Sterol Regulatory Element Binding Proteins (SREBPs)

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Abstract: Sterol regulatory element binding proteins (SREBPs) are transcription factors that bind to the sterol regulatory element DNA sequence TCACNCCAC. SREBPs belong to the basic-helix-loop-helix leucine zipper class of transcription factors. Unactivated SREBPs are attached to the nuclear envelope and endoplasmic reticulum membranes. In cells with low levels of sterols, SREBPs are cleaved to a water soluble N-terminal domain which is translocated to the nucleus. These activated SREBPs then bind to specific sterol regulatory element DNA sequences which upregulate the synthesis of enzymes involved in sterol biosynthesis. Sterols in turn inhibit the cleavage of SREBPs and therefore synthesis of additional sterols is reduced through a negative feed back loop. [The Journal of American Science. 2008;4(2):88-94]. (ISSN 1545-1003).

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1. Introduction

Sterol regulatory element binding proteins (SREBPs) are transcription factors that bind to the sterol regulatory element DNA sequence TCACNCCAC (Chen, Chen et al. 2006; Rasmussen, Blobaum et al. 2008). SREBPs belong to the basic-helix-loop-helix leucine zipper class of transcription factors (Brown and Goldstein 1997). Unactivated SREBPs are attached to the nuclear envelope and endoplasmic reticulum membranes (Sakai, Nohturfft et al. 1997). In cells with low levels of sterols, SREBPs are cleaved to a water soluble N-terminal domain which is translocated to the nucleus (Zhang, Shin et al. 2005). These activated SREBPs then bind to specific sterol regulatory element DNA sequences which upregulate the synthesis of enzymes involved in sterol biosynthesis (Yokoyama, Wang et al. 1993; Wang, Sato et al. 1994). Sterols in turn inhibit the cleavage of SREBPs and therefore synthesis of additional sterols is reduced through a negative feed back loop (Wikipedia, 2008).

Beginning with the discovery of the SREBPs in 1993, a productive combination of biochemistry, molecular biology and genetics, has brought to light the complex mechanisms by which animal cells maintain the proper levels of intracellular lipid (fats and oils) in the face of widely varying circumstances (lipid homeostasis) (Brown and Goldstein 1999; Brown, Ye et al. 2000). These studies exposed a signaling mechanism of beguiling complexity that is responsible for the end-product feedback regulation of gene transcription. For example, when cellular cholesterol levels fall below the level needed, the cell makes more of the enzymes necessary to make cholesterol. A principal step in this response is to make more of the mRNA transcripts that direct the synthesis of these enzymes. Conversely, when there is enough cholesterol around, the cell stops making those mRNAs and the level of the enzymes falls. As a result, the cell quits making cholesterol once it has enough.

The defining feature of the SREBP pathway is the proteolytic release of a membrane-bound transcription factor, SREBP. Proteolytic cleavage frees it to move through the cytoplasm to the nucleus. Once in the nucleus, SREBP can bind to specific DNA sequences that are found in the control regions of the genes that encode enzymes needed to make lipids. This binding to DNA leads to the increased transcription of the target genes.

The ~120 kDa SREBP precursor protein is anchored in the membranes of the *e*ndoplasmic *r*eticulum and nuclear envelope by virtue of two membrane-spanning helices in the middle of the protein. The precursor has a hairpin orientation in the membrane, so that both the amino-terminal transcription factor domain and the COOH-terminal regulatory domain face the cytoplasm. The two membrane-spanning

helices are separated by a loop of about 30 amino acids that lies in the lumen of the *e*ndoplasmic *r*eticulum. Two separate, site-specific proteolytic cleavages are necessary for release of the transcriptionally active amino-terminal domain. Regulation of SREBP cleavage employs a notable feature of eukaryotic cells, subcellular compartmentalization defined by intracellular membranes, to ensure that cleavage occurs only when needed.

2. SREBP-1 and SREBP-2

The mammalian gene for SREBP-1 contains two promoters that control the production of two proteins, SREBP-1a and -1c, and each contains a unique N-terminal transcriptional activation domain, but they are otherwise identical. The relative level of each mRNA varies from tissue to tissue and they respond differently to regulatory stimuli. SREBP-1c is more abundantly expressed in liver, where its level is also regulated by insulin and liver X receptor activators, and it is also autoregulated by SREBPs. In contrast, SREBP-1a mRNA levels are relatively low and constant in different tissues and few studies have specifically analysed its pattern of expression and regulation. According to the studies by Zhang and Shin, the promoter for SREBP-1a is contained in a very small promoter-proximal region containing two Sp1 sites. The small and relatively simple structure for its promoter provides an explanation for the low level of SREBP-1a expression. Additionally, since Sp1 has been implicated in the modest regulation of several genes by insulin, its involvement in the expression of the SREBP-1a promoter provides an explanation for the modest insulin regulation observed in animal experiments (Zhang, Shin et al. 2005). SREBP-2 regulates the genes of cholesterol metabolism.

SREBP-1a is a unique membrane-bound transcription factor highly expressed in actively growing cells and involved in the biosynthesis of cholesterol, fatty acids, and phospholipids. Because mammalian cells need to synthesize membrane lipids for cell replication, the functional relevance of SREBP-1a in cell proliferation has been considered a biological adaptation (Nakakuki, Shimano et al. 2007).

The 5' end of the mRNA-encoding SREBP-1 exists in two forms, designated 1a and 1c. The divergence results from the use of two transcription start sites that produce two separate 5' exons, each of which is spliced to a common exon 2. Mutations in the sterol regulatory element binding protein gene (SREBF)-1 may contribute to insulin resistance states. However, the variants described to date do not affect the SREBP function (Vernia, Eberle et al. 2006).

3. SREBP and diabetes

Diabetic renal disease is associated with lipid deposits in the kidney. In 2002, Sun et al made the study to determine whether there is altered regulation of the sterol regulatory element-binding proteins (SREBPs) in the diabetic kidney and whether SREBPs mediate the abnormal renal lipid metabolism and diabetic renal disease. In streptozotocin-induced diabetes in the rat, there were marked increases in SREBP-1 and fatty acid synthase (FAS) expression, resulting in increased triglyceride (TG) accumulation. Treatment of diabetic rats with insulin prevented the increased renal expression of SREBP-1 and the accumulation of TG. The role of hyperglycemia in the up-regulation of SREBP-1 was confirmed in renal cells cultured in a high glucose media. High glucose induced increased expression of SREBP-1a and -1c mRNA, SREBP-1 protein, and FAS, resulting in increased TG content. To determine a direct role for SREBP in mediating the increase in renal lipids and glomerulosclerosis, they studied SREBP-1a transgenic mice with increased renal expression of SREBP-1. The increase in SREBP-1 was associated with increased expression of FAS and acetyl CoA carboxylase, resulting in increased TG content, increased expression of transforming growth factor beta1 and vascular endothelial growth factor, mesangial expansion, glomerulosclerosis, and proteinuria. Their study therefore indicates that renal SREBP-1 expression is increased in diabetes and that SREBP-1 plays an important role in the increased lipid synthesis, TG accumulation, mesangial expansion, glomerulosclerosis, and proteinuria by increasing the expression of transforming growth factor beta and vascular endothelial growth factor (Sun, Halaihel et al. 2002).

SREBP-1c is intimately involved in the regulation of lipid and glucose metabolism and SREBP-1c gene might influence diabetes risk and plasma cholesterol level (Laudes, Barroso et al. 2004).

ABC transporter A1 (ABCA1) mediates and rate-limits biogenesis of high density lipoprotein (HDL), and hepatic ABCA1 plays a major role in regulating plasma HDL levels. HDL generation is also responsible for release of cellular cholesterol. In peripheral cells ABCA1 is up-regulated by the liver X receptor (LXR) system when cell cholesterol increases. However, cholesterol feeding has failed to show a significant increase in hepatic ABCA1 gene expression, and its expression is up-regulated by statins (3-hydroy-3-methylglutaryl-CoA reductase inhibitors), suggesting distinct regulation. Compactin activated the

novel liver-type promoter in rat hepatoma McARH7777 cells by binding SREBP-2. In contrast, compactin repressed the previously identified peripheral-type promoter in an LXR-responsive element-dependent but not E-box-dependent manner. Thus, compactin increased the liver-type transcript and decreased the peripheral-type transcript. The same two transcripts were also dominant in human and mouse livers, whereas the intestine contains only the peripheral-type transcript. Treatment of rats with pravastatin and a bile acid binding resin (colestimide), which is known to activate SREBP-2 in the liver, caused a reduction in the hepatic cholesterol level and the same differential responses in vivo, leading to increases in hepatic ABCA1 mRNA and protein and plasma HDL levels. The dual promoter system driven by SREBP-2 and LXR regulates hepatic ABCA1 expression and may mediate the unique response of hepatic ABCA1 gene expression to cellular cholesterol status (Tamehiro, Shigemoto-Mogami et al. 2007).

4. SREBP protein and gene strcuture

(1) Human SREBP1 protein sequence (Olsen, Blagoev et al. 2006):

1 mdeppfseaa leqalgepcd ldaalltdie dmlqlinnqd sdfpglfdpp yagsgaggtd
61 paspdtsspg slspppatls ssleaflsgp qaapsplspp qpaptplkmy psmpafspgp
121 gikeesvpls ilqtptpqpl pgallpqsfp apappqfsst pvlgypsppg gfstgsppgn
181 tqqplpglpl asppgvppvs lhtqvqsvvp qqlltvtaap taapvtttvt sqiqqvpvll
241 qphfikadsl lltamktdga tvkaaglspl vsgttvqtgp lptlvsggti latvplvvda
301 eklpinrlaa gskapasaqs rgekrtahna iekryrssin dkiielkdlv vgteaklnks
361 avlrkaidyi rflqhsnqkl kqenlslrta vhkskslkdl vsacgsggnt dvlmegvkte
421 vedtltppps dagspfqssp lslgsrgsgs ggsgsdsepd spvfedskak peqrpslhsr
481 gmldrsrlal ctlvflclsc nplasllgar glpspsdtts vyhspgrnvl gtesrdgpgw
541 aqwllppvvw llngllvlvs lvllfvygep vtrphsgpav yfwrhrkqad ldlargdfaq
601 aaqqlwlalr algrplptsh ldlacsllwn lirhllqrlw vgrwlagrag glqqdcalrv
661 dasasardaa lvyhklhqlh tmgkhtgghl tatnlalsal nlaecagdav svatlaeiyv
721 aaalrvktsl pralhfltrf flssarqacl aqsgsvppam qwlchpvghr ffvdgdwsvl
781 stpweslysl agnpvdplaq vtqlfrehll eralncvtqp npspgsadgd kefsdalgyl
841 qllnscsdaa gapaysfsis ssmatttgvd pvakwwaslt avvihwlrrd eeaaerlcpl
901 vehlprvlqe serplpraal hsfkaarall gcakaesgpa slticekasg ylqdslattp
961 asssidkavq lflcdlllvv rtslwrqqqp papapaaqgt ssrpqasale lrgfqrdlss
1021 lrrlaqsfrp amrrvflhea tarlmagasp trthqlldrs lrrragpggk ggavaelepr
1081 ptrrehaeal llascylppg flsapgqrvg mlaeaartle klgdrrllhd cqqmlmrlgg
1141 gttvtss

(2) Human SREBP2 protein sequence (Sjoblom, Jones et al. 2006):

1 mddsgelggl etmetltelg deltlgdide mlqfvsnqvg efpdlfseql cssfpgsggs
61 gsssgssgss ssssngrgss sgavdpsvqr sftqvtlpsf spsaaspqap tlqvkvspts
121 vpttpratpi lqprpqpqpq pqtqlqqqtv mitptfsttp qtriiqqpli yqnaatsfqv
181 lqpqvqslvt ssqvqpvtiq qqvqtvqaqr vltqtangtl qtlapatvqt vaapqvqqvp
241 vlvqpqiikt dslvlttlkt dgspvmaavq npaltalttp iqtaalqvpt lvgssgtilt
301 tmpvmmgqek vpikqvpggv kqleppkege rrtthniiek ryrssindki ielkdlvmgt
361 dakmhksgvl rkaidyikyl qqvnhklrqe nmvlklanqk nkllkgidlg slvdnevdlk
421 iedfnqnvll msppasdsgs qagfspysid sepgsplldd akvkdepdsp pvalgmvdrs
481 rillcvltfl clsfnpltsl lqwggahdsd qhphsgsgrs vlsfesgsgg wfdwmmptll
541 lwlvngvivl svfvkllvhg epvirphsrs svtfwrhrkq adldlargdf aaaagnlqtc
601 lavlgralpt srldlacsls wnviryslqk lrlvrwllkk vfqcrratpa teagfedeak
661 tsardaalay hrlhqlhitg klpagsacsd vhmalcavnl aecaeekipp stlveihlta
721 amglktrcgg klgflasyfl sraqslcgpe hsavpdslrw lchplgqkff merswsvksa
781 akeslycaqr npadpiaqvh qafcknller aieslvkpqa kkkagdqeee scefssaley
841 lkllhsfvds vgvmspplsr ssvlksalgp diicrwwtsa itvaiswlqg ddaavrshft
901 kveripkale vtesplvkai fhacramhas lpgkadgqqs sfchcerasg hlwsslnvsg
961 atsdpalnhv vqlltcdlll slrtalwqkq asasqavget yhasgaelag fqrdlgslrr
1021 lahsfrpayr kvflheatvr lmagasptrt hqllehslrr rttqstkhge vdawpgqrer
1081 ataillacrh lplsflsspg qravllaeaa rtlekvgdrr scndcqqmiv klgggtaiaa
1141 s

(3) Human SREBP1 gene sequence (Furuta, Pai et al. 2008):

1 agcagagctg cggccggggg aacccagttt ccgaggaact tttcgccggc gccgggccgc
61 ctctgaggcc agggcaggac acgaacgcgc ggagcggcgg cggcgactga gagccggggc
121 cgcggcggcg ctccctagga agggccgtac gaggcggcgg gcccggcggg cctcccggag
181 gaggcggctg cgccatggac gagccaccct tcagcgaggc ggctttggag caggcgctgg
241 gcgagccgtg cgatctggac gcggcgctgc tgaccgacat cgaagacatg cttcagctta
301 tcaacaacca agacagtgac ttccctggcc tatttgaccc accctatgct gggagtgggg
361 caggggggcac agaccctgcc agccccgata ccagctcccc aggcagcttg tctccacctc
421 ctgccacatt gagctcctct cttgaagcct tcctgagcgg gccgcaggca gcgccctcac
481 ccctgtcccc tccccagcct gcacccactc cattgaagat gtacccgtcc atgcccgctt
541 tctcccctgg gcctggtatc aaggaagagt cagtgccact gagcatcctg cagacccccа
601 ccccacagcc cctgccaggg gccctcctgc cacagagctt cccagcccca gccccaccgc
661 agttcagctc caccctgtg ttaggctacc ccagccctcc gggaggcttc tctacaggaa
721 gccctcccgg gaacacccag cagccgctgc ctggcctgcc actggcttcc ccgccagggg
781 tcccgcccgt ctccttgcac acccaggtcc agagtgtggt cccccagcag ctactgacag
841 tcacagctgc ccccacggca gcccctgtaa cgaccactgt gacctcgcag atccagcagg
901 tcccggtcct gctgcagccc cacttcatca aggcagactc gctgcttctg acagccatga
961 agacagacgg agccactgtg aaggcggcag gtctcagtcc cctggtctct ggcaccactg
1021 tgcagacagg gcctttgccg accctggtga gtggcggaac catcttggca acagtcccac
1081 tggtcgtaga tgcggagaag ctgcctatca accggctcgc agctggcagc aaggccccgg
1141 cctctgccca gagccgtgga gagaagcgca cagcccacaa cgccattgag aagcgctacc
1201 gctcctccat caatgacaaa atcattgagc tcaaggatct ggtggtgggc actgaggcaa
1261 agctgaataa atctgctgtc ttgcgcaagg ccatcgacta cattcgcttt ctgcaacaca
1321 gcaaccagaa actcaagcag gagaacctaa gtctgcgcac tgctgtccac aaaagcaaat
1381 ctctgaagga tctggtgtcg gcctgtggca gtggagggaa cacagacgtg ctcatggagg
1441 gcgtgaagac tgaggtggag gacacactga ccccaccccc ctcggatgct ggctcacctt
1501 tccagagcag ccccttgtcc cttggcagca ggggcagtgg cagcggtggc agtggcagtg
1561 actcggagcc tgacagccca gtctttgagg acagcaaggc aaagccagag cagcggccgt
1621 ctctgcacag ccggggcatg ctggaccgct cccgcctggc cctgtgcacg ctcgtcttcc
1681 tctgcctgtc ctgcaacccc ttggcctcct tgctgggggc ccgggggctt cccagcccct
1741 cagataccac cagcgtctac catagccctg ggcgcaacgt gctgggcacc gagagcagag
1801 atggccctgg ctgggcccag tggctgctgc ccccagtggt ctggctgctc aatgggctgt
1861 tggtgctcgt ctccttggtg cttctctttg tctacggtga gccagtcaca cggccccact
1921 caggccccgc cgtgtacttc tggaggcatc gcaagcaggc tgacctggac ctggcccggg
1981 gagactttgc ccaggctgcc cagcagctgt ggctggccct gcgggcactg ggccggcccc
2041 tgcccacctc ccacctggac ctggcttgta gcctcctctg gaacctcatc cgtcacctgc
2101 tgcagcgtct ctgggtgggc cgctggctgg caggccgggc agggggcctg cagcaggact
2161 gtgctctgcg agtggatgct agcgccagcg cccgagacgc agccctggtc taccataagc
2221 tgcaccagct gcacaccatg gggaagcaca caggcgggca cctcactgcc accaacctgg
2281 cgctgagtgc cctgaacctg gcagagtgtg caggggatgc cgtgtctgtg gcgacgctgg
2341 ccgagatcta tgtggcggct gcattgagag tgaagaccag tctcccacgg gccttgcatt
2401 ttctgacacg cttcttcctg agcagtgccc gccaggcctg cctggcacag agtggctcag
2461 tgcctcctgc catgcagtgg ctctgccacc ccgtgggcca ccgtttcttc gtggatgggg
2521 actggtccgt gctcagtacc ccatgggaga gcctgtacag cttggccggg aacccagtgg
2581 acccccctggc ccaggtgact cagctattcc gggaacatct cttagagcga gcactgaact
2641 gtgtgaccca gcccaacccc agccctgggt cagctgatgg ggacaaggaa ttctcggatg
2701 ccctcgggta cctgcagctg ctgaacagct gttctgatgc tgcgggggct cctgcctaca
2761 gcttctccat cagttccagc atggccacca ccaccggcgt agacccggtg gccaagtggt
2821 gggcctctct gacagctgtg gtgatccact ggctgcggcg ggatgaggag gcggctgagc
2881 ggctgtgccc gctggtggag cacctgcccc gggtgctgca ggagtctgag agacccctgc
2941 ccagggcagc tctgcactcc ttcaaggctg cccgggccct gctgggctgt gccaaggcag
3001 agtctggtcc agccagcctg accatctgtg agaaggccag tgggtacctg caggacagcc
3061 tggctaccac accagccagc agctccattg acaaggccgt gcagctgttc ctgtgtgacc
3121 tgcttcttgt ggtgcgcacc agcctgtggc ggcagcagca gcccccggcc ccggccccag
3181 cagcccaggg caccagcagc aggccccagg cttccgccct tgagctgcgt ggcttccaac
3241 gggacctgag cagcctgagg cggctggcac agagcttccg gcccgccatg cggagggtgt

3301 tcctacatga ggccacggcc cggctgatgg cgggggccag ccccacacgg acacaccagc
3361 tcctcgaccg cagtctgagg cggcgggcag gccccggtgg caaaggaggc gcggtggcgg
3421 agctggagcc gcggcccacg cggcgggagc acgcggaggc cttgctgctg gcctcctgct
3481 acctgccccc cggcttcctg tcggcgcccg ggcagcgcgt gggcatgctg gctgaggcgg
3541 cgcgcacact cgagaagctt ggcgatcgcc ggctgctgca cgactgtcag cagatgctca
3601 tgcgcctggg cggtgggacc actgtcactt ccagctagac cccgtgtccc cggcctcagc
3661 acccctgtct ctagccactt tggtcccgtg cagcttctgt cctgcgtcga agctttgaag
3721 gccgaaggca gtgcaagaga ctctggcctc cacagttcga cctgcggctg ctgtgtgcct
3781 tcgcggtgga aggcccgagg ggcgcgatct tgaccctaag accggcggcc atgatggtgc
3841 tgacctctgg tggccgatcg gggcactgca ggggccgagc cattttgggg ggccccccctc
3901 cttgctctgc aggcacctta gtggcttttt tcctcctgtg tacagggaag agaggggtac
3961 atttccctgt gctgacggaa gccaacttgg ctttcccgga ctgcaagcag ggctctgccc
4021 cagaggcctc tctctccgtc gtgggagaga gacgtgtaca tagtgtaggt cagcgtgctt
4081 agcctcctga cctgaggctc ctgtgctact ttgccttttg caaactttat tttcatagat
4141 tgagaagttt tgtacagaga attaaaaatg aaattattta taatctggaa aaaa

(4) Human SREBP2 gene sequence (Lee and Kong 2007):

1 gccctttctg tgcggcgccc gggcgcaacg caaacatggc ggcgggtggc acccgtcggt
61 gaggcggtgc cgggcggggg ttgtcgggtg tcatgggcgg tggcgacggc accgcccccg
121 cgtctccctg agcgggacgg caggggggggc ttctgcgctg agccgggcga tggacgacag
181 cggcgagctg ggtggtctgg agaccatgga gaccctcacg gagctgggcg acgagctgac
241 cctgggagac atcgacgaga tgctgcaatt tgtcagtaat caagtgggag agttccctga
301 cttgttttca gaacagctgt gtagctcctt tcctggcagt ggtggtagtg gtagcagcag
361 cggcagcagt ggcagcagca gcagcagcag caatggcagg ggcagcagca gcggagctgt
421 ggacccttca gtgcaacggt cattcaccca ggtcacatta ccttccttct ctccctcggc
481 ggcctcccca caggctccaa ctctgcaagt caaggtttct cccacctcag ttcccaccac
541 acccagggca actcctattc ttcagccccg cccccagccc cagcctcaac ctcaaactca
601 gctgcaacaa cagacggtaa tgatcacgcc aacattcagc accactccgc agacgaggat
661 catccagcag cctttgatat accagaatgc agctactagc tttcaagtcc ttcagcctca
721 agtccaaagc ctggtgacat cctcccaggt acagccggtc accattcagc agcaggtgca
781 gacagtacag gcccagcggg tgctgacaca aacggccaat ggcacgctgc agacccttgc
841 cccggctacg gtgcagacag ttgctgcgcc acaggtgcag caggtcccgg tcctggtcca
901 gcctcagatc atcaagacag attcccttgt tttgaccaca ctgaagacag atggcagccc
961 tgttatggct gcggtccaga acccggccct caccgccctc accaccccta tccagacggc
1021 tgcccttcaa gtaccaaccc tggtgggcag cagtgggacc attctgacca caatgcctgt
1081 aatgatgggg caagagaaag tgcccattaa gcaggtacct gggggagtca agcagcttga
1141 gccccccaaa gaaggagaaa ggcggacaac ccataatatc attgagaaac gatatcgctc
1201 ctccatcaat gacaaaatca tcgaattgaa agacctggtc atggggacag acgccaagat
1261 gcacaagtct ggcgttctga ggaaggccat tgattacatc aaatacttgc agcaggtcaa
1321 tcataaactg cgccaggaga acatggtgct gaagctggca aatcaaaaga acaagcttct
1381 aaagggcatc gacctaggca gtctggtgga caatgaggtg gacctgaaga tcgaggactt
1441 taatcagaat gtccttctga tgtccccccc agcctctgac tcagggtccc aggctggctt
1501 ctctccctac tccattgact ctgagccagg aagccctcta ttggatgatg caaaggtcaa
1561 agatgagcca gactctcctc ctgtggcgct gggcatggta gaccgctcac ggattcttct
1621 gtgtgtcctc accttcctgt gcctctcctt taacccccctg acttccctgc tgcagtgggg
1681 aggggcccac gactctgacc agcacccaca ctcaggctct ggccgcagtg tcctgtcatt
1741 cgagtcaggt tctgggggct ggtttgactg gatgatgcct actcttctct tatggctggt
1801 aaatggtgtg attgtcctga gcgtctttgt gaagctgctg gttcatgggg agccagtgat
1861 ccggccacac tcgcgctcct cggtcacctt ctggaggcac cggaaacagg cagatctgga
1921 tctcgccaga ggagattttg cagctgctgc cggcaaccta caaacctgcc tggcagtttt
1981 gggccgggca ctgcccacct cccgcctgga cctggcctgc agcctctcct ggaacgtgat
2041 ccgctacagc ctgcagaagc tacgcctggt gcgctggctg ctcaagaaag tcttccagtg
2101 ccggcgggcc acgccagcca ctgaggcagg ctttgaagac gaagctaaga ccagcgcccg
2161 ggatgcggct ctggcctatc accggctgca ccagctgcac atcacaggga agcttcctgc
2221 aggatccgcc tgttccgatg tacacatggc gttgtgtgcc gtgaacctgg ctgaatgtgc
2281 agaggagaag atcccaccga gcacactggt tgagatccat ctgactgctg ccatggggct

2341 caagacccgg tgtggaggca agctgggctt cctggccagc tacttcctca gccgagccca
2401 gagcctgtgt ggccccgagc acagtgctgt tcctgactcc ctgcgctggc tctgccaccc
2461 cctgggccag aagtttttca tggagcggag ctggtctgtg aagtcagctg ccaaggagag
2521 tctatactgt gcccagagga acccagctga ccccattgcg caggtccacc aggccttctg
2581 caagaacctg ctggagcgag ctatagagtc cttggtgaaa cctcaggcca agaagaaggc
2641 tggagaccag gaagaagaga gctgtgaatt ctccagtgct ctggagtact tgaaattact
2701 tcattctttt gtggactctg tgggggttat gagcccccca ctctccagga gctccgtgct
2761 caagtccgcc ctgggtccag acatcatctg tcggtggtgg acgtctgcaa tcactgtggc
2821 catcagctgg ctccagggag acgatgcagc tgtgcgctct cattttacca aagtggaacg
2881 catccccaag gccctggaag tgacagagag ccccctggtg aaggccatct tccatgcctg
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4261 ggcattattt tttaattttt taaaaaataa atggtatctt atttaaaaaa aaaaaaaaaa
4321 aaaaa

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