CLAIMS

1. A mammalian cell comprising a recombinant polynucleotide that encodes an endoplasmic reticulum degradation-enhancing alpha-mannosidase-like protein 2 (EDEM2) ~~a stress-induced mannose-binding lectin~~ and a polynucleotide that encodes a multi-subunit protein.

2. The cell of claim 1, ~~wherein the stress-induced mannose-binding lectin is an endoplasmic reticulum degradation-enhancing alpha-mannosidase-like protein 2 (EDEM2), preferably~~ wherein the EDEM2 comprises an amino acid sequence of SEQ ID NO: 8 or the EDEM2 comprises an amino acid sequence that is at least 92% identical to SEQ ID NO: 1.

3. The cell of claims 1 or 2, wherein the multi-subunit protein is an antibody.

4. The cell of claim 3, wherein the antibody comprises amino acid sequences of SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46.

5. The cell of any one of claims 1 to 4, wherein

(a) the cell comprises a polynucleotide that encodes an unfolded protein response transcription factor that operates upstream of EDEM2, preferably wherein the transcription factor is a spliced form of XBP-1, more preferably wherein the XBP-1 comprises an amino acid sequence of SEQ ID NO: 13 or the XBP-1 comprises an amino acid sequence that is at least 86% identical to SEQ ID NO: 9;

~~(b) the cell is a mammalian cell; and/or~~

(b~~c~~) the mammalian cell is a CHO cell.

6. A cell line derived from the cell of any one of claims 1 to 5, wherein the cell line:

(a) produces the protein at a titer of at least 3 g/L, preferably which produces the protein at a titer of at least 5 g/L, more preferably which produces the protein at a titer of at least 8 g/L;

(b) has an integrated cell density that is at least about 30% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin;

(c) has an integrated cell density that is at least about 50% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin;

(d) has an integrated cell density that is at least about 60% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin; and/or

(e) has an integrated cell density that is at least about 90% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin.

~~7. An isolated polynucleotide comprising a nucleotide sequence, which encodes an EDEM2, operably linked to a promoter, preferably wherein:~~

~~(a) the EDEM2 comprises the amino acid sequence of SEQ ID NO: 8 or consists of the amino acid sequence of SEQ ID NO: 8;~~

~~(b) the EDEM2 comprises an amino acid sequence that is at least 92% identical to SEQ ID NO: 1 or consists of an amino acid sequence that is at least 92% identical to SEQ ID NO: 1;~~

~~(c) the EDEM2 comprises the amino acid sequence of SEQ ID NO: 1 or consists of the amino acid sequence of SEQ ID NO: 1;~~

~~(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 16;~~

~~(e) the polynucleotide comprises a promoter sequence selected from the group consisting of a mammalian ubiquitin C promoter, a SV40 promoter and a CMV-IE promoter; and/or~~

~~(f) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 14 or SEQ ID NO: 15 or consists essentially of the nucleotide sequence of SEQ ID NO: 14 or SEQ ID NO: 15.~~

~~8. The isolated polynucleotide of claim 7, wherein the polynucleotide encodes an Xbp-1 protein wherein~~

~~(a) the Xbp-1 protein comprises the amino acid sequence of SEQ ID NO: 13 or consists of the amino acid sequence of SEQ ID NO: 13;~~

~~(b) the Xbp-1 protein comprises an amino acid sequence that is at least 86% identical to SEQ ID NO: 9 or consists of an amino acid sequence that is at least 86% identical to SEQ ID NO: 9;~~

~~(c) the Xbp-1 protein comprises the amino acid sequence of SEQ ID NO: 9 or consists of the amino acid sequence of SEQ ID NO: 9;~~

~~(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 18; and/or~~

~~(e) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 17 or consists essentially of the nucleotide sequence of SEQ ID NO: 17.~~

~~9. The isolated polynucleotide of claim 7 or 8 comprising a nucleotide sequence which:~~

~~(a) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 43;~~

~~(b) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 44;~~

~~(c) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44;~~

~~(d) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 45;~~

~~(e) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 46; and/or~~

~~(f) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46.~~

~~10. The isolated polynucleotide of any one of claims 7 to 9 comprising a nucleotide sequence which encodes an anti-GDF8 antibody heavy chain wherein:~~

~~(a) the anti-GDF8 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 20;~~

~~(b) the anti-GDF8 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 19; or consists of the amino acid sequence of SEQ ID NO: 19;~~

~~(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 23; and/or~~

~~(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 24 or consists essentially of the nucleotide sequence of SEQ ID NO: 24.~~

~~11. The isolated polynucleotide of any one of claims 7 to 10 comprising a nucleotide sequence which encodes an anti-GDF8 antibody light chain wherein:~~

~~(a) the anti-GDF8 antibody light chain comprises the amino acid sequence of SEQ ID NO: 22;~~

~~(b) the anti-GDF8 antibody light chain comprises the amino acid sequence of SEQ ID NO: 21 or consists of the amino acid sequence of SEQ ID NO: 21;~~

~~(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 25; and/or~~

~~(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 26 or consists essentially of the nucleotide sequence of SEQ ID NO: 26.~~

~~12. The isolated polynucleotide of any one of claims 7 to 10 comprising a nucleotide sequence which encodes an anti-ANG2 antibody heavy chain wherein:~~

~~(a) the anti-ANG2 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 28;~~

~~(b) the anti-ANG2 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 27 or consists of the amino acid sequence of SEQ ID NO: 27;~~

~~(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 31; and/or~~

~~(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 32 or consists essentially of the nucleotide sequence of SEQ ID NO: 32.~~

~~13. The isolated polynucleotide of any one of claims 7 to 10 comprising a nucleotide sequence which encodes an anti-ANG2 antibody light chain wherein:~~

~~(a) the anti-ANG2 antibody light chain comprises the amino acid sequence of SEQ ID NO: 30;~~

(b) the anti-ANG2 antibody light chain comprises the amino acid sequence of SEQ ID NO: 29 or consists of the amino acid sequence of SEQ ID NO: 29;

(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 33; and/or

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 34 or consists essentially of the nucleotide sequence of SEQ ID NO: 34.

14. The isolated polynucleotide of any one of claims 7 to 10 comprising a nucleotide sequence which encodes an anti-AngPtl4 antibody heavy chain wherein:

(a) the anti-AngPtl4 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 36;

(b) the anti-AngPtl4 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 35 or consists of the amino acid sequence of SEQ ID NO: 35;

(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 39; and/or

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 40 or consists essentially of the nucleotide sequence of SEQ ID NO: 40.

15. The isolated polynucleotide of any one of claims 7 to 10 comprising a nucleotide sequence which encodes an anti-AngPtl4 antibody light chain wherein:

(a) the anti-AngPtl4 antibody light chain comprises the amino acid sequence of SEQ ID NO: 38;

(b) the anti-AngPtl4 antibody light chain comprises the amino acid sequence of SEQ ID NO: 37 or consists of the amino acid sequence of SEQ ID NO: 37;

(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 41; or

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 42 or consists essentially of the nucleotide sequence of SEQ ID NO: 42.

16. A cell comprising an isolated polynucleotide of claim 7 and (b) a polynucleotide encoding a multi-subunit protein.

~~17. The cell of claim 16, wherein the multi-subunit protein is an antibody, preferably where the antibody comprises an amino acid sequence of claim 9, more preferably wherein the antibody comprises an amino acid sequence of claim 9, part (c) and (f).~~

~~18. The cell of claim 16 or 17:~~

~~(a) further comprising a polynucleotide of claim 9;~~

~~(b) comprising a polynucleotide of claim 10 and a polynucleotide of claim 11;~~

~~(c) comprising a polynucleotide of claim 12 and a polynucleotide of claim 13; or~~

~~(d) comprising a polynucleotide of claim 14 and a polynucleotide of claim 15,~~ ~~preferably wherein the cell is a Chinese hamster ovary (CHO) cell.~~

~~19. A method of making a multi-subunit protein comprising the step of culturing a cell of claim 16 or 17 in medium, wherein the multi-subunit protein is secreted by the cell into the medium, preferably wherein:~~

~~(a) the secreted multi-subunit protein attains a titer in the medium of about at least 3 g/L;~~

~~(b) the secreted multi-subunit protein attains a titer in the medium of about at least 5 g/L;~~

~~(c) the secreted multi-subunit protein attains a titer in the medium of about at least 6 g/L; or~~

~~(d) the secreted multi-subunit protein attains a titer in the medium of about at least 8 g/L.~~

~~20. The method of claim 19, wherein:~~

~~(a) the cell divides in the medium to an integrated cell density of about at least 5 x 10^7 cell-day/mL;~~

~~(b) the cell divides in the medium to produce an integrated cell density of about at least 1 x 10^8 cell-day/mL; or~~

~~(c) the cell divides in the medium to produce an integrated cell density of about at least 1.5 x 10^8 cell-day/mL; preferably further comprising the step of purifying the secreted multi-subunit protein from the medium.~~

~~21. A multi-subunit protein produced according to a method of claim 19 or 20, preferably wherein the multi-subunit protein is an antibody.~~

~~22. The multi-subunit protein of claim 21, wherein the multi-subunit protein is an antibody that comprises an amino acid sequence of SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46, preferably wherein:~~

~~(a) the antibody is an anti-GDF8 antibody, preferably wherein the antibody comprises amino acid sequences of SEQ ID NO: 20 and SEQ ID NO: 22;~~

~~(b) the antibody is an anti-ANG2 antibody, preferably wherein the antibody comprises amino acid sequences of SEQ ID NO: 28 and SEQ ID NO: 30; or~~

~~(c) the antibody is an anti-AngPtl4 antibody, preferably wherein the antibody comprises amino acid sequences of SEQ ID NO: 36 and SEQ ID NO: 38.~~

~~23~~7. An ex vivo mammalian cell comprising:

(i) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16

(ii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, and (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18;

(iii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(iv) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 23, and (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 25;

(v) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 31, and (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 33;

(vi) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 39, and (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 41;

(vii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and (d) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(viii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 23, and (d) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 25;

(ix) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 31, and (d) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 33;

(x) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 39, and (d) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 41;

(xi) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15;

(xii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, and (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17;

(xiii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(xiv) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 24, and (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 26;

(xv) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 32, and (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 4;

(xvi) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 40, and (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 42;

(xvii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and (d) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(xviii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 24, and (d) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 26;

(xix) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 32, and (d) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 34; or

(xx) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 40, and (d) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 42.

CLAIMS

1. A cell comprising a recombinant polynucleotide that encodes a stress-induced mannose-binding lectin and a polynucleotide that encodes a multi-subunit protein.

2. The cell of claim 1, wherein the stress-induced mannose-binding lectin is an endoplasmic reticulum degradation-enhancing alpha-mannosidase-like protein 2 (EDEM2), preferably wherein the EDEM2 comprises an amino acid sequence of SEQ ID NO: 8 or the EDEM2 comprises an amino acid sequence that is at least 92% identical to SEQ ID NO: 1.

3. The cell of claims 1 or 2, wherein the multi-subunit protein is an antibody.

4. The cell of claim 3, wherein the antibody comprises amino acid sequences of SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46.

5. The cell of any one of claims 1 to 4, wherein

(a) the cell comprises a polynucleotide that encodes an unfolded protein response transcription factor that operates upstream of EDEM2, preferably wherein the transcription factor is a spliced form of XBP-1, more preferably wherein the XBP-1 comprises an amino acid sequence of SEQ ID NO: 13 or the XBP-1 comprises an amino acid sequence that is at least 86% identical to SEQ ID NO: 9;

(b) the cell is a mammalian cell; and/or

(c) the cell is a CHO cell.

6. A cell line derived from the cell of any one of claims 1 to 5, wherein the cell line:

(a) produces the protein at a titer of at least 3 g/L, preferably which produces the protein at a titer of at least 5 g/L, more preferably which produces the protein at a titer of at least 8 g/L;

(b) has an integrated cell density that is at least about 30% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin;

(c) has an integrated cell density that is at least about 50% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin;

(d) has an integrated cell density that is at least about 60% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin; and/or

(e) has an integrated cell density that is at least about 90% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin.

7. An isolated polynucleotide comprising a nucleotide sequence, which encodes an EDEM2, operably linked to a promoter, preferably wherein:

(a) the EDEM2 comprises the amino acid sequence of SEQ ID NO: 8 or consists of the amino acid sequence of SEQ ID NO: 8;

(b) the EDEM2 comprises an amino acid sequence that is at least 92% identical to SEQ ID NO: 1 or consists of an amino acid sequence that is at least 92% identical to SEQ ID NO: 1;

(c) the EDEM2 comprises the amino acid sequence of SEQ ID NO: 1 or consists of the amino acid sequence of SEQ ID NO: 1;

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 16;

(e) the polynucleotide comprises a promoter sequence selected from the group consisting of a mammalian ubiquitin C promoter, a SV40 promoter and a CMV-IE promoter; and/or

(f) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 14 or SEQ ID NO: 15 or consists essentially of the nucleotide sequence of SEQ ID NO: 14 or SEQ ID NO: 15.

8. The isolated polynucleotide of claim 7, wherein the polynucleotide encodes an Xbp-1 protein wherein

(a) the Xbp-1 protein comprises the amino acid sequence of SEQ ID NO: 13 or consists of the amino acid sequence of SEQ ID NO: 13;

(b) the Xbp-1 protein comprises an amino acid sequence that is at least 86% identical to SEQ ID NO: 9 or consists of an amino acid sequence that is at least 86% identical to SEQ ID NO: 9;

(c) the Xbp-1 protein comprises the amino acid sequence of SEQ ID NO: 9 or consists of the amino acid sequence of SEQ ID NO: 9;

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 18; and/or

(e) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 17 or consists essentially of the nucleotide sequence of SEQ ID NO: 17.

9. The isolated polynucleotide of claim 7 or 8 comprising a nucleotide sequence which:

(a) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 43;

(b) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 44;

(c) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44;

(d) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 45;

(e) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 46; and/or

(f) encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46.

10. The isolated polynucleotide of any one of claims 7 to 9 comprising a nucleotide sequence which encodes an anti-GDF8 antibody heavy chain wherein:

(a) the anti-GDF8 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 20;

(b) the anti-GDF8 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 19; or consists of the amino acid sequence of SEQ ID NO: 19;

(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 23; and/or

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 24 or consists essentially of the nucleotide sequence of SEQ ID NO: 24.

11. The isolated polynucleotide of any one of claims 7 to 10 comprising a nucleotide sequence which encodes an anti-GDF8 antibody light chain wherein:

(a) the anti-GDF8 antibody light chain comprises the amino acid sequence of SEQ ID NO: 22;

(b) the anti-GDF8 antibody light chain comprises the amino acid sequence of SEQ ID NO: 21 or consists of the amino acid sequence of SEQ ID NO: 21;

(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 25; and/or

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 26 or consists essentially of the nucleotide sequence of SEQ ID NO: 26.

12. The isolated polynucleotide of any one of claims 7 to 10 comprising a nucleotide sequence which encodes an anti-ANG2 antibody heavy chain wherein:

(a) the anti-ANG2 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 28;

(b) the anti-ANG2 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 27 or consists of the amino acid sequence of SEQ ID NO: 27;

(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 31; and/or

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 32 or consists essentially of the nucleotide sequence of SEQ ID NO: 32.

13. The isolated polynucleotide of any one of claims 7 to 10 comprising a nucleotide sequence which encodes an anti-ANG2 antibody light chain wherein:

(a) the anti-ANG2 antibody light chain comprises the amino acid sequence of SEQ ID NO: 30;

(b) the anti-ANG2 antibody light chain comprises the amino acid sequence of SEQ ID NO: 29 or consists of the amino acid sequence of SEQ ID NO: 29;

(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 33; and/or

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 34 or consists essentially of the nucleotide sequence of SEQ ID NO: 34.

14. The isolated polynucleotide of any one of claims 7 to 10 comprising a nucleotide sequence which encodes an anti-AngPtl4 antibody heavy chain wherein:

(a) the anti-AngPtl4 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 36;

(b) the anti-AngPtl4 antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 35 or consists of the amino acid sequence of SEQ ID NO: 35;

(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 39; and/or

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 40 or consists essentially of the nucleotide sequence of SEQ ID NO: 40.

15. The isolated polynucleotide of any one of claims 7 to 10 comprising a nucleotide sequence which encodes an anti-AngPtl4 antibody light chain wherein:

(a) the anti-AngPtl4 antibody light chain comprises the amino acid sequence of SEQ ID NO: 38;

(b) the anti-AngPtl4 antibody light chain comprises the amino acid sequence of SEQ ID NO: 37 or consists of the amino acid sequence of SEQ ID NO: 37;

(c) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 41; or

(d) the polynucleotide comprises the nucleotide sequence of SEQ ID NO: 42 or consists essentially of the nucleotide sequence of SEQ ID NO: 42.

16. A cell comprising an isolated polynucleotide of claim 7 and (b) a polynucleotide encoding a multi-subunit protein.

17. The cell of claim 16, wherein the multi-subunit protein is an antibody, preferably where the antibody comprises an amino acid sequence of claim 9, more preferably wherein the antibody comprises an amino acid sequence of claim 9, part (c) and (f).

18. The cell of claim 16 or 17:

(a) further comprising a polynucleotide of claim 9;

(b) comprising a polynucleotide of claim 10 and a polynucleotide of claim 11;

(c) comprising a polynucleotide of claim 12 and a polynucleotide of claim 13; or

(d) comprising a polynucleotide of claim 14 and a polynucleotide of claim 15, preferably wherein the cell is a Chinese hamster ovary (CHO) cell.

19. A method of making a multi-subunit protein comprising the step of culturing a cell of claim 16 or 17 in medium, wherein the multi-subunit protein is secreted by the cell into the medium, preferably wherein:

(a) the secreted multi-subunit protein attains a titer in the medium of about at least 3 g/L;

(b) the secreted multi-subunit protein attains a titer in the medium of about at least 5 g/L;

(c) the secreted multi-subunit protein attains a titer in the medium of about at least 6 g/L; or

(d) the secreted multi-subunit protein attains a titer in the medium of about at least 8 g/L.

20. The method of claim 19, wherein:

(a) the cell divides in the medium to an integrated cell density of about at least 5 x 10^7 cell-day/mL;

(b) the cell divides in the medium to produce an integrated cell density of about at least 1 x 10^8 cell-day/mL; or

(c) the cell divides in the medium to produce an integrated cell density of about at least 1.5 x 10^8 cell-day/mL; preferably further comprising the step of purifying the secreted multi-subunit protein from the medium.

21. A multi-subunit protein produced according to a method of claim 19 or 20, preferably wherein the multi-subunit protein is an antibody.

22. The multi-subunit protein of claim 21, wherein the multi-subunit protein is an antibody that comprises an amino acid sequence of SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46, preferably wherein:

(a) the antibody is an anti-GDF8 antibody, preferably wherein the antibody comprises amino acid sequences of SEQ ID NO: 20 and SEQ ID NO: 22;

(b) the antibody is an anti-ANG2 antibody, preferably wherein the antibody comprises amino acid sequences of SEQ ID NO: 28 and SEQ ID NO: 30; or

(c) the antibody is an anti-AngPtl4 antibody, preferably wherein the antibody comprises amino acid sequences of SEQ ID NO: 36 and SEQ ID NO: 38.

23. An ex vivo mammalian cell comprising:

(i) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16

(ii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, and (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18;

(iii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(iv) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 23, and (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 25;

(v) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 31, and (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 33;

(vi) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 39, and (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 41;

(vii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ

ID NO: 43 and SEQ ID NO: 44, and (d) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(viii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 23, and (d) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 25;

(ix) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 31, and (d) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 33;

(x) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 39, and (d) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 41;

(xi) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15;

(xii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, and (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17;

(xiii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(xiv) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 24, and (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 26;

(xv) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 32, and (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 4;

(xvi) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 40, and (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 42;

(xvii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and (d) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(xviii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 24, and (d) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 26;

(xix) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 32, and (d) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 34; or

(xx) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 40, and (d) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 42.

CLAIMS

1. A mammalian cell comprising a recombinant polynucleotide that encodes an endoplasmic reticulum degradation-enhancing alpha-mannosidase-like protein 2 (EDEM2) and a polynucleotide that encodes a multi-subunit protein.

2. The cell of claim 1, wherein the EDEM2 comprises an amino acid sequence of SEQ ID NO: 8 or the EDEM2 comprises an amino acid sequence that is at least 92% identical to SEQ ID NO: 1.

3. The cell of claims 1 or 2, wherein the multi-subunit protein is an antibody.

4. The cell of claim 3, wherein the antibody comprises amino acid sequences of SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46.

5. The cell of any one of claims 1 to 4, wherein

(a) the cell comprises a polynucleotide that encodes an unfolded protein response transcription factor that operates upstream of EDEM2, preferably wherein the transcription factor is a spliced form of XBP-1, more preferably wherein the XBP-1 comprises an amino acid sequence of SEQ ID NO: 13 or the XBP-1 comprises an amino acid sequence that is at least 86% identical to SEQ ID NO: 9;

(b) the mammalian cell is a CHO cell.

6. A cell line derived from the cell of any one of claims 1 to 5, wherein the cell line:

(a) produces the protein at a titer of at least 3 g/L, preferably which produces the protein at a titer of at least 5 g/L, more preferably which produces the protein at a titer of at least 8 g/L;

(b) has an integrated cell density that is at least about 30% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin;

(c) has an integrated cell density that is at least about 50% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin;

(d) has an integrated cell density that is at least about 60% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin; and/or

(e) has an integrated cell density that is at least about 90% greater than the integrated cell density of a cell line that does not comprise the recombinant polynucleotide that encodes a stress-induced mannose-binding lectin.

7. An ex vivo mammalian cell comprising:

(i) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16

(ii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, and (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18;

(iii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(iv) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 23, and (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 25;

(v) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 31, and (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 33;

(vi) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 39, and (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 41;

(vii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ

ID NO: 43 and SEQ ID NO: 44, and (d) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(viii) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 23, and (d) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 25;

(ix) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 31, and (d) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 33;

(x) (a) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 16, (b) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 18, (c) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 39, and (d) a polynucleotide, which comprises a nucleic acid sequence of SEQ ID NO: 41;

(xi) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15;

(xii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, and (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17;

(xiii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(xiv) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 24, and (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 26;

(xv) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 32, and (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 4;

(xvi) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 40, and (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 42;

(xvii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 43 and SEQ ID NO: 44, and (d) a polynucleotide, which encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 45 and SEQ ID NO: 46;

(xviii) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 24, and (d) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 26;

(xix) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 32, and (d) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 34; or

(xx) (a) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 14 or 15, (b) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 17, (c) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 40, and (d) a polynucleotide, which consists of a nucleic acid sequence of SEQ ID NO: 42.