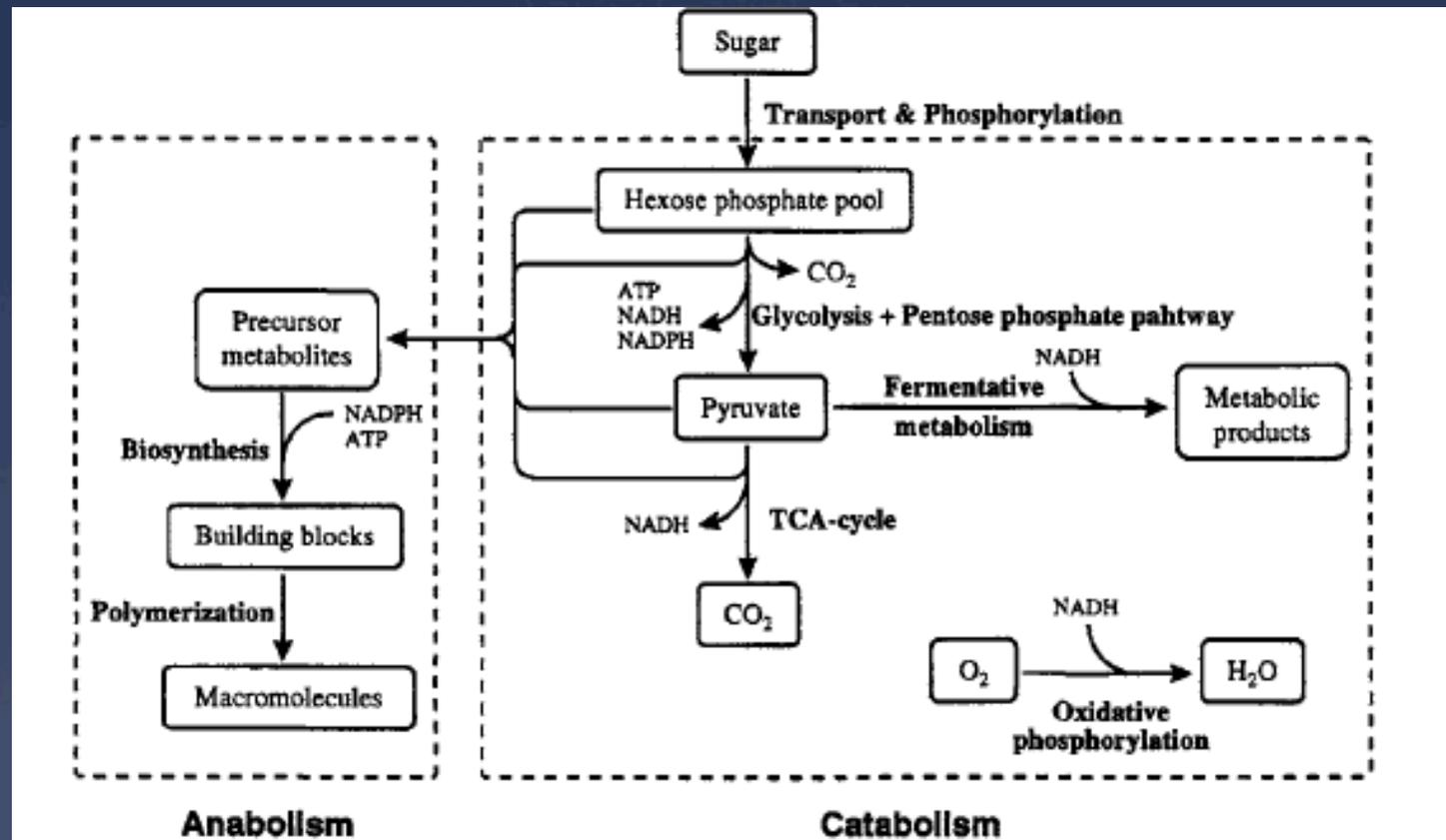


Metabolismo III

BIOSSÍNTESE

Síntese de uma célula a partir de açúcares



Biossíntese

* Composição em macromoléculas de *E. coli*

Macromolecule	Percentage of total dry weight	Different kinds of molecules
Protein	55.0	1050
RNA	20.5	
rRNA	16.7	3
tRNA	3.0	60
mRNA	0.8	400
DNA	3.1	1
Lipid	9.1	4
Lipopolysaccharide	3.4	1
Peptidoglycan	2.5	1
Glycogen	2.5	1
Soluble pool	3.9	

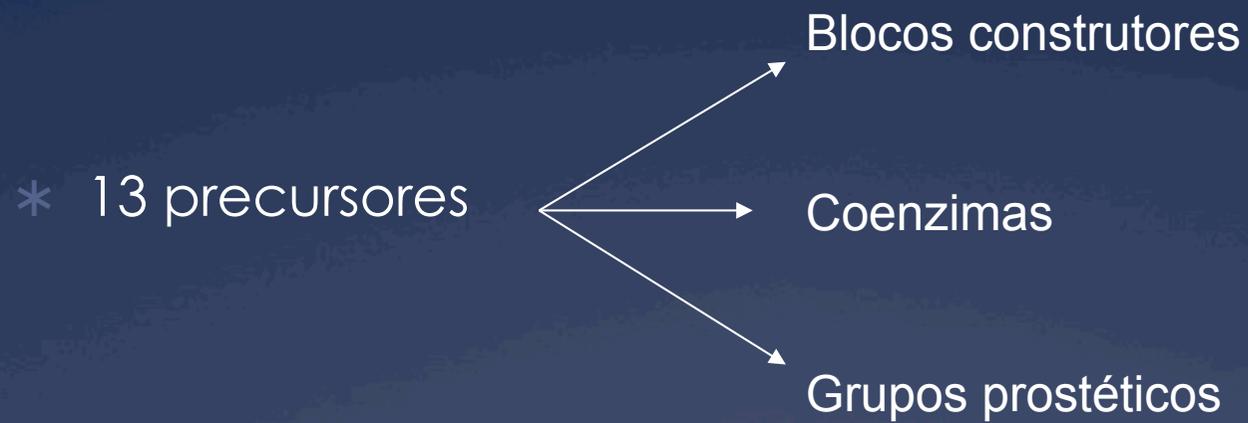
^a The data are taken from Ingraham *et al.* (1983).

70% da célula = H₂O . Demais componentes = Massa celular seca

Biossíntese

- * Reações biossintéticas
 - * Produzem
 - * os blocos construtores usados na polimerização
 - * Coenzimas
 - * São reações sequenciais (vias)
 - * controladas em bloco
 - * Enzimas oriundas de um mRNA transcrito partir de um operon
 - * Iniciam-se a partir de um dos 13 metabólitos precursores ou ramificação de via correlata

Biossíntese

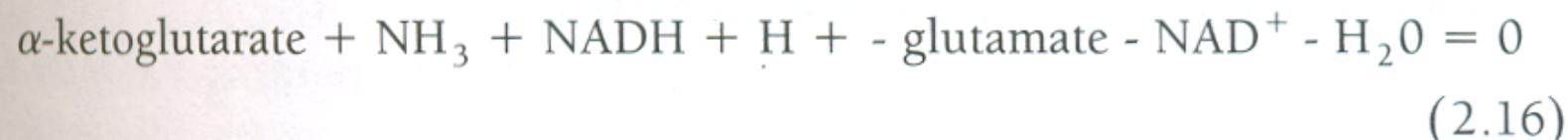


Número entre
75-100

Biossíntese de aminoácidos

Breakdown product	Amino acids
Pyruvate	Alanine (1), serine (1), cysteine (3), and glycine (2)
Acetyl-CoA	Threonine (1), lysine (10), leucine (8), tyrosine (7), phenylalanine (8), and tryptophan (12)
α -Ketoglutarate	Glutamate (1), glutamine (2), proline (3), arginine (4) and histidine (5)
Succinyl-CoA	Methionine (9), isoleucine (9), and valine (8)
Oxaloacetate	Aspartate (1) and asparagine (2)

^a The figure in the parenthesis is the number of steps in the breakdown pathway in the higher eukaryotes. For most of the amino acids where this number is one the breakdown product is directly formed by deamination according to eq. (2.16).



Biossíntese de aminoácidos

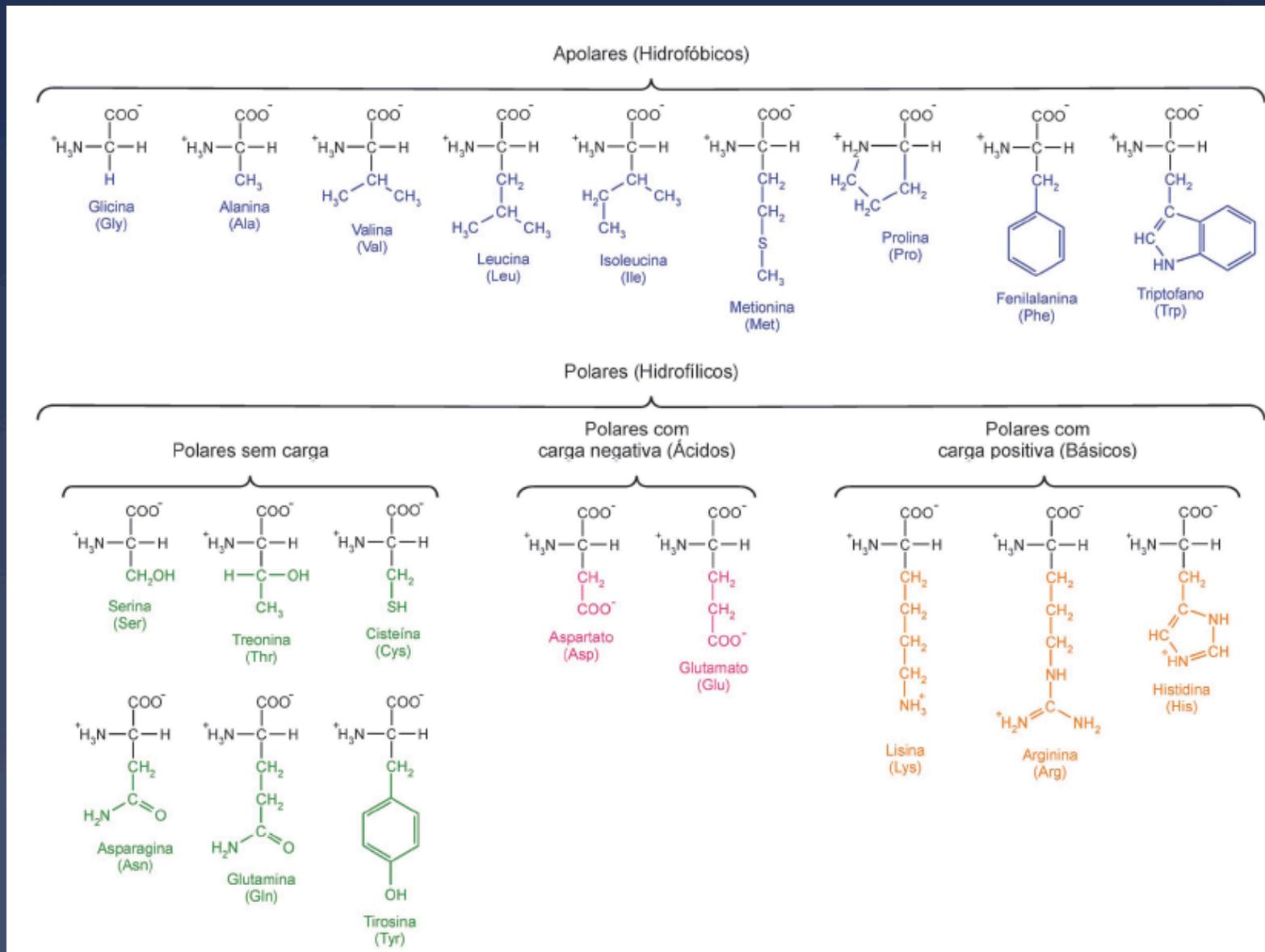
* Aminoácidos :

* Precursores de proteínas

* Aminoácidos :

* Precursores de metabólitos secundários
ex. Penicilina

Estrutura dos aminoácidos



Biossíntese de aminoácidos

- * Etapa inicial:

Assimilação de nitrogênio

- * Fixação de uma molécula de amônia

- * Incorporação a uma molécula orgânica

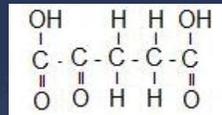
Isto ocorre pela biossíntese de L-glutamato a partir de α -cetogluturato

Biossíntese de *L*-glutamato a partir de α -cetoglutarato

- * **VIA GDH** Glutamato desidrogenase
- * **VIA GS-GOGAT** glutamina amida-2-oxoglutarato aminotransferase (*ou glutamato sintase*)

Biossíntese de *L*-glutamato a partir de α -cetoglutarato

VIA GDH



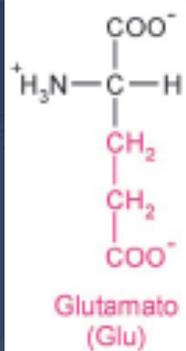
L-glutamate + NADP⁺ + H₂O - α -ketoglutarate

- NH₃ - NADPH - H⁺ = 0

Enzima envolvida:

GDH

Glutamato desidrogenase ligada a NADP



NADP-GDH NAD-GDH (reação contrária)



Reprimida por glutamato

Reprimida por glicose

Ativa no crescimento em glicose

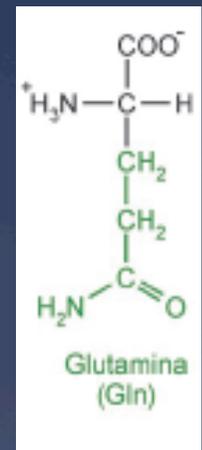
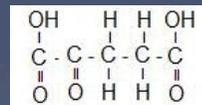
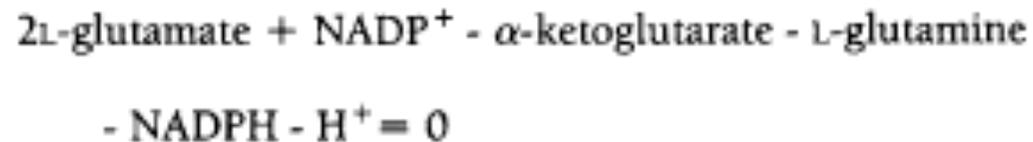
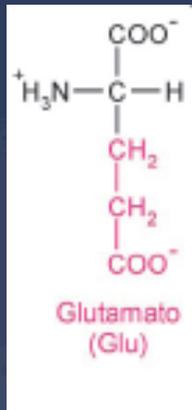
Biossíntese de L-glutamato a partir de α -cetoglutarato

VIA GS-GOGAT

2 etapas:

1) L-glutamina atua como um amino doador para o α -cetoglutarato

São formados 2 moléculas de L- glutamato



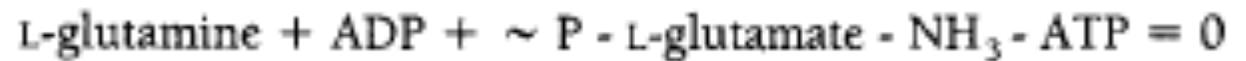
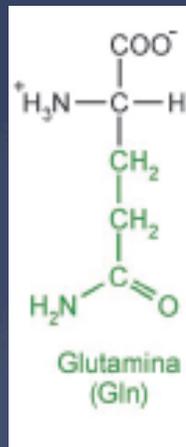
GOGAT = glutamina amida-2-oxoglutarato aminotransferase
(ou glutamato sintase)

Biossíntese de *L*-glutamina a partir de α -cetoglutarato

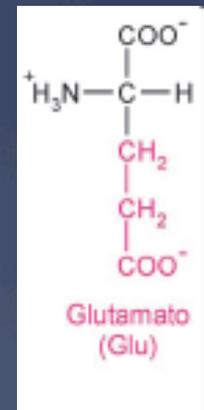
VIA GS-GOGAT

2 etapas:

2) Regeneração da glutamina



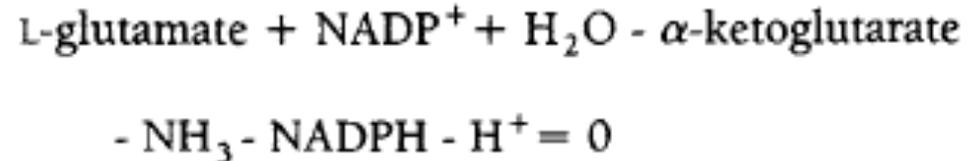
GS = Glutamina sintase



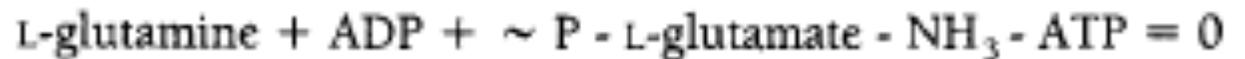
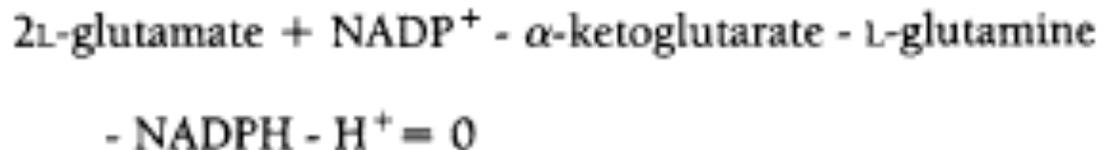
Biossíntese de *L*-glutamato a partir de α -cetoglutarato

Soma das equações em cada caso

VIA GDH



VIA GS-GOGAT



Síntese de glutamato a partir de α -cetoglutarato

Com GS-GOGAT há gasto de ATP

Biossíntese de *L*-glutamato a partir de α -cetoglutarato

* **GS-GOGAT**

- * Sistema de alta afinidade para assimilação de amônia
- * Ativo em baixas concentrações de amônia

- * GOGAT (glutamato sintase) é reprimida por amônia

- * GS (glutamina sintase) é reprimida por glutamina
- * Inibição por qualquer via relacionada a *L*-glutamina:
 - * AMP
 - * GTP
 - * *L*-glicina
 - * *L*-histidina

Biossíntese de *L*-glutamato a partir de α -cetoglutarato

- * *L*-glutamina
 - * Doador de nitrogênio (amônia) para vários compostos nitrogenados
 - * Importante ponto de ramificação para o metabolismo celular

Biossíntese de aminoácidos

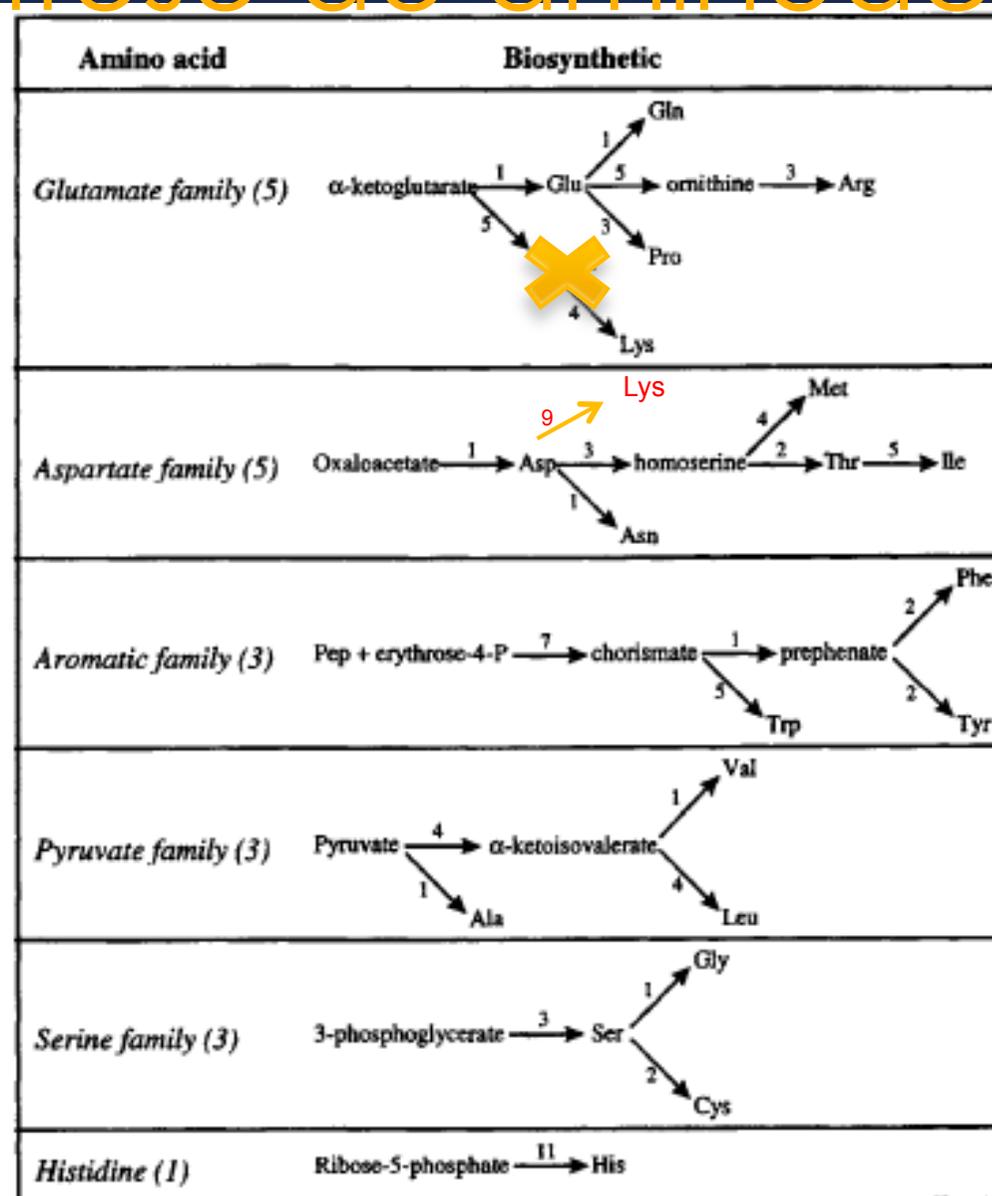
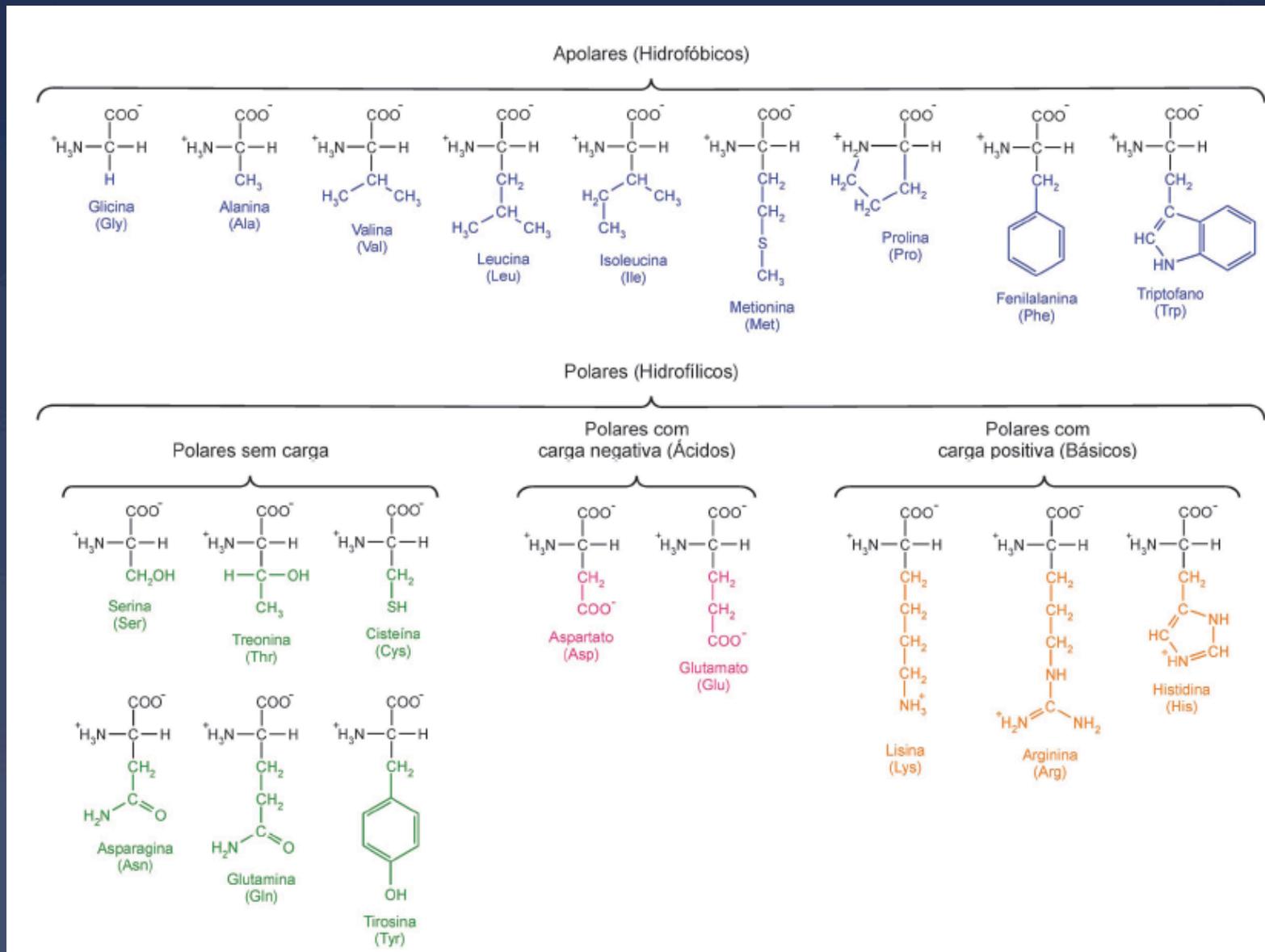


FIGURE 2.12 Overview of amino acid biosynthesis in eukaryotes. The amino acids are classified into five families according to the specific precursor metabolite or amino acid that serves as the starting point for their synthesis. L-Histidine, which has a complex biosynthetic pathway, does not group with any of the other amino acids. The numbers indicate the reaction steps in the pathway. Except for L-lysine, these numbers are the same for bacteria. In bacteria L-lysine is synthesized from aspartate via diaminopimelic acid (an important building block for bacteria cell wall) in a sequence of nine reactions.

Estrutura dos aminoácidos



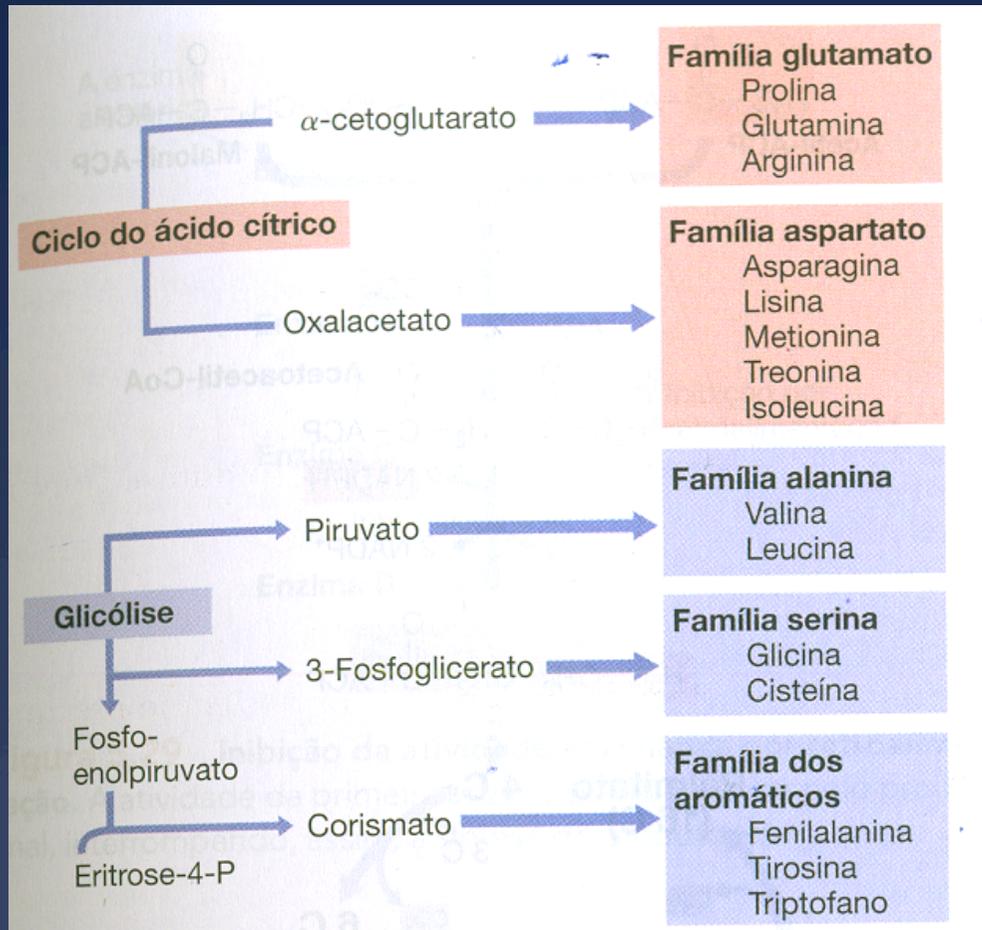
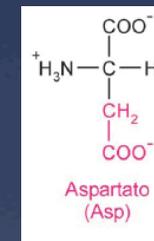
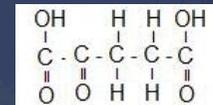
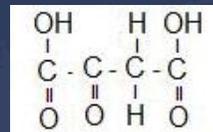
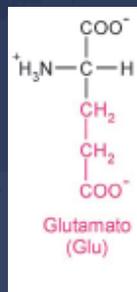
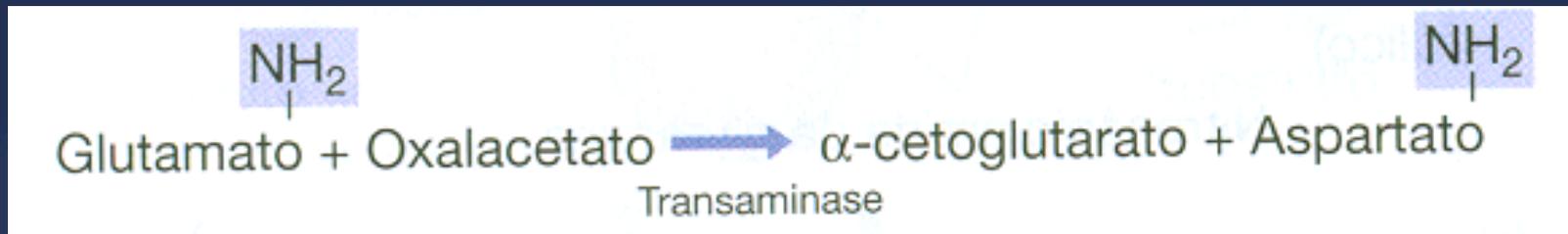


Figura 5.25 Famílias de aminoácidos. A maioria dos aminoácidos é derivada do ciclo do ácido cítrico ou da glicólise. A síntese dos vários aminoácidos de uma família frequentemente requer muitas etapas distintas, enzimaticamente catalisadas, iniciadas a partir do aminoácido parental (apresentado em negrito).

As reações de transaminase transferem um grupo amino para um ácido orgânico



Custos metabólicos para produzir aa em bactérias e fungos

Amino acid	Precursor metabolites ^a	ATP ^b	NADH	NADPH	1-C ^c	NH ₃	S ^d
L-Alanine	1 pyr	0	0	-1	0	-1	0
L-Arginine	1 α kg	-7	1	-4	0	-4	0
L-Asparagine	1 oaa	-3	0	-1	0	-2	0
L-Aspartate	1 oaa	0	0	-1	0	-1	0
L-Cysteine ^e	1 pga	-4	1	-5	0	-1	-1
L-Glutamate	1 α kg	0	0	-1	0	-1	0
L-Glutamine	1 α kg	-1	0	-1	0	-2	0
L-Glycine	1 pga	0	1	-1	1	-1	0
L-Histidine	1 penP	-6	3	-1	-1	-3	0
L-Isoleucine	1 oaa, 1 pyr	-2	0	-5	0	-1	0
L-Leucine	2pyr, 1 acCoA	0	1	-2	0	-1	0
L-Lysine (fungi)	1 akg, 1 acCoA	-2	2	-4	0	-2	0
L-Lysine	1 pyr, 1 oaa	-3	0	-4	0	-2	0
L-Methionine	1 oaa	-7	0	-8	-1	-1	-1
L-Phenylalanine	2 pep, 1 eryP	-1	0	-2	0	-1	0
L-Proline	1 α kg	-1	0	-3	0	-1	0
L-Serine	1 pga	0	1	-1	0	-1	0
L-Threonine	1 oaa	-2	0	-3	0	-1	0
L-Tryptophan	1 pep, 1 eryP, 1 penP	-5	2	-3	0	-2	0
L-Tyrosine	2 pep, 1 eryP	-1	1	-2	0	-1	0
L-Valine	2 pyr	0	0	-2	0	-1	0

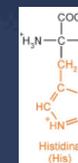
^a acCoA, acetyl-CoA; eryP, erythrose-4-phosphate; fruP, fructose-6-phosphate; gluP, glucose-6-phosphate; α kg, α -ketoglutarate; glyP, glyceraldehyde-3-phosphate; oaa, oxaloacetate; penP, ribose-5-phosphate; pep, phosphoenolpyruvate; pga, 3-phosphoglycerate; pyr, pyruvate.

^b For those reactions where ATP is hydrolyzed to AMP, it is assumed that two ATPs are used.

^c 5,10-Methylene tetrahydrofolate is used as one-carbon donor which is converted to tetrahydrofolate. Other forms of tetrahydrofolate used in the biosynthesis of L-methionine and L-histidine are converted to this basis.

^d Sulfate is used as S-source, which is reduced to H₂S before assimilation.

^e Direct sulphydrylation of L-serine is assumed.



Biossíntese de ácidos nucleicos, ácidos graxos e outros blocos construtores

- * Nucleotídios - precursores de RNA e DNA na forma de ribonucleotídios e desoxiribonucleotídios

- * São constituintes de diversos cofatores:

- * NADH

- * NADPH

- * FAD

- * CoA

- * ATP tem diferentes funções no metabolismo

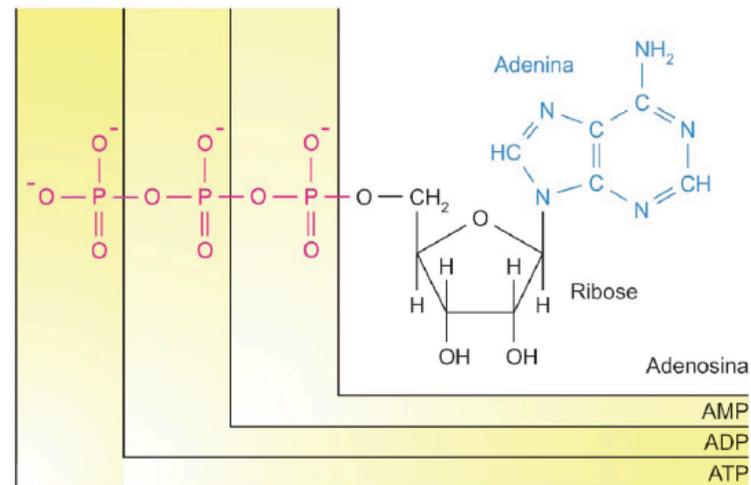
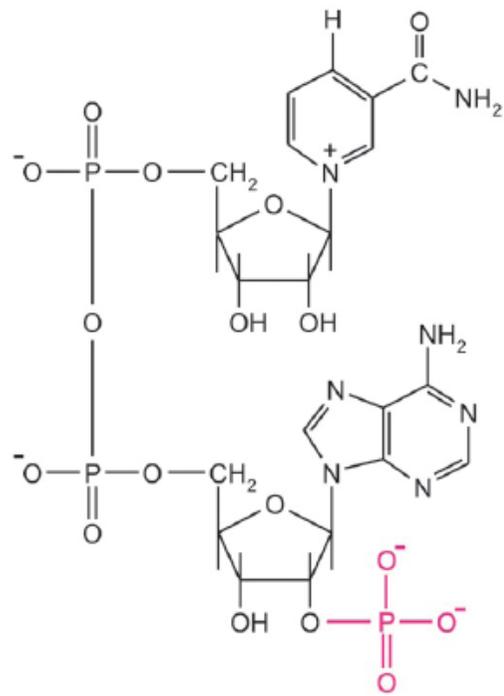
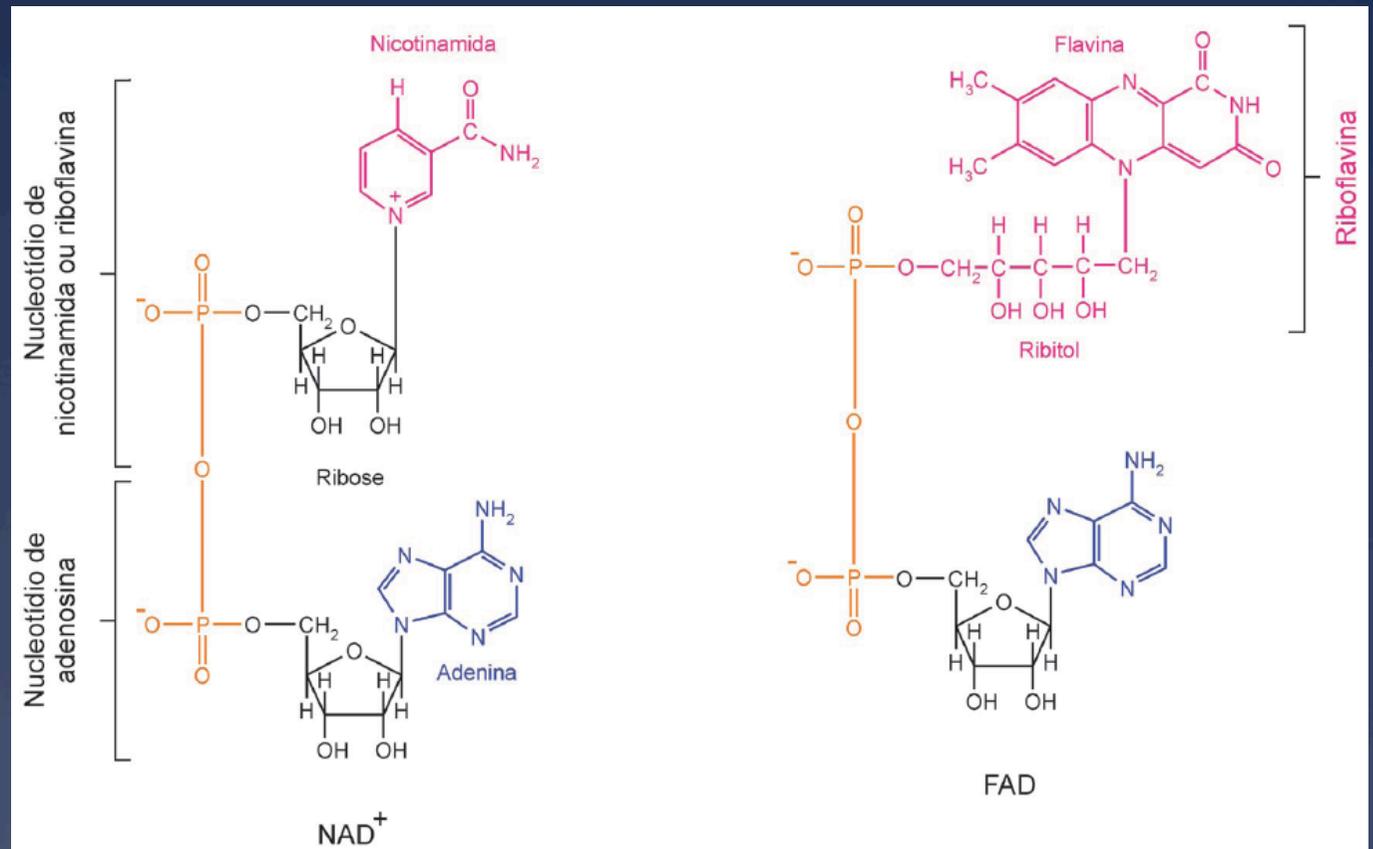


Fig. 4.1 Estrutura da adenosina, adenosina monofosfato (AMP), adenosina difosfato (ADP) e adenosina trifosfato (ATP). Nos três nucleotídeos (AMP, ADP e ATP), o grupo fosfato está unido à ribose da adenosina por ligação éster fosfórico ($\Delta G^{0'}$ de hidrólise = $-15 \text{ kJ} \cdot \text{mol}^{-1}$); no ADP e no ATP, a ligação com o(s) outro(s) grupo(s) fosfato é do tipo anidrido fosfórico ($\Delta G^{0'}$ de hidrólise = $-31 \text{ kJ} \cdot \text{mol}^{-1}$).

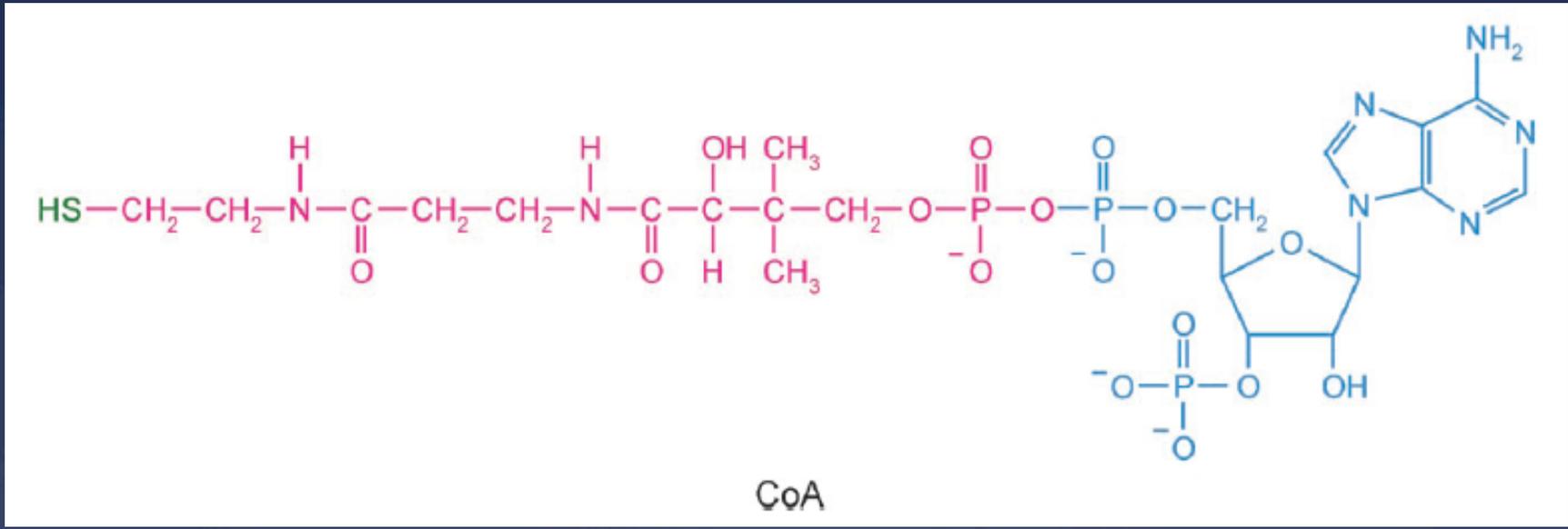


NADP⁺



NAD⁺

FAD



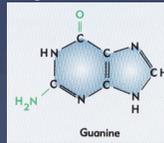
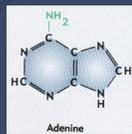
A coenzima A se une a grupos acila por ligações tioéster com a sulfidril terminal (verde) do grupo fosfopanteteína (vermelho).
A fosfopanteteína está ligada ao grupo fosfato da 3' fosfoadenosina (azul) que compõe a Coenzima A.

Biossíntese de ácidos nucleicos, ácidos graxos e outros blocos construtores

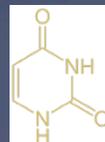
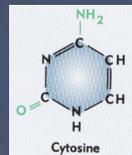
* Precusores dos nucleotídios:

* Ribose 5P e 3 fosfoglicerato

* Purinas (A, G)



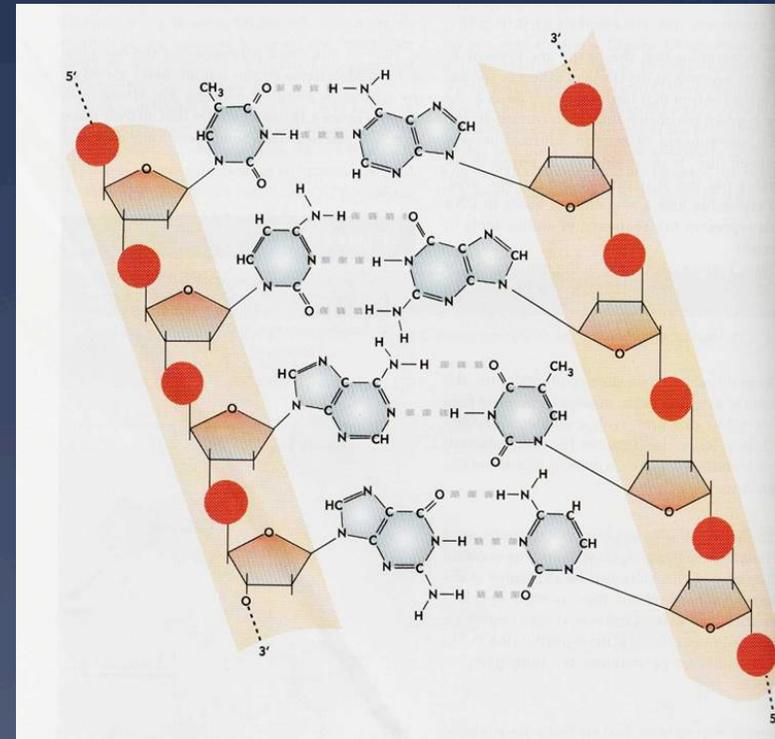
* Pirimidinas (T, C, U)



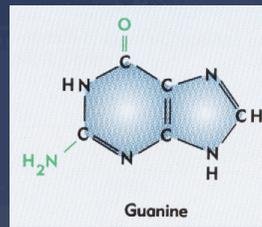
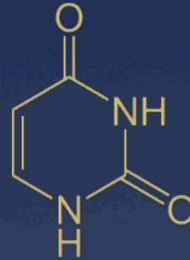
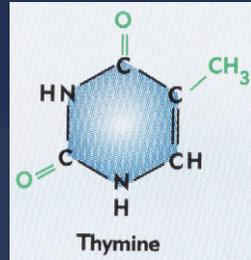
* Ribose 5P e oxaloacetato

Estrutura dos nucleotídeos

- * Base nitrogenada heterocíclica (purina ou pirimidina)
- * Um açúcar: ribose (no RNA) ou 2-desoxirribose (no DNA)
- * Um grupo fosforil



Estrutura dos nucleotídeos



- * AMP
- * TMP (U no RNA)
- * CMP
- * GMP geram
- * dAMP
- * dTMP
- * dCMP
- * dGMP

Bases nitrogenadas

dTMP resulta da metilação de dUMP

Estrutura dos nucleotídeos

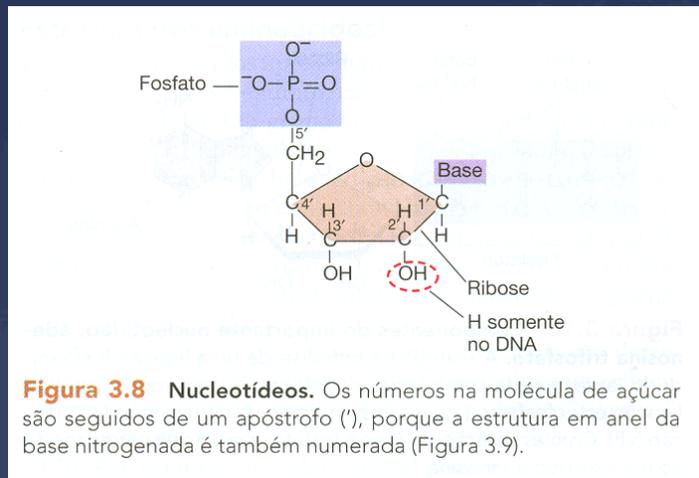
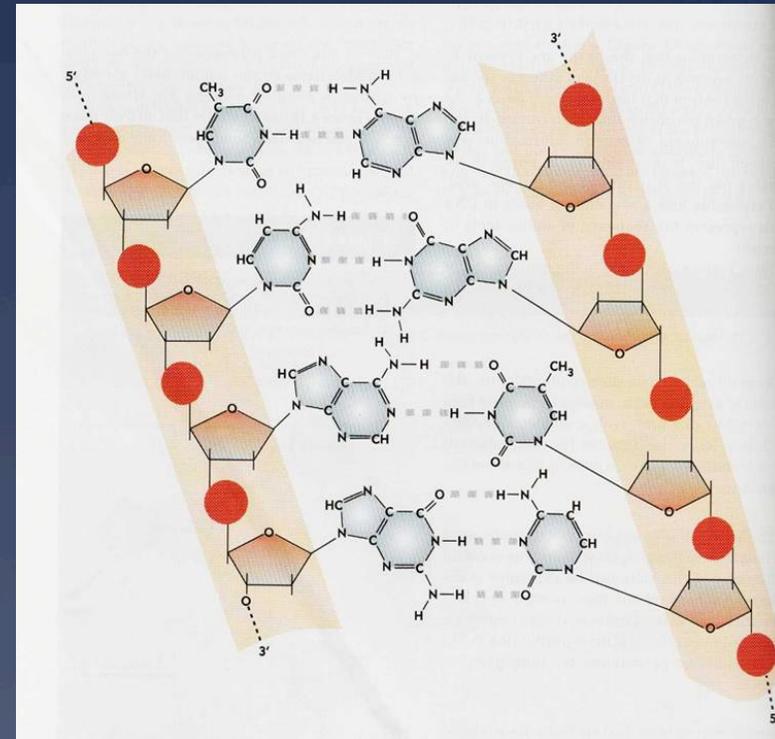
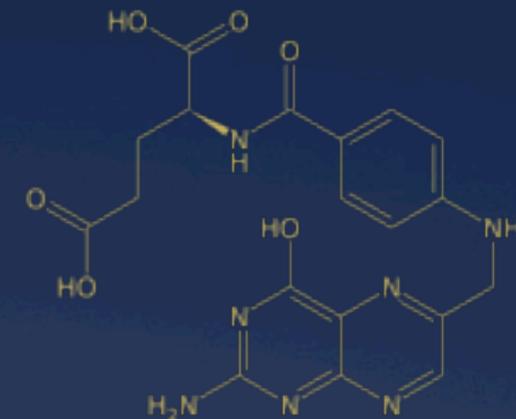
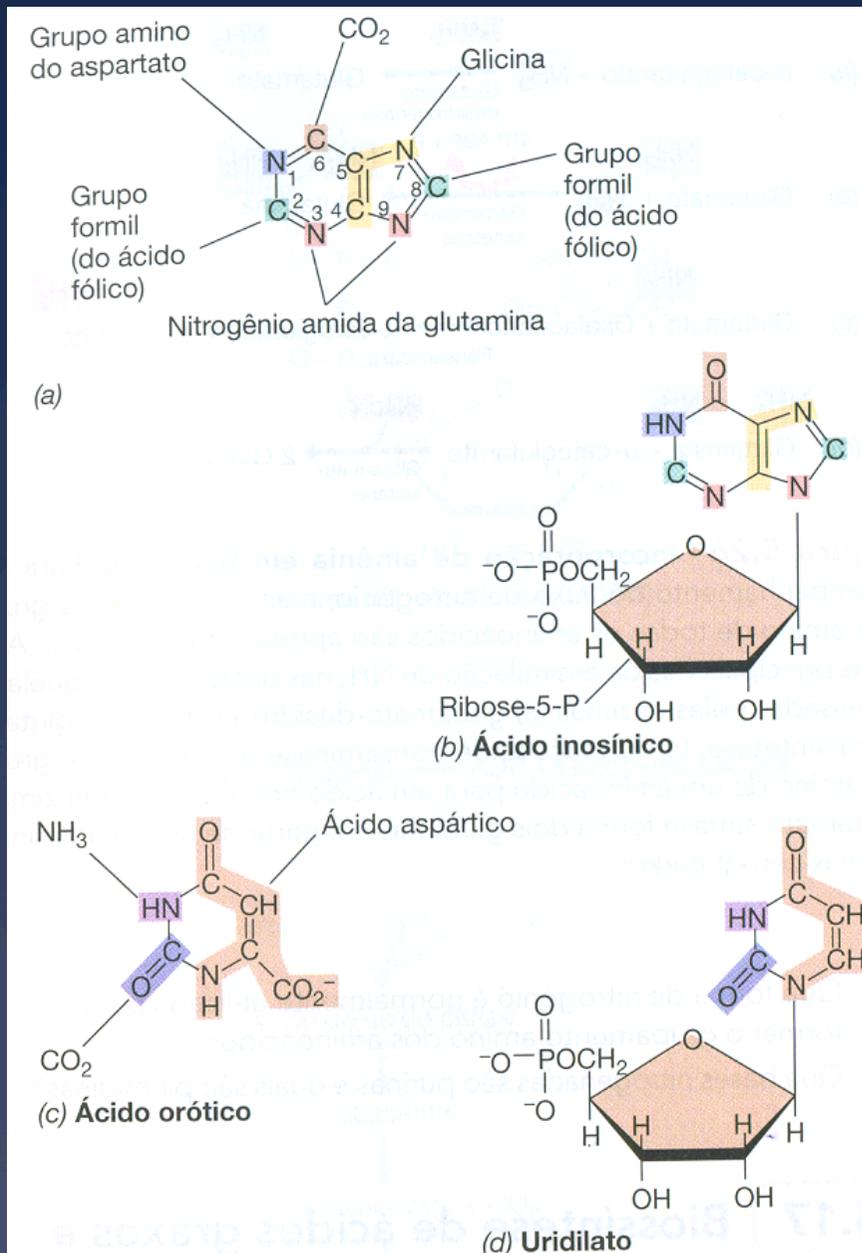


Figura 3.8 Nucleotídeos. Os números na molécula de açúcar são seguidos de um apóstrofo ('), porque a estrutura em anel da base nitrogenada é também numerada (Figura 3.9).



OH na posição 2' é substituída por H às custas de NADPH (ribose ou desoxirribose)



Ácido fólico (vitamina B9, pteroil-L-glutamato)

2-amino-4-oxo-6-methylpteridine

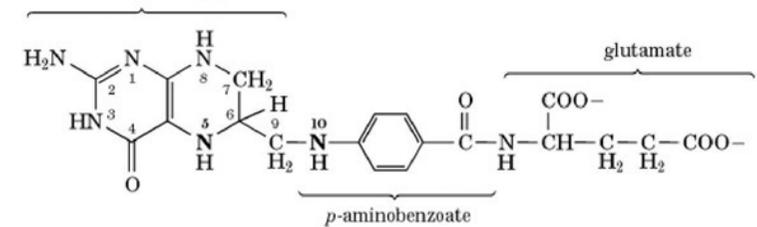


Figura 5.27 Biossíntese de purinas e pirimidinas. (a) Os precursores do esqueleto da purina. (b) Ácido inosínico, o precursor de todos os nucleotídeos purínicos. (c) O precursor do esqueleto de pirimidina, ácido orótico. (d) Uridilato, o precursor de todos os nucleotídeos pirimidínicos. O uridilato é formado a partir do orotato, após uma descarboxilação e a adição de ribose-5-fosfato.

Custos metabólicos para a biossíntese de nucleotídeos

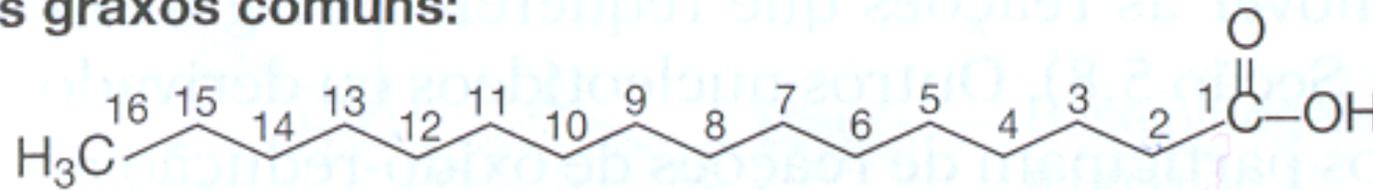
Nucleotide	Precursor metabolite ^a	ATP	NADH	NADPH	1-C	NH ₃
AMP	1 pga, 1 penP	-9	3	-1	-1	-5
GMP	1 pga, 1 penP	-11	3	0	-1	-5
UMP	1 oaa, 1 penP	-5	0	-1	0	-2
CMP	1 oaa, 1 penP	-7	0	-1	0	-3
dAMP	1 pga, 1 penP	-9	3	-2	-1	-5
dGMP	1 pga, 1 penP	-11	3	-1	-1	-5
dTMP ^b	1 oaa, 1 penP	-5	0	-3	-1	-2
dCMP	1 oaa, 1 penP	-7	0	-2	0	-3

^a See Table 2.4 for nomenclature.

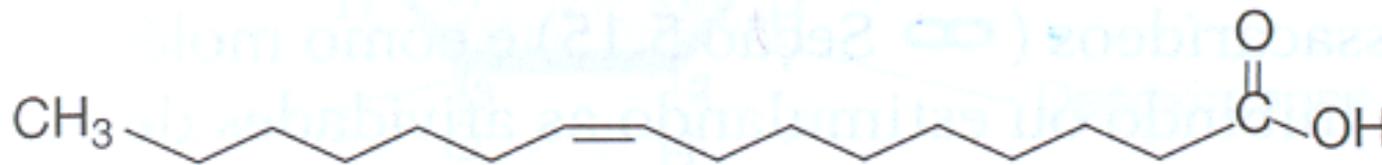
^b The costs for dTMP biosynthesis are the same as for synthesis from dUMP. dTMP may also be synthesized from dCMP with higher costs, i.e., nine ATPs. For *E. coli*, Ingraham *et al.* (1983) state that 75% of the dTMP is synthesized from dCMP and 25% from dUMP.

Biossíntese de ácidos graxos

Ácidos graxos comuns:



C₁₆ saturado (palmítico)



C₁₆ monoinsaturado (palmitoleico)

Os ácidos graxos diferem quanto ao comprimento, à posição e ao número de ligações duplas.

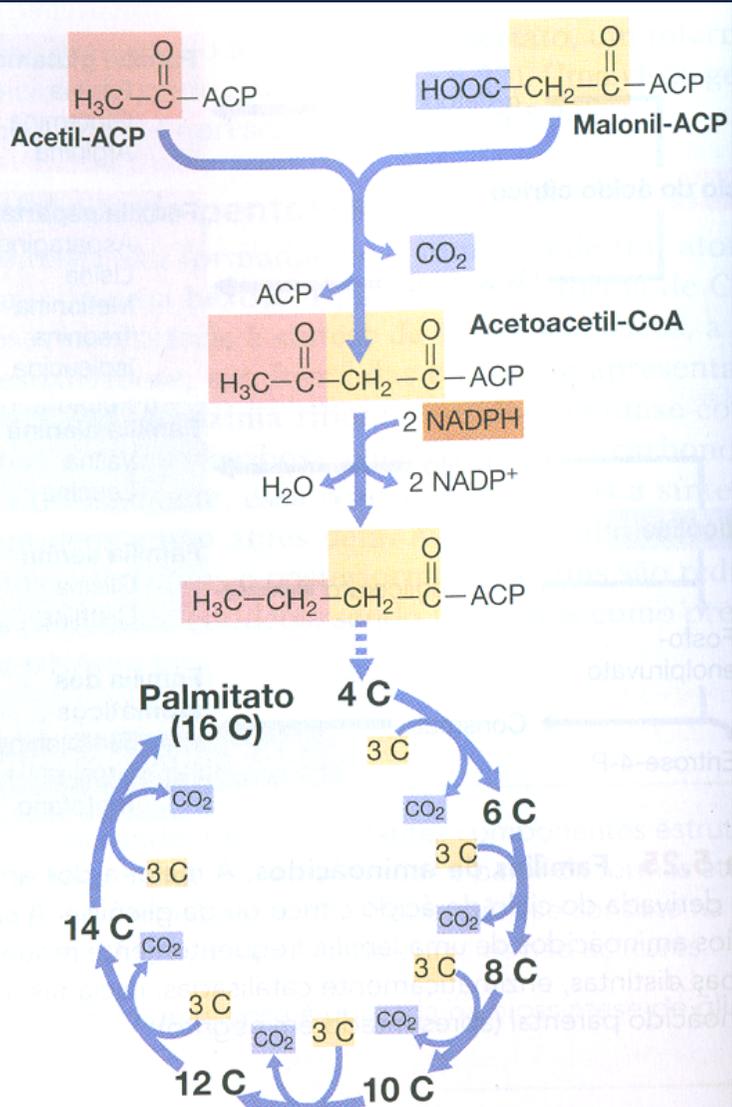
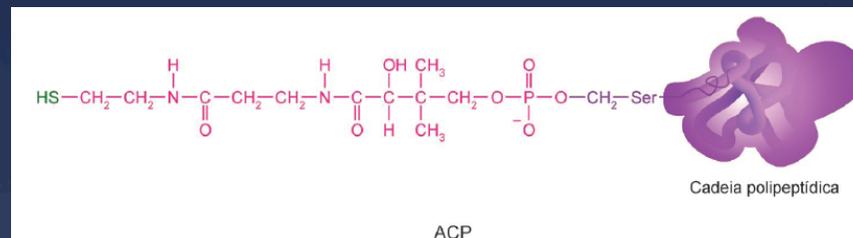
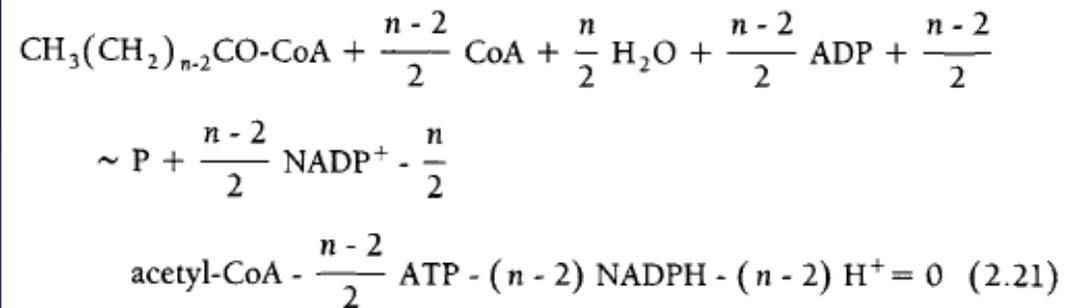


Figura 5.28 A biossíntese de ácidos graxos. É apresentada a biossíntese do ácido graxo C₁₆, palmitato (Figura 3.7). ACP, proteína carreadora de acil. A condensação de acetil-ACP e malonil-ACP forma acetoacetyl-CoA. Cada adição sucessiva de uma unidade acetil é oriunda do malonil-ACP.



ACP é o carreador de acil

Biossíntese de ácidos graxos



Biossíntese de ácidos graxos

* Outros precursores importantes para a síntese de lipídios:

→ EMP

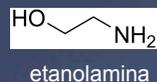
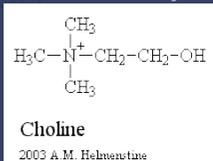
* Glicerol 3P (esqueleto de fosfolipídios e triacil gliceróis)

* Molécula alcoólica dos fosfolipídios

* colina em fungos

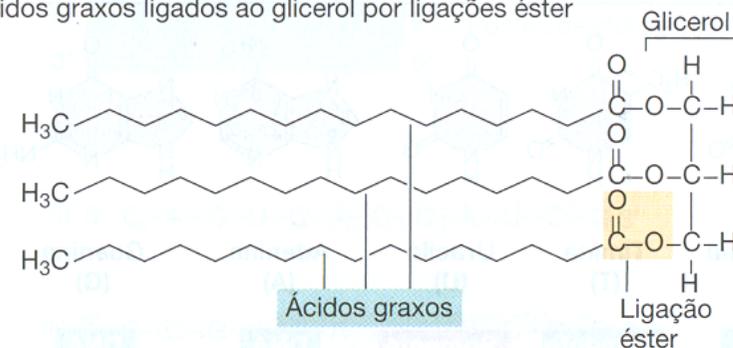
* Fosfatidiletanolaminas, fosfatidilgliceróis e cardiolipinas em bactérias

* Esteróis (fungos e leveduras)



Lipídeos simples (triglicerídeos):

Ácidos graxos ligados ao glicerol por ligações éster

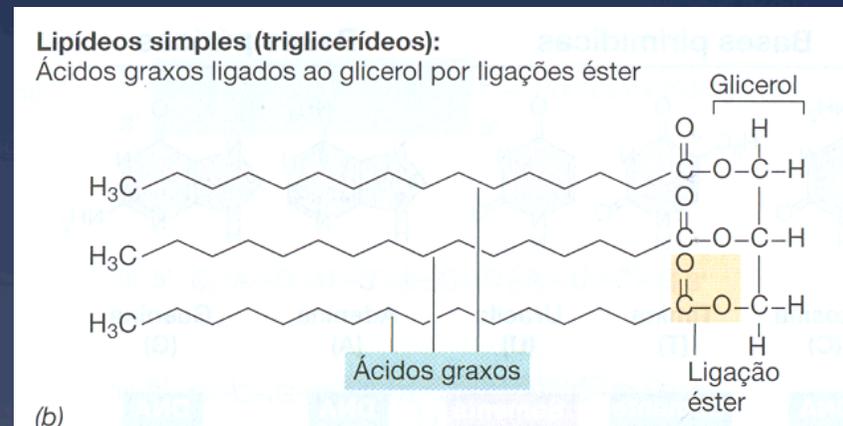


(b)

36

Montagem final de lipídios

- * Três carbonos do glicerol são esterificados com ácidos graxos

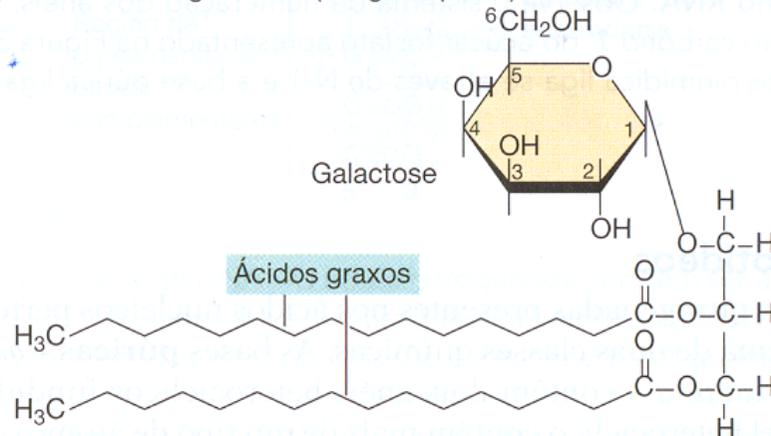


Montagem final de lipídios

- * Em lipídeos complexos o C do glicerol se liga a
 - * fosfato,
 - * etanolamina,
 - * um açúcar
 - * ou outra substância polar

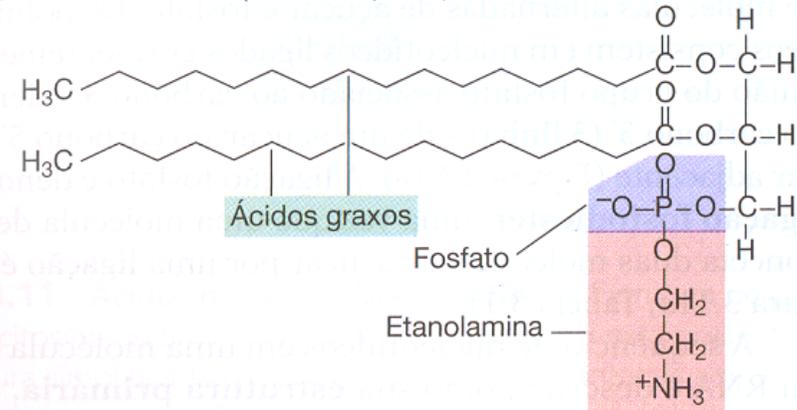
Lipídeo complexo:

Diglicerídeo monogalactosil (um glicolipídeo)

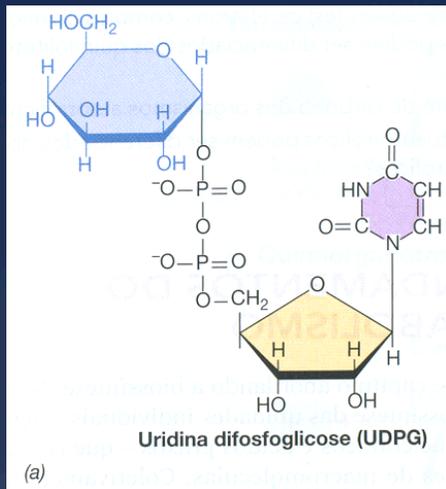


Lipídeo complexo:

Fosfatidiletanolamina (um fosfolipídeo)



Biossíntese de carboidratos



Os polissacarídeos são sintetizados a partir de formas ativadas de glicose como UDPG

N-acetilglicosamina, ácido *N*-acetil murâmico (no peptídioglicano)

LPS (membrana externa de Gram negativos)

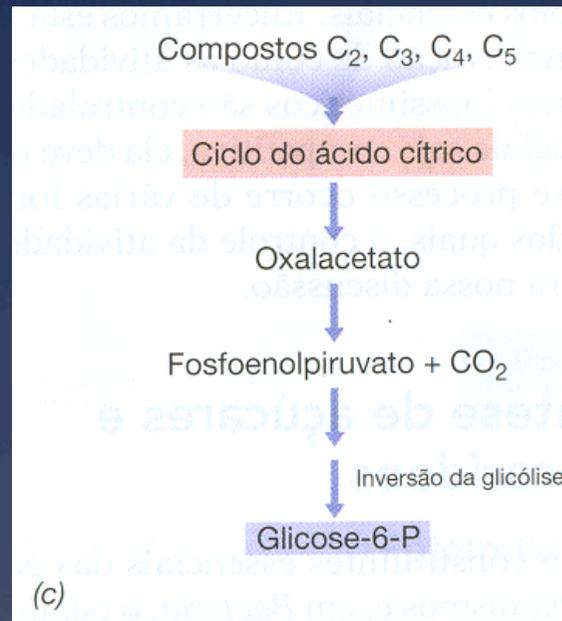
Biossíntese de carboidratos



(b)

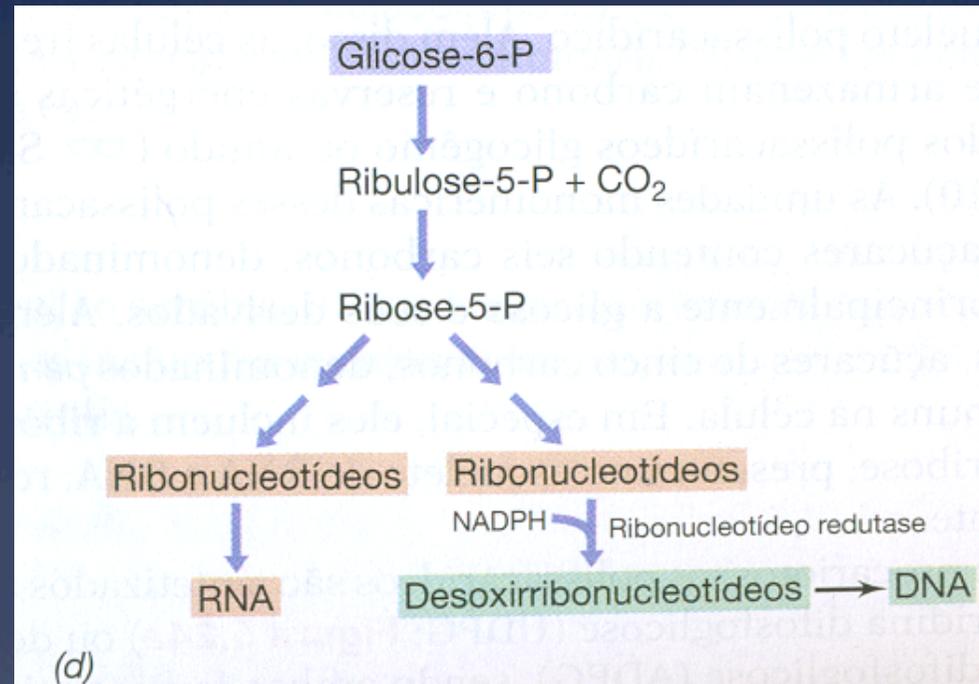
O Glicogênio é sintetizado a partir de ADPG (adenosina-difosfoglicose) pela adição sequencial de glicose

Biossíntese de carboidratos



Gliconeogênese – quando há necessidade de glicose, sua síntese ocorre a partir de outros compostos

Biossíntese de carboidratos



As pentoses são oriundas das hexoses, que são descarboxiladas.

Biossíntese de carboidratos

Biossíntese do peptidoglicano requer 5 monômeros:

UDP-*N*-acetilglicosamina (UDP-NAG),
ácido UDP-*N*-acetilmurâmico (UDP-NAM),
alanina D e L,
diaminopimelato e
glutamato.

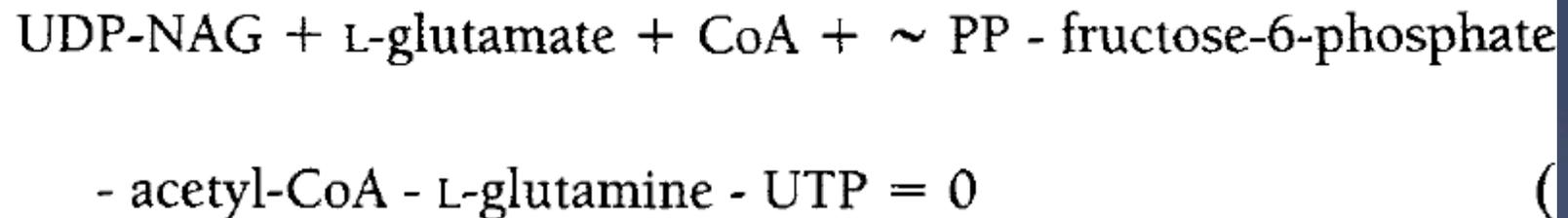


TABLE 2.7 Metabolic Costs for Biosynthesis of Lipids and Carbohydrate Building Blocks

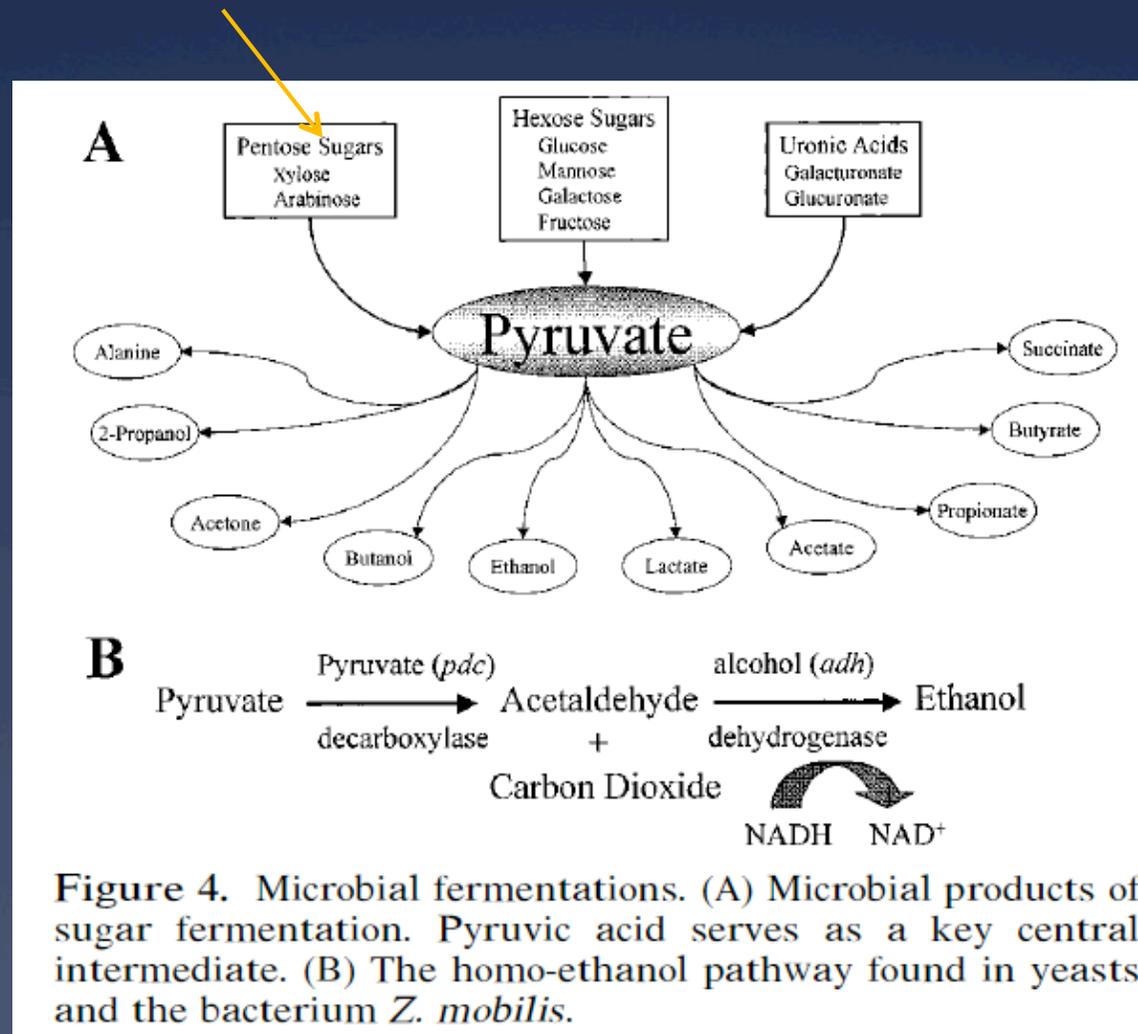
Building block	Precursor metabolite ^a	ATP	NADH	NADPH	1-C	NH ₃
Glycerol-3-phosphate	1 glyP	0	-1	0	0	0
Palmitoyl-CoA	8 acCoA	-7	0	-14	0	0
Palmitoleoyl-CoA ^b	8 acCoA	-7	0	-14	0	0
Stearoyl-CoA	9 acCoA	-8	0	-16	0	0
Oleoyl-CoA	9 acCoA	-8	1	-16	0	0
Linoleoyl-CoA	9 acCoA	-8	2	-16	0	0
Linolenoyl-CoA	9 acCoA	-8	3	-16	0	0
Ethanolamine ^c	1 pga	0	1	-1	0	-1
Choline	1 pga	0	1	-1	-3	-1
Inositol	1 gluP	0	1	0	0	0
Ergosterol	18 acCoA	-18	0	-13	0	0
UDP-Glucose	1 gluP	-1	0	0	0	0
UDP-Galactose	1 gluP	-1	0	0	0	0
UDP-NAG	1 fruP, 1 acCoA	-2	0	0	0	-1
UDP-NAM	1 fruP, 1 pep, 1 acCoA	-2	0	-1	0	-1
Diaminopimelate	1 oaa, 1 pyr	-2	0	-3	0	-2

^a See Table 2.4 for nomenclature.

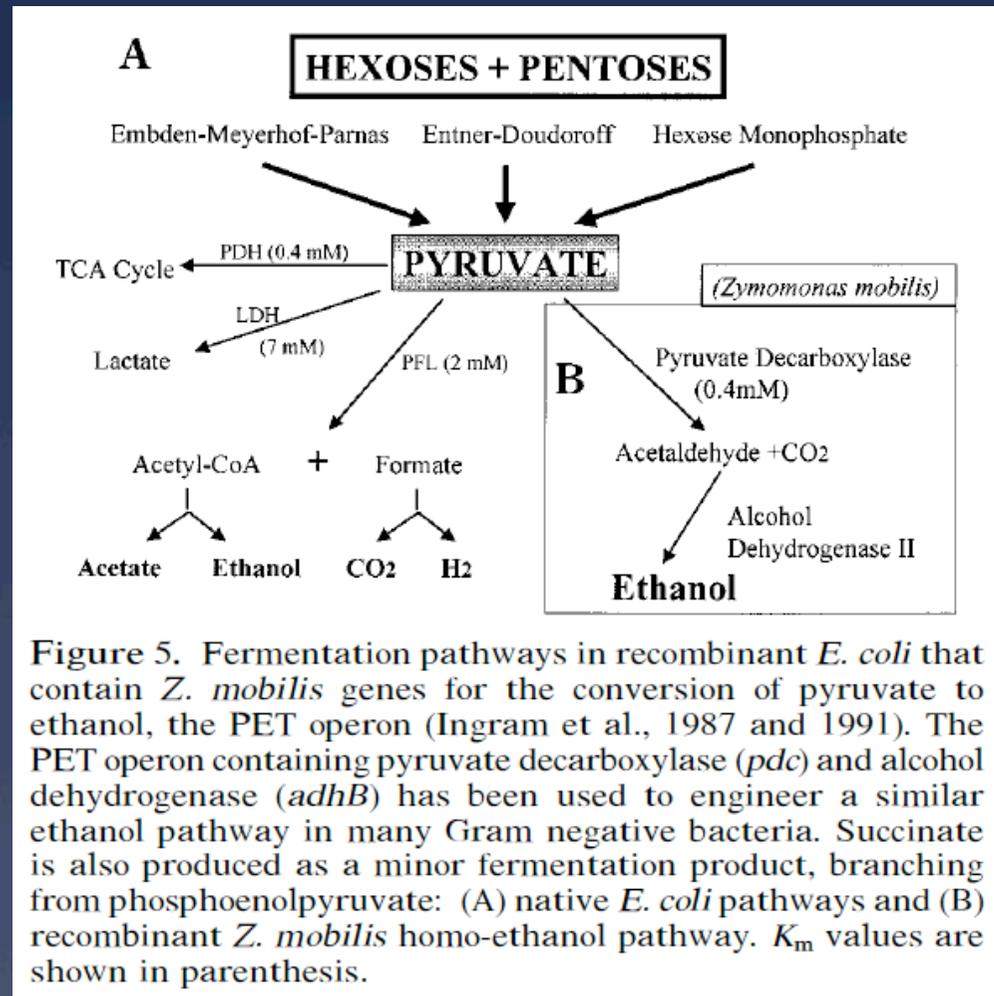
^b The costs are for the biosynthesis of palmitoleoyl-CoA via the anaerobic pathway.

^c Because the pathway from squalene to ergosterol is not known in detail, the metabolic cost for the biosynthesis of ergosterol is taken to be the same as that for squalene.

Produtos biotecnológicos



Produtos biotecnológicos

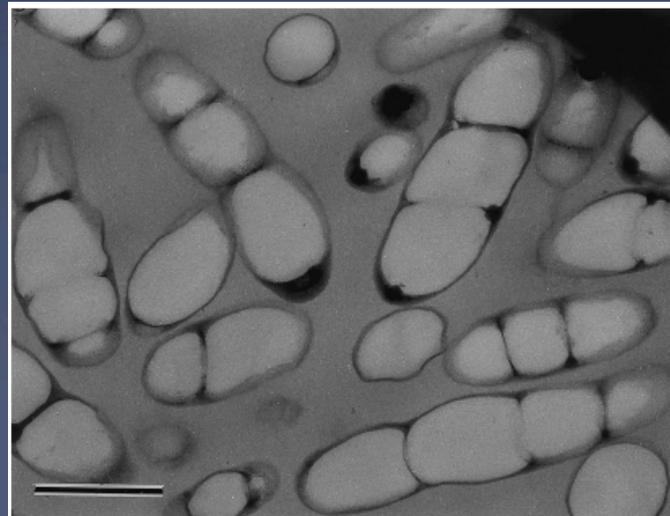
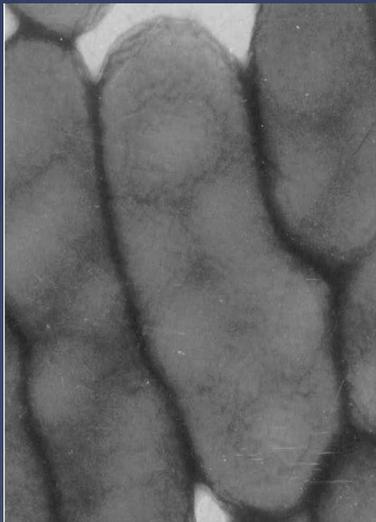
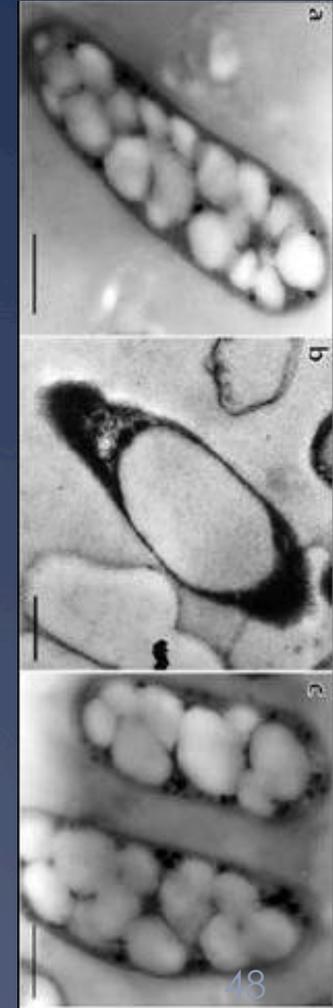
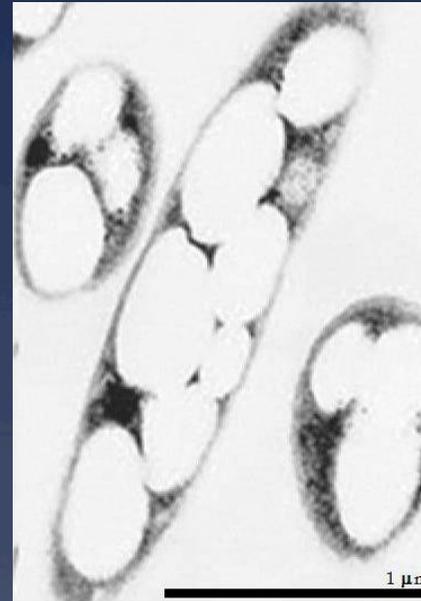


Produtos biotecnológicos

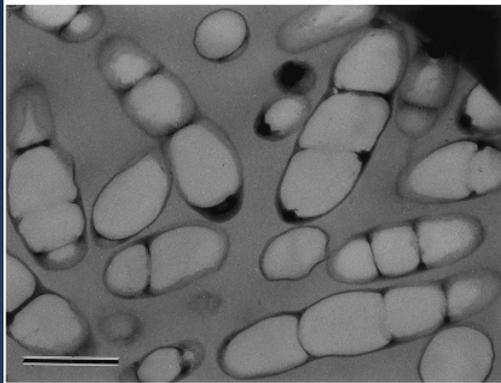
“Polihidroxicanoatos”

PHA

PHA são acumulados por bactérias



PHA são acumulados por bactérias



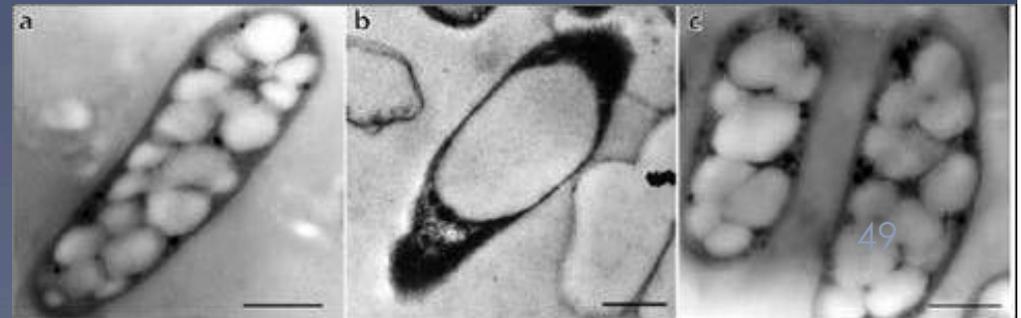
Condições para acúmulo mais expressivo

Meio de cultivo desbalanceado:

- excesso de fonte de C e
- carência de um nutriente essencial (N, P, O...)

Função dos grânulos de PHA para a célula:

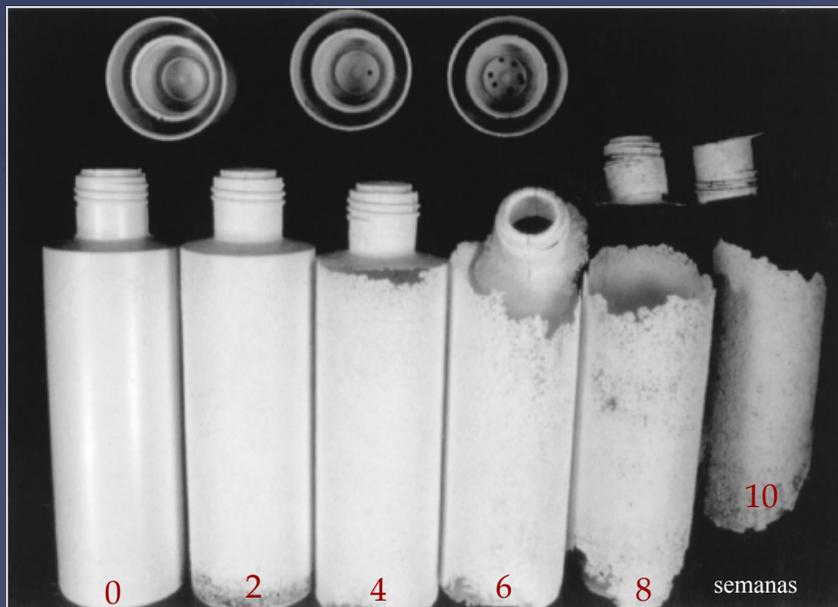
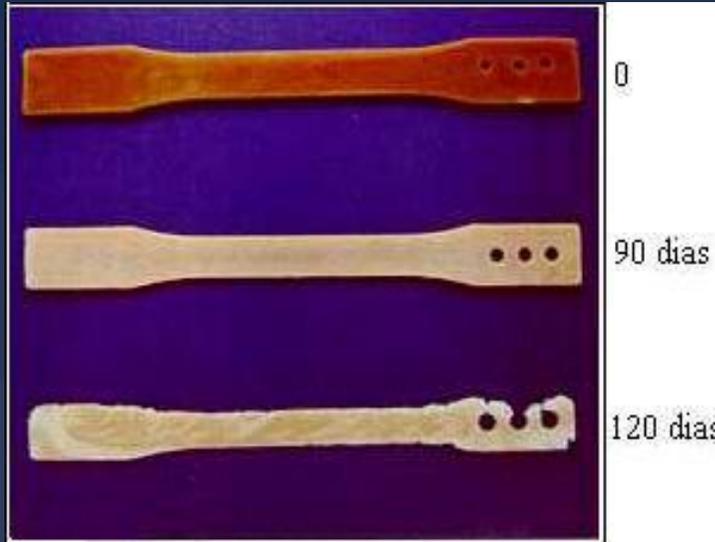
- Fonte de Carbono,
- Fonte de Energia e
- equivalentes redutores



PHA são materiais termoplásticos

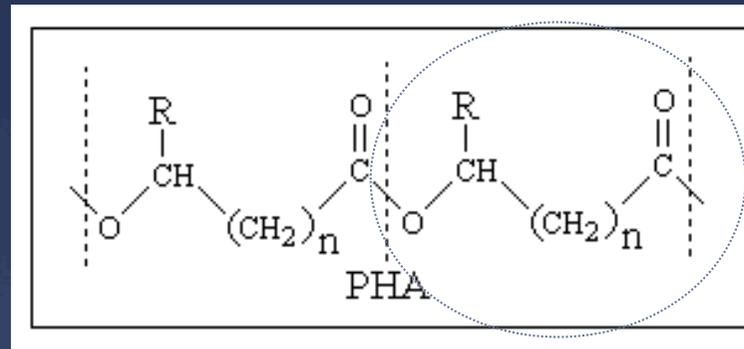
Biodegradáveis e biocompatíveis

Aplicações



Madison & Huisman, 1999

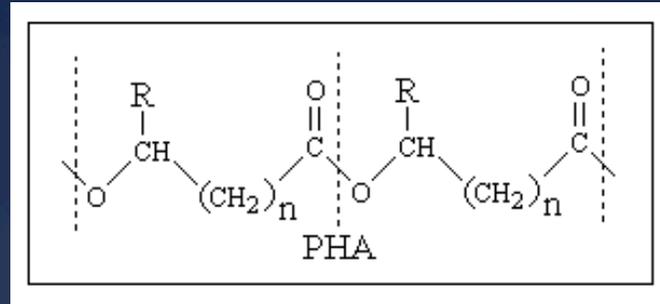
Estrutura química dos PHA



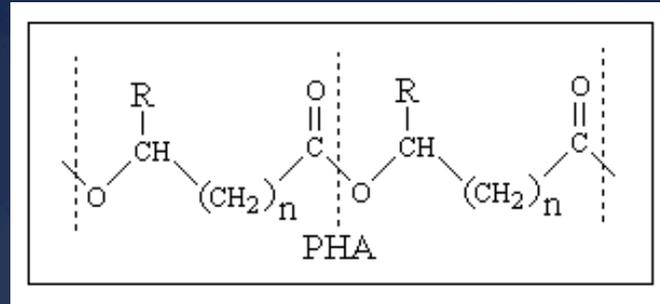
100 - 30000

n = 1	R =	hydrogen	poly (-3-hydroxypropionate)
		methyl	poly (-3-hydroxybutyrate)
		ethyl	poly (-3-hydroxyvalerate)
		propyl	poly (-3-hydroxyhexanoate)
		pentyl	poly (-3-hydroxyoctanoate)
		nonyl	poly (-3-hydroxydodecanoate)
n = 2	R =	hydrogen	poly (-4-hydroxybutyrate)
n = 3	R =	hydrogen	poly (-5-hydroxyvalerate)

Aplicações x propriedades x composição dos PHA



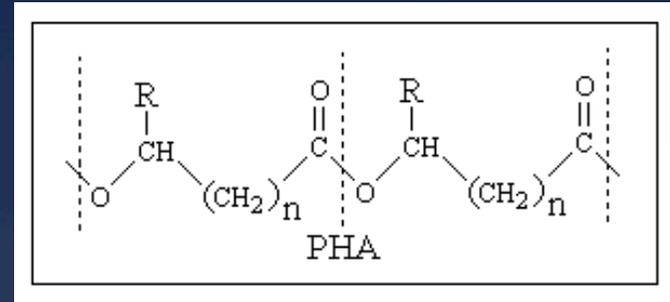
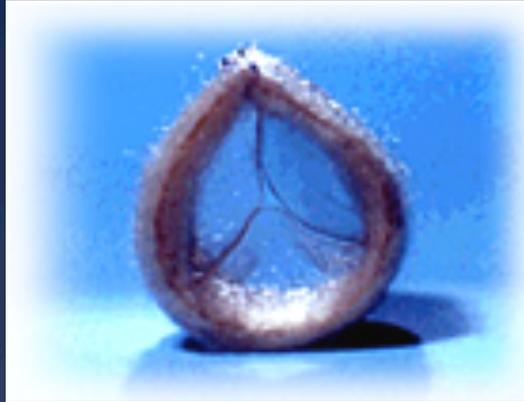
Aplicações x propriedades x composição dos PHA



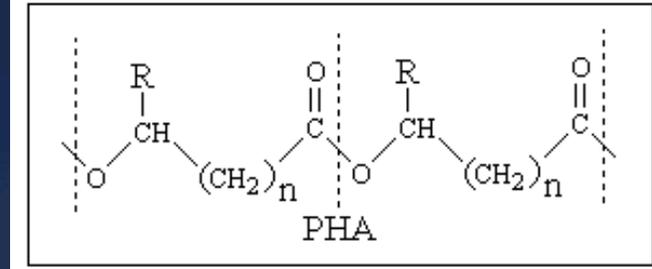
Bucci, 2003

Aplicações x propriedades x composição dos PHA

(www.tepha.com)



Propriedades dos PHA e polipropileno



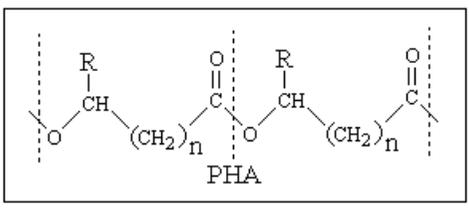
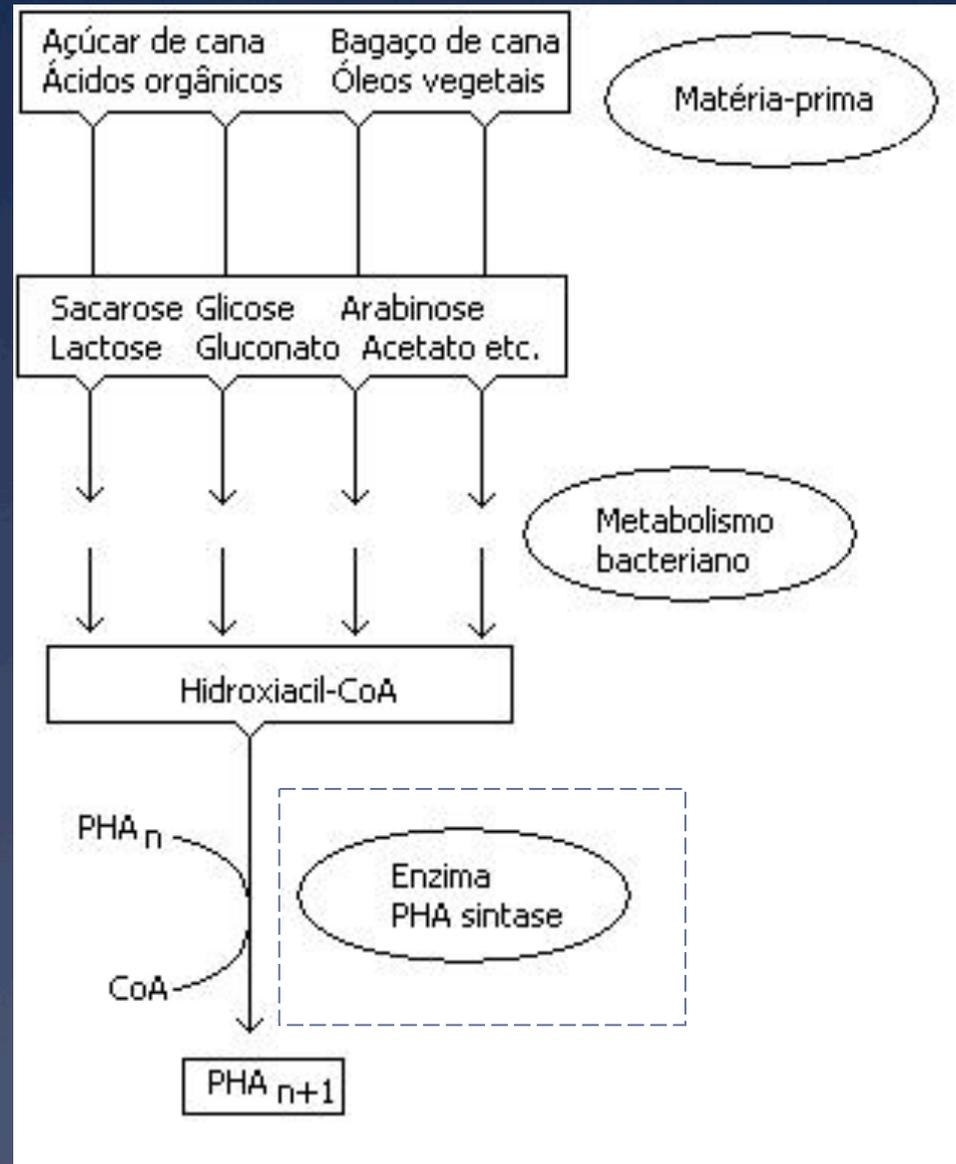
Parâmetro

	P(3HB)	P(3HB-3HV)	P(3HB-4HB)	P(3HO-3HH)	PP
T_m (°C)	177	145	150	61	176
T_g (°C)	2	-1	-7	-36	-10
Cristalinidade (%)	70	56	45	30	60
Extensão até ruptura (%)	5	50	444	300	400

- P(3HB) poly(3-hydroxybutyrate),
- P(3HB-3HV) poly(3-hydroxybutyrate-co-3-hydroxyvalerate) containing 20% 3HV,
- P(3HB-4HB) poly(3-hydroxybutyrate-co-4-hydroxybutyrate) containing 16% 4HB,
- P(3HO-3HH) poly(3-hydroxyoctanoate-co-3-hydroxyhexanoate) containing 11% 3HH,
- PP polypropylene.
- T_m melting temperature.
- T_g glass transition temperature.

Madison e Huisman 1999

Como as bactérias sintetizam PHA?



PHAScl

C₄-C₅

SCL - short chain length

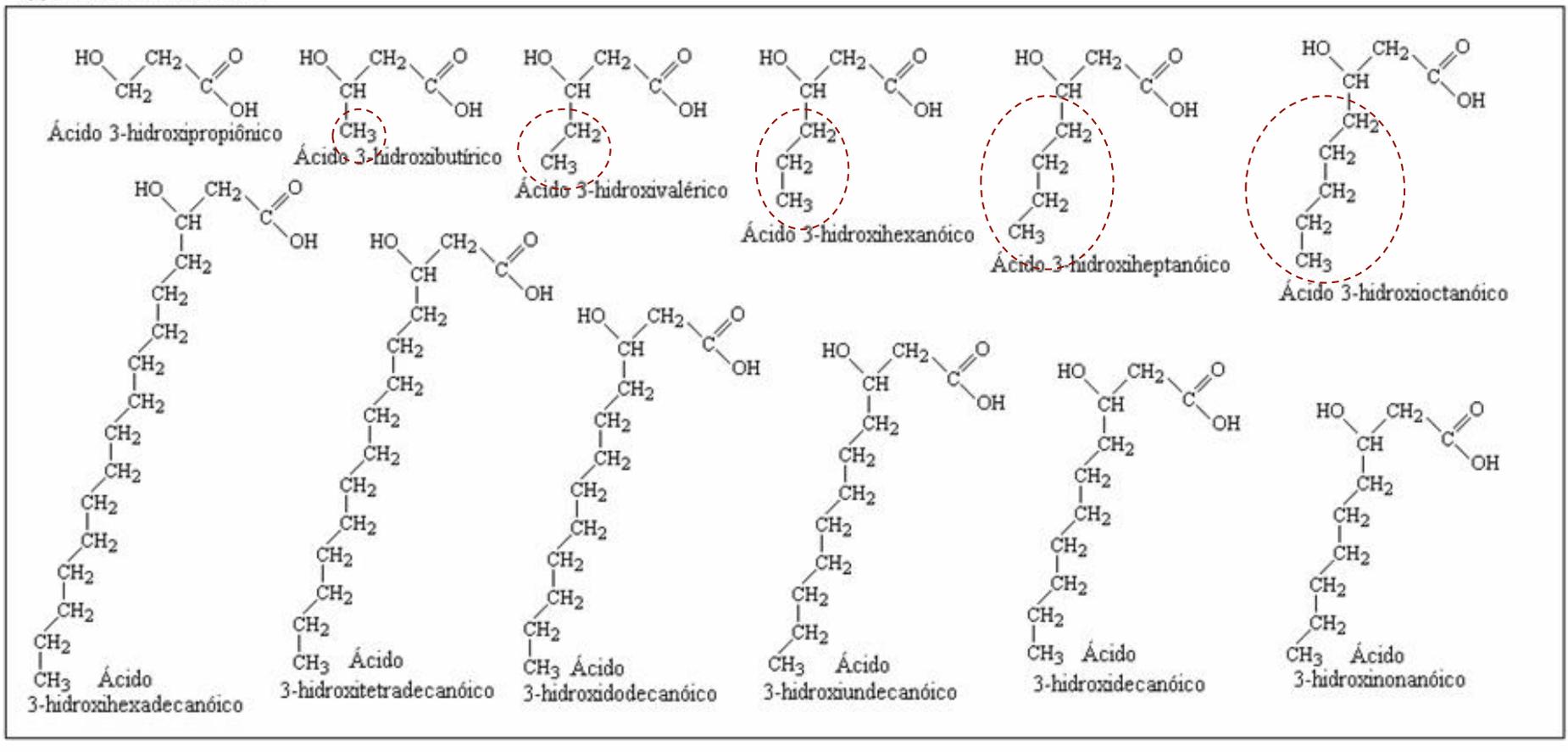
PHAmcl

C₆ - C₁₆

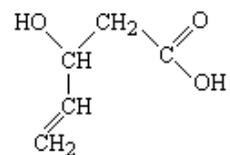
MCL - medium chain length

Biodiversidade como fator chave

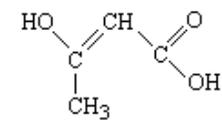
(I) 3-hidroxiálcanoatos



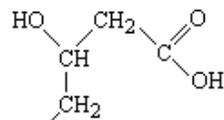
(I) 3-hidroxiácidos



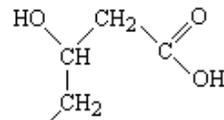
Ácido 3-hidroxi-4-pentenóico



Ácido 3-hidroxi-2-butenóico

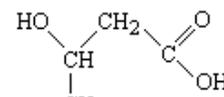


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3-hidroxi-5-cis-dodecenóico

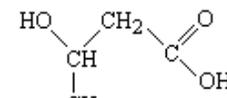


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3-hidroxi-5,8-cis-cis-tetradecenóico

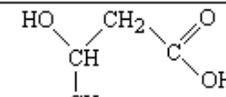
(II) 3-hidroxiácidos com grupos metila



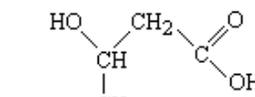
Ácido
3-hidroxi-4-metiloctanóico



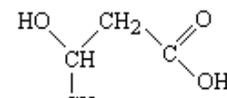
Ácido
3-hidroxi-4-metilvalérico



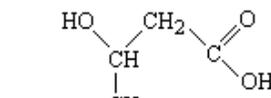
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3-hidroxi-6-metiloctanóico



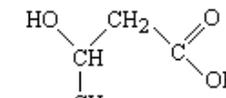
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Ácido
3-hidroxi-4-metilhexanóico

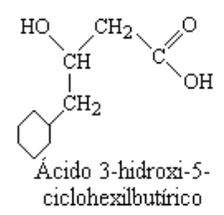
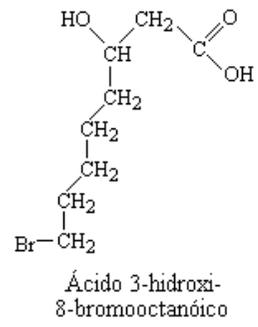
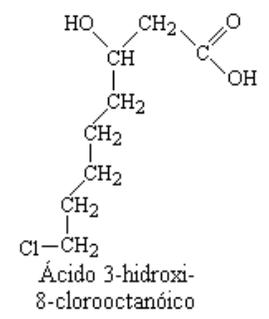
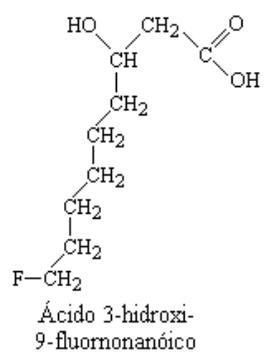
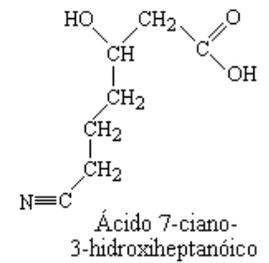
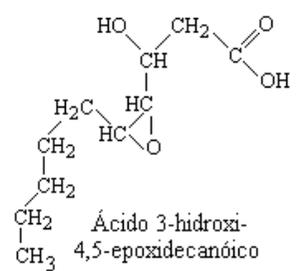
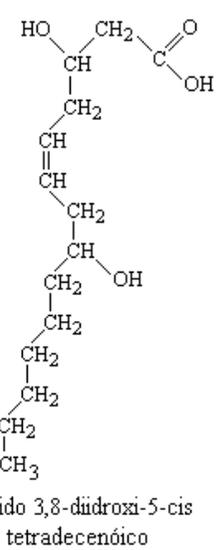
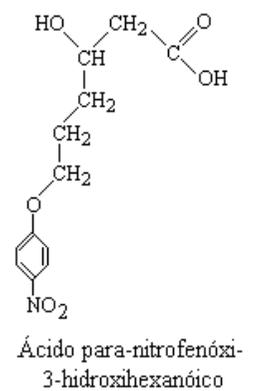
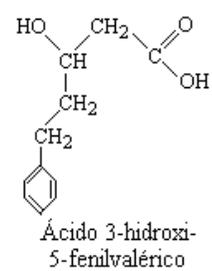
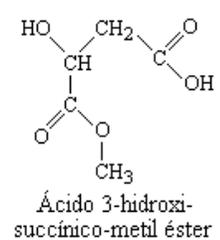
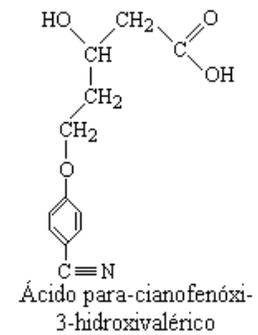
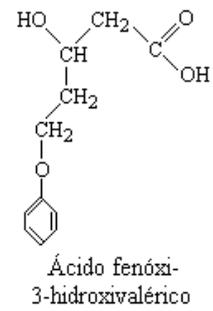
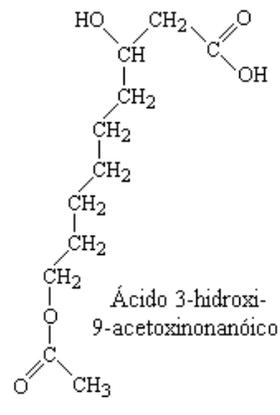
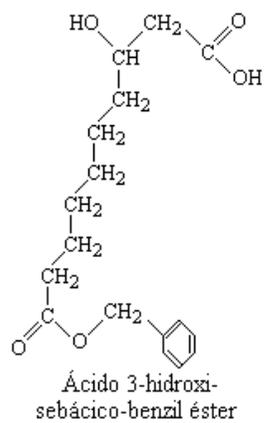
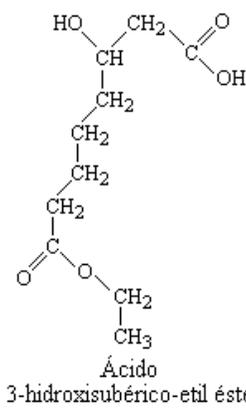
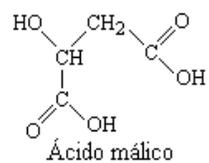


Ácido
3-hidroxi-5-metilhexanóico

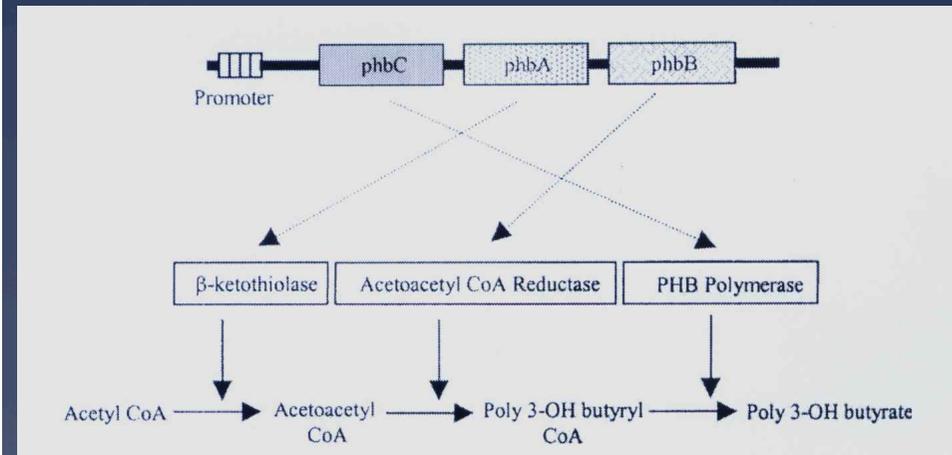
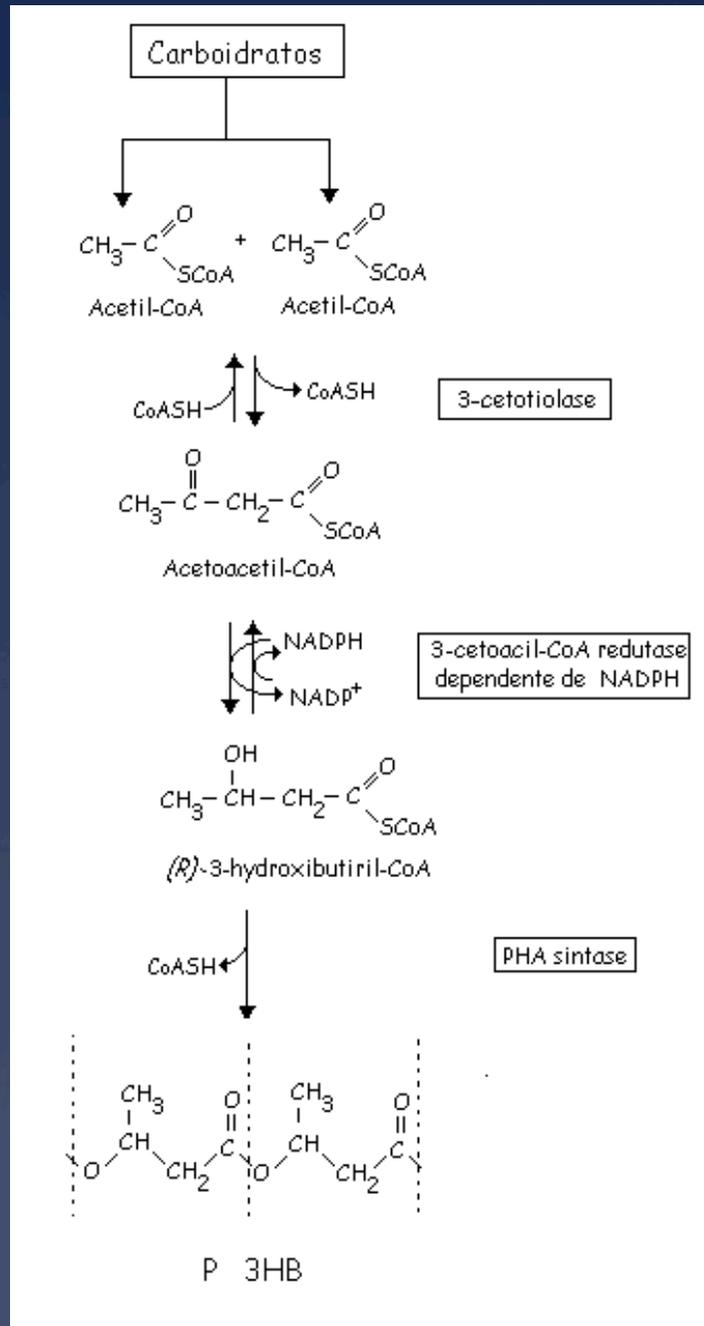


Ácido 3-hidroxi-6-metilheptanóico

(v) 3-hidroxiálcanoatos com diferente grupos funcionais



Via de síntese de PHA

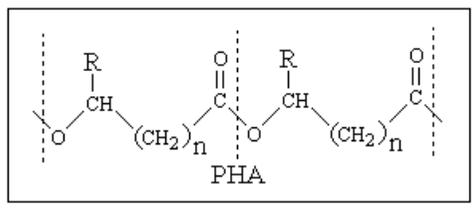


Especificidade da enzima PHA sintase

Class	Subunits	Species	Substrate
I	 ~60–73 kDa	<i>Cupriavidus necator</i>	3HA _{SCL} -CoA (~C3–C5) 4HA _{SCL} -CoA, 5HA _{SCL} -CoA, 3MA _{SCL} -CoA
II	 ~60–65 kDa	<i>Pseudomonas aeruginosa</i>	3HA _{MCL} -CoA (~≥C5)
III	 ~40 kDa ~40 kDa	<i>Allochromatium vinosum</i>	3HA _{MCL} -CoA (3HA _{MCL} -CoA [~C6–C8], 4HA-CoA, 5HA-CoA)
IV	 ~40 kDa ~22 kDa	<i>Bacillus megaterium</i>	3HA _{SCL} -CoA

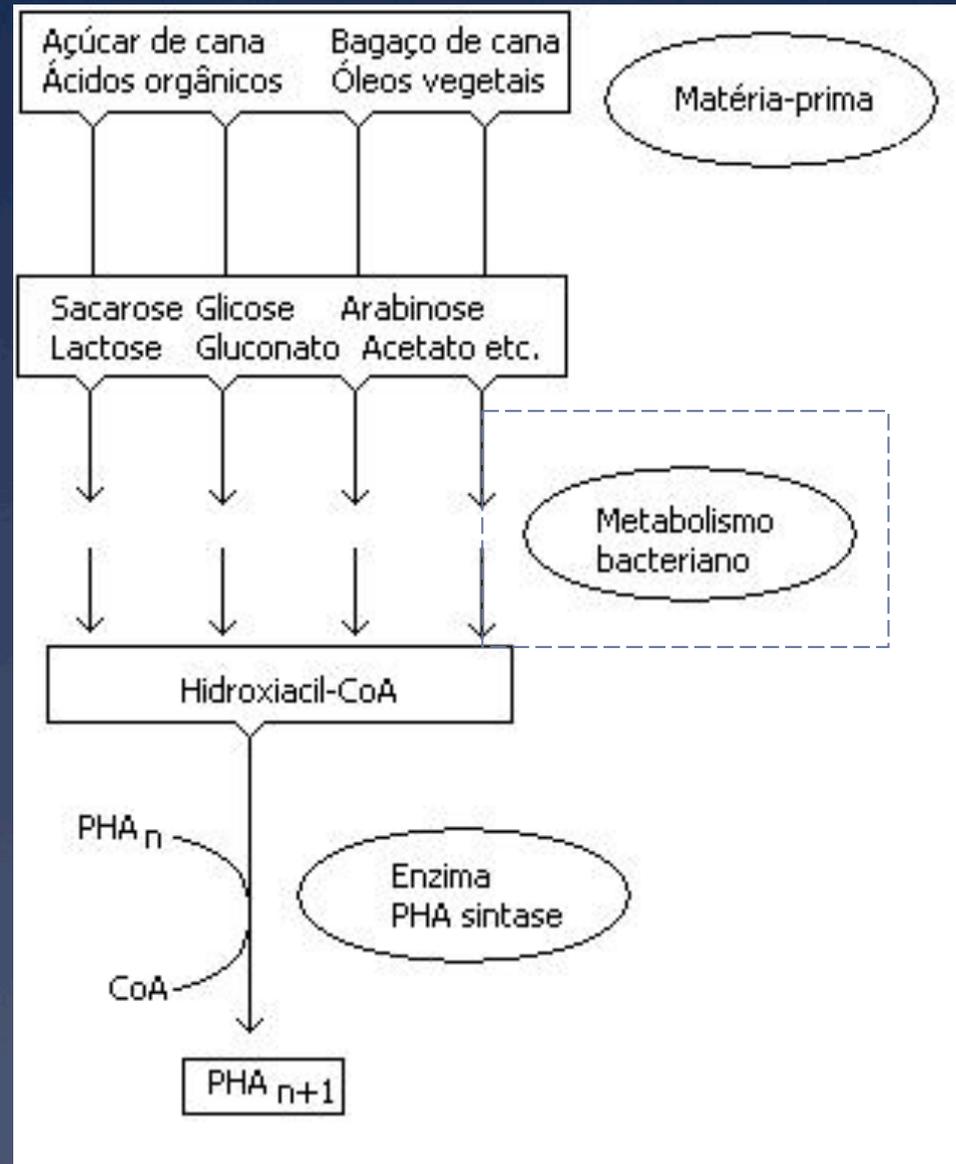
Rehm, 2003

Fatores interferentes na composição do PHA



PHAScl

C₄-C₅



PHAmcl

C₆ - C₁₆

Biodiversidade como fator chave

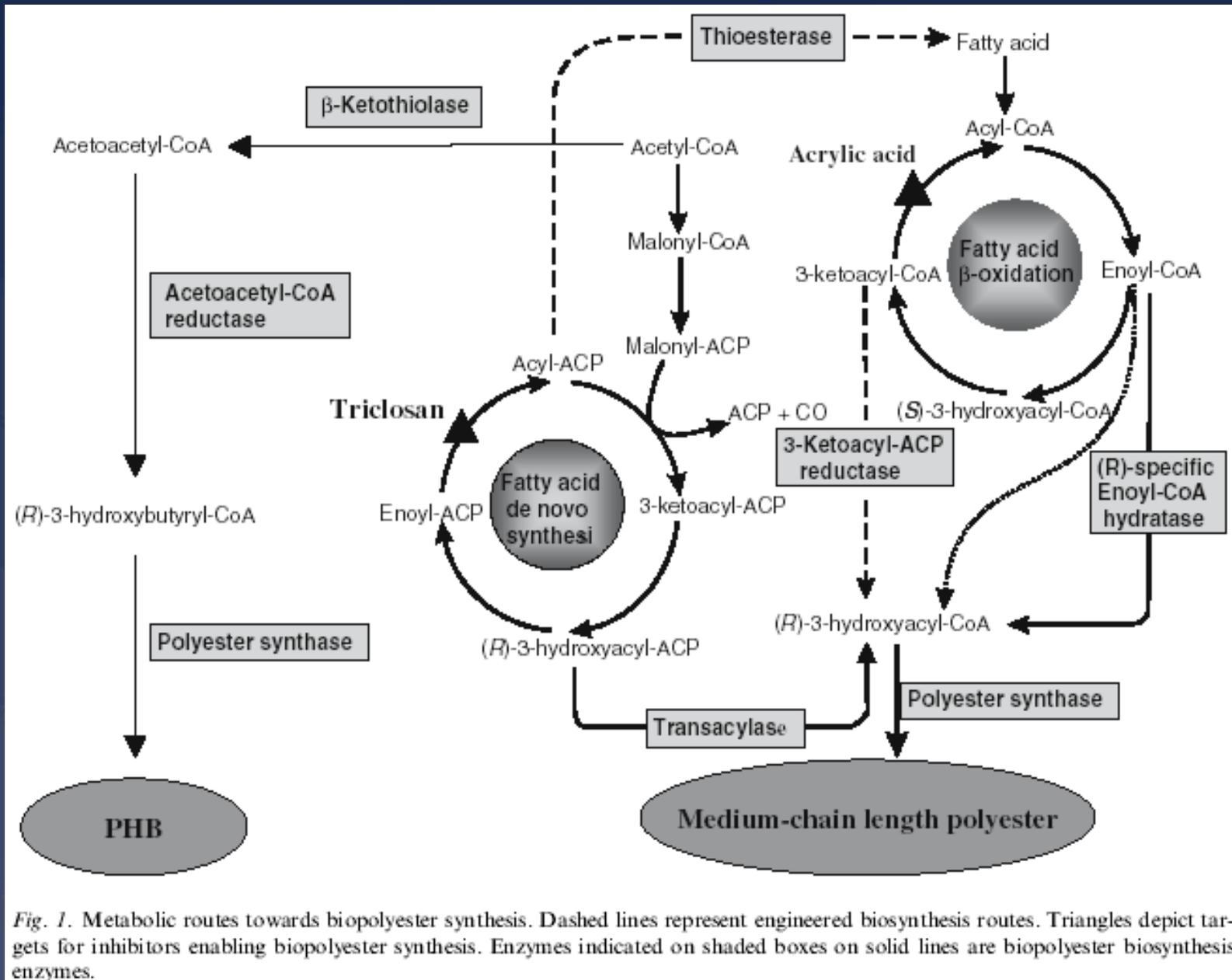
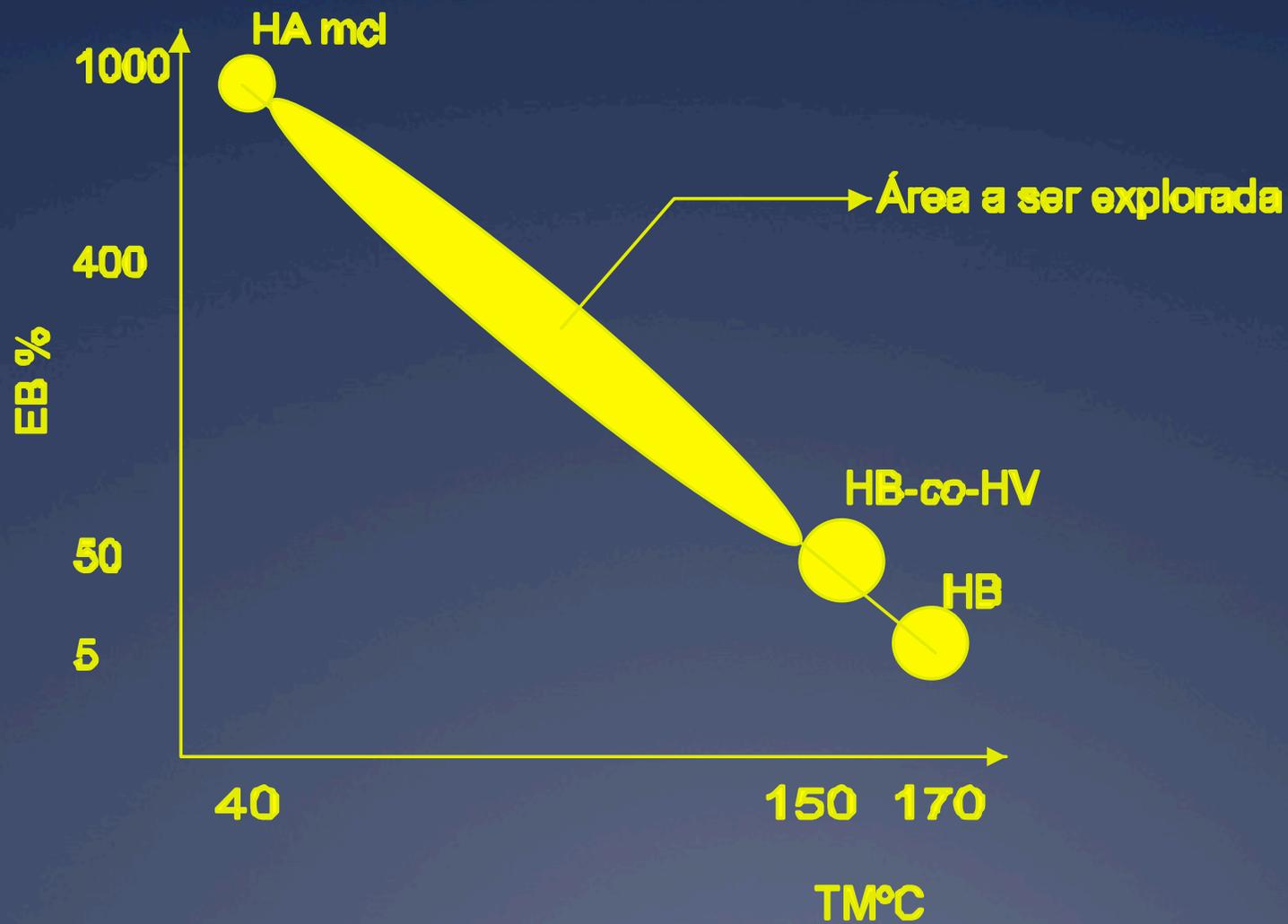


Fig. 1. Metabolic routes towards biopolyester synthesis. Dashed lines represent engineered biosynthesis routes. Triangles depict targets for inhibitors enabling biopolyester synthesis. Enzymes indicated on shaded boxes on solid lines are biopolyester biosynthesis enzymes.

Perspectivas para a produção de PHA no Brasil

Propriedades



- The Physiology and Biochemistry of Prokaryotes by David White, 3rd ed., 2007, Oxford University Press
- Physiology of the Bacterial Cell: A Molecular Approach, Frederick C. Neidhardt, John L. Ingraham, Moselio Schaechter, 1990, Sinauer Associates Inc
- Microbiologia de Brock, Madigan, MT, Martinko, JM, Dunlap, PV, Clarack, DP, 12^a ed. Artmed, 2010
- Metabolic Engineering – principles & methodologies, Stephanopoulos, GN, Aristidou, AA, Nielsen, J, 1998, Academic Press,