 6, that result in expression of single forms of the IL-31 molecule. Because the heterogeneity of forms is believed to be a result of multiple intramolecular disulfide bonding patterns, specific embodiments of the present invention includes mutations to the cysteine residues within the wildtype IL-31 sequences. The mature human IL-31 polypeptide is shown in SEQ ID NO:13, with SEQ ID NO:49 showing the mature human IL-31 polypeptide with a start methionine. Molecules of the mature human IL-31 polypeptide can have disulfide bonds between the cysteine residue at position 46 and position 107 of SEQ ID NO:13, between position 46 and 121 of SEQ ID NO:13, and between position 107 and 121 of SEQ ID NO:13. A mutation of any of these three cysteines results in a mutant form of the human IL-31 protein that will only form one disulfide bond. Thus a mutation at postion 46 will result in a protein that forms a disulfide bond between position 107 and position 121 of SEQ ID NO:13; a mutation at position 107 will result in a protein that forms a disulfide bond between position 46 and position 121 of SEQ ID NO:13; and a mutation at position 121 will result in a protein that forms a disulfide bond between position 46 and position 107 of SEQ ID NO:13. The cysteines in these positions can be mutated, for example, to a serine, alanine, threonine, valine, or asparagine. For example, a human IL-31 protein having a mutation from cysteine to serine at position 46 of SEQ ID NO:13 is shown in SEQ ID NO:14; a human IL-31 protein having a mutation from cysteine to serine at position 107 of SEQ ID NO:13 is shown in SEQ ID NO:15; a human IL-31 protein having a mutation from cysteine to serine at position 121 of SEQ ID NO:13 is shown in SEQ ID NO:16.

[0051] When human IL-31 is expressed in *E. coli,* an N-terminal or amino-terminal Methionine is present. SEQ ID NOs:17-19, for example, show the nucleotide and amino acid residue sequences for IL-31 when the N-terminal Met is present in these mutants.

[0052] Similar mutations can be made to the mouse IL-31 polypeptide sequence. The mature mouse IL-31 polypeptide is shown in SEQ ID NO:20. Molecules of the mature murine IL-31 polypeptide can have disulfide bonds between the cysteine residue at position 44 and position 87 of SEQ ID NO:20, between position 44 and 107 of SEQ ID NO:20, between position 44 and 121 of SEQ ID NO:20; between position 44 and 133 of SEQ ID NO:20; between position 87 and 107of SEQ ID NO:20; between position 87 and 121 of SEQ ID NO:20; between position 87 and 133 of SEQ ID NO:20; between position 107 and 121 of SEQ ID NO:20; between position 107 and 133 of SEQ ID NO:20; and between position 121 and 133 of SEQ ID NO:20. A mutation of any of these cysteines results in a mutant form of the mouse IL-31 protein. The cysteines in these positions can be mutated, for example, to a serine, alanine, threonine, valine, or asparagine. For example, a mouse IL-31 protein having a mutation from cysteine to serine at position 44 of SEQ ID

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