

a a a f o o a Ca
 a a a b o o Ca
 a a f a [6 8]. T
 c a f e a e h a -
 c , e a o f c e f e a o , e e o f
 e e a e a a (ECM), a a e a c e e ,
 a h o a a a a a [7 12]. T e a -
 a GSH a b b b c c a h /
 a a a h c a o o c h a a c e
 e (e b a e e) f o a o / f e e a -
 c a (e a e e / a a c a e) - e a e a
 f a a a [13-15]. A a a o o o f GSH
 e f a a b o o h a o f a -
 h a c o . F o h a GSH e e a e c a e
 e e a f (ELF) IPF [16, 17], ARDS
 [18], CF [19], a a f [20] a a o -
 o f c e c (HIV)- a a e [21]. I c o a ,
 o a a o c o c e a o , c e e z e
 f o (GSSG), a e e e b b c a h a o o a
 f a e h h a h a (a b 1) [22]. G -
 a e e e h c e a e h c e a o e l f
 o f c e c , e e a e e c a h
 e l f h o f a c e h [23, 24]. H o e h GSH h
 e e e c e a h e l f o f IPF a HIV-
 a e e e e h e l f [25, 26]. A GSH c o -
 c e a h e l f h a c o b e e a b a a c e
 b e e e a h a a a a a a a a
 a f f a a o e e e a h e a e a -
 a e .
 I a b o o e e a o a , a o a , a
 f a h a o a a - f h a o a e a e
 a c a o f e e e - e AP-1 a NF-κB [5]. A p h
 a AP-1- e a o a e e e e e (ARE) a o
 a b o o b o o a e e e e e o f γ h -
 a c e e e a e (γ-GCS), e a e -
 z e de novo GSH e . γ-GCS c o o f a
 c a a c e a b (γ-GCS-HS) a a e a o
 b h (γ-GCS-LS). I a c o b o o e a
 h o o e (5'-f a) h e o f b o h h a
 c a a c γ-GCS-HS a e a o γ-GCS-LS h e c o -
 a a a AP-1 a ARE e e e e c a e
 c o a f o γ-GCS e e e e e h h e
 [27 30]. I e b e a f f e e c e e l f
 a e e e e a o f h a o e a e

Table 1. – Epithelial lining fluid reduced glutathione (GSH) concentration in inflammatory lung diseases

	GSH μM		[Ref.]
	C	Pa	
C ()	339±112		[24]
S	544±97.6		[24]
I f b h	429±34	97±18	[16]
A c e e a o e	651±103.1	31.5±8.4	[18]
L a o a f	302.6±40.8	94.0±9.7	[20]
C c f b	257±21	78±13	[19]
HIV- e e e e	245±12	170±23	[21]
A a	23.3±3*	36.5±9.4*	[22]

*: GSH e z e a e e (μM- e e -1). HIV: h a o f c e c h .

a e o o c a e e o o c a e a o o f GSH
 e b h AP-1 a ARE a c a o b o a a
 f a h a o a a - f a a o a e , e e /
 b e a o a / o a o c e . H o e e , e
 o c a c c a o f a o e e e h f
 a e h f a a o h e a h a o b o o
 . T h b a a c e a e e c a a b h o f γ-GCS
 a - h f a a o e e e e e e e e e
 o a e e a f a a o e e e a b e a
 e e a o f c e b o e e a e . T e a o f
 e e a e : 1) o c c b e e c e o f h a e
 h e f a a o a h h o c o o f e
 a c o f a c NF-κB h AP-1; 2) e e h e
 e a o , a a a e a b o o f c e h -
 a o e a γ-GCS e e e e f a a o a
 o h a e e ; 3) c e e b e e o f γ-GCS
 versus - f a a o e b b a a c e c e b -
 / o e a c e ; a 4) a e b o e a o c e a
 e a e c o o f a o b a o e a e h
 h a - c e h a f a h a . h

Role of cell-derived oxidants in inflammation

T e e e c o o f a e e e a a e a e
 b o h a e a b e o f e a e h e e a h
 f a a o . I f a a o c e a e e e e e
 a a c o c c a o a e e e e a a c b
 a a e o f e e e a o o f e a o e a IL-8.
 O c e c , h f a a o c e b o c e a c h a e a
 e e a ROS e e e e a f f c e e e o f a e -
 c e a o e (e o c o c e a o). T e e -
 c a f o a h h o e a h a h o
 h h a h e a o f CD18 h e h [31, 32],
 c h h e a e a e a e a e
 a h h e c o o e o a e (NADPH) a o e -
 e o e - e e a h h e [1]. A c a o f h a c -
 a e , e o a o o e e a e O₂ , c
 h a c o b e H₂O₂ b e e e h a b
 (SOD), a h o f a c a , f o e e e z a c a
 e e e e o f F e²⁺ a a c o a e a c . I e o -
 h , e e e e a e a c a e e f o a o f e
 e c e o f c e b h ROS, c a a b e h e a e
 b h e a c e [33, 34] h a a o a e -
 f a a o b e c c , e e b a f
 f a a o a o a e h (f . 1).
 ROS a e e a c e a , e e e a e c o o o
 c e e b h e h , e e e a c e h a GSH a o z o
 e b a e h (e a a o), c a
 c o e a t a h e a c . T e a e . OH h e
 e f o a h o f a o d e o f e e e e
 h e c e e b a e , c a e e e h
 f c h a a e a h c h e a , o o a a e o f
 e o b o c c c a c (DNA) a b o a e e a c e
 [35]. ROS a e a e e e c e (RNS) h a a c e
 c e a a o a c e e e e (e.g. e z e , a e)
 c a e e e , e e a c e e e , f o
 a h e h c o o f e e e e f a a o
 h a e [36]. M a h o f e f f c o f o f a
 a a a b e e a e b h e c o a e e a o f
 f a a o e a o h a 4- e -2- e -
 a , h c o o c e h a h c e a e e

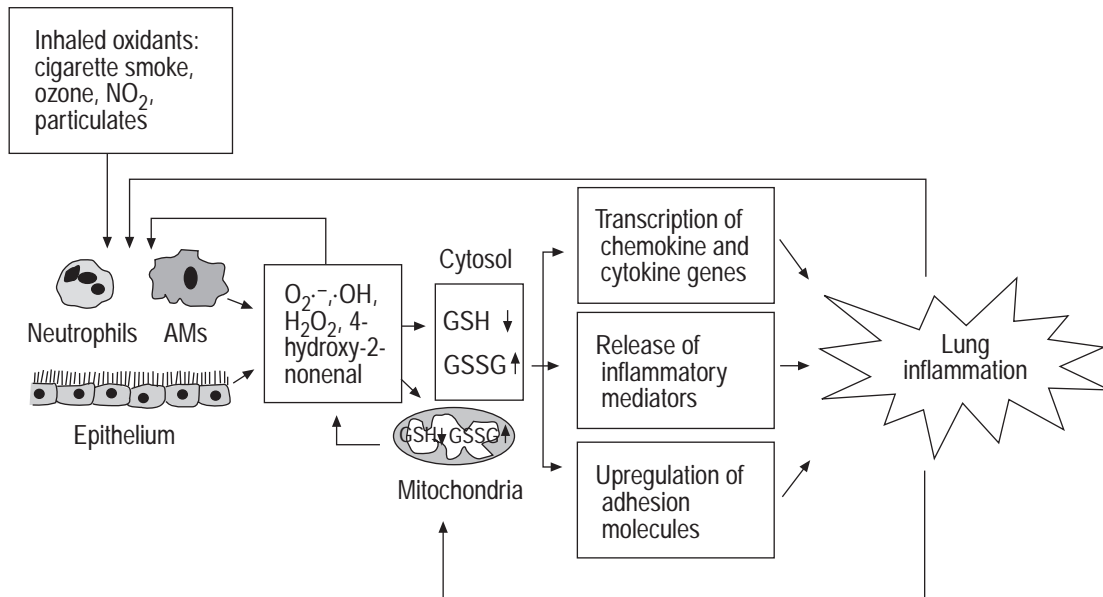


Fig. 1. Mechanism of lung inflammation. Inhaled oxidants (cigarette smoke, ozone, NO₂, particulates) enter the lung, affecting Neutrophils, AMs, and Epithelium. This leads to the production of reactive oxygen species (O₂^{-·}, OH[·], H₂O₂) and 4-hydroxy-2-nonenal. These species cause a decrease in GSH and an increase in GSSG in the cytosol, and a decrease in GSH and an increase in GSSG in the mitochondria. This redox shift leads to the transcription of chemokine and cytokine genes, the release of inflammatory mediators, and the upregulation of adhesion molecules, all of which culminate in lung inflammation.

of a - a e f a a . T f a a e b a c a a e a / e e a b e a a e f e a a e h a h e (GSH). A c a a e f a a h e c a e a e a e f e f a a e a e ; ↓ : h e e a e ; ↑ : c e a e .

Activation of redox-sensitive transcription factors

Nuclear factor-κB

Oxidative stress is a key factor in the activation of NF-κB. In the cytosol, GSH/GSSG ratio is maintained at a high level. However, oxidative stress leads to a decrease in GSH/GSSG ratio, which activates NF-κB. This is mediated by the phosphorylation of IκB, which releases NF-κB from its inactive state. Activated NF-κB then translocates to the nucleus, where it binds to DNA and initiates the transcription of target genes. These genes include chemokines, cytokines, and adhesion molecules, which are involved in the inflammatory response. For example, TNF-α, IL-1β, IL-6, IL-8, E-selectin, ICAM-1, and VCAM-1 are all upregulated by NF-κB. This process is also regulated by various signaling pathways, including the MAPK pathway. In summary, oxidative stress leads to the activation of NF-κB, which in turn triggers the expression of inflammatory mediators, leading to lung inflammation.

Inhaled oxidants in lung inflammation

Inhaled oxidants such as cigarette smoke, ozone, and NO₂ are major contributors to lung inflammation. These oxidants enter the lung and cause oxidative damage to various cell types, including neutrophils, alveolar macrophages (AMs), and epithelial cells. This damage leads to the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which further exacerbate the inflammatory response. For example, cigarette smoke contains a complex mixture of oxidants, including superoxide, hydrogen peroxide, and hydroxyl radicals, which can cause lipid peroxidation and DNA damage. Ozone is a strong oxidant that can cause acute lung injury. NO₂ is a reactive nitrogen species that can cause oxidative stress and inflammation. Particulates, such as those found in cigarette smoke, can also cause oxidative damage and inflammation. The resulting inflammation is characterized by the recruitment of inflammatory cells, the release of inflammatory mediators, and the upregulation of adhesion molecules. This process is regulated by various signaling pathways, including the NF-κB pathway. In summary, inhaled oxidants are a major cause of lung inflammation, and their effects are mediated through oxidative stress and the activation of inflammatory pathways.

GSH b a ••• ca • a ac ••• z NADPH.
h ••• h h h h a a

Regulation of glutathione and γ -glutamylcysteine synthetase

At transcriptional level

I • fca • a ca ac za • of • of
••• a ah a ••• ce h of γ -GCS
• a h ••• of effc • a ac •••
hca a e • fa a a ea e h GSH
• a • fa a • ea • T •
a • ca a h ••• ca ca of GSH -
• a • ah ••• II a h a • ea ce
h ••• a ••• a a a h a a
a fa a • (ab • 2). T ea h' • a
f a • a • a ••• ha ••• (5'-
f a) ••• f h a γ -GCS-HS ••• -
a • b a a ••• h ••• (AP-1) b •••

Table 2. — Inducers of glutathione and γ -glutamylcysteine synthetase

A •	[Ref.]
O a	
H ••• •••	[30, 70]
Me a •••	[30, 70 72]
C a ••• •••	[13, 29]
D ••• a h ••• •••	[73, 74]
Xa h •/ a h h ••• a •••	[71]
t-b h ••• h ••• a a ••• •••	[27, 67, 68, 75]
4-H h ••• -2- ••• a h ••• •••	[37, 76]
Oz •••	[77]
H ••• a •••	[71]
P ••• ca • a •••	
β -Na ••• f a ••• •••	[28, 78]
A ••• h h •••	[79]
B a ••• ••• a ••• •••	[80]
B a ••• h ••• ••• •••	[81]
P ••• h ••• ca ba a ••• •••	[82, 83]
5, 10 ••• h ••• ••• (1,2-b) ••• •••	[84]
C ••• h •••	
TNF- α •••	[85, 86]
IL-1 β •••	[87]
N ••• ••• •••	
N ••• ••• •••	[88]
DETA NONOa •••	[89]
S- ••• ••• ca ••• •••	[90]
Ra a •••	
I ••• z ••• a a •••	[91, 92]
Me a •••	
Se •••	[93]
I •••	[94]
Ca •••	[95]
Me c •••	[96]
C ••• ••• a ••• ca ••• •••	
Ch a h •••	[66, 97]
Me a a •••	[98]
G ••• h fac •••	
N ••• h ••• fac •••	[99]
Ac f b ••• h ••• fac •••	[100]
O •••	
Hh a ••• •••	[101]
O z ••• •••	[69]

TNF- α : ••• ca ••• fac ••• - α IL: ••• •••

[30, 66 69]. T ••• ••• ce fo ••• b ••• ••• ca •••
••• ••• h ••• ••• f ••• h-GCS-HS TATA b •••
a ••• ce ••• ••• c h a a ••• a ••• - e a
ce [30, 67, 68].

MULCAHY a ••• ce ••• [28, 78], ••• ••• a ••• •••
••• a a ARE ••• a a a h ••• ••• hTPA- •••
••• ••• ••• (TRE) a a ••• ••• ••• •••
••• ••• (••• f ca a ••• a ••• ARE), ••• a a
••• ••• ••• a ••• f ••• γ -GCS-HS a h-GCS-LS,
h ••• ••• h ••• a a a a ••• ce ••• b ••• c,
h ••• ce ••• a a β - a ••• f a ••• ••• ce f ca
h ••• ce ••• T ••• a ••• h h a ••• a AP-1
••• a f ••• h ••• ce ••• h ••• h ••• f ••• γ -GCS-
LS ••• [78]. h ••• ••• ••• GALLOWAY h a ••• •••
••• [27, 75] ••• ab ••• ••• a a ••• ce fo
ARE ••• ••• ce ••• f γ -GCS-LS b ••• a ••• ca t-
b h ••• ••• h ••• G2 ce ••• T ••• ••• h a
a AP1 ••• a ••• ce ca ••• ••• h ••• ba a h •••
a ••• f ••• b h ••• T ••• ce ••• ••• h a ••• •••
••• ce ••• f ••• h a ••• ••• ••• h a ••• b •••
••• ce f ce ••• •••

E ••• ••• ce a ••• a ••• ca ••• a 2(3)-t-
b -4- ••• h ••• ••• a b a e h ••• ••• ••• a
••• a h ••• ••• ce ••• ca ••• h a 5,10-
••• (1,2-b) h ••• a ••• ••• ce h a a •••
(PDTc), a ••• - ••• f a ••• a h ce ••• •••
••• a ••• γ -GCS-HS a γ -GCS-LS a ••• ••• e-
a ce a ••• ce ••• ce [75, 80 84]. Th a - ••• h •••
a ce a ••• h a a ce ••• (4- h -3- ••• ••• a-
ce ••• ••• •••) a ••• ce GSH h ••• ••• h a
a ••• h ••• ••• a ce [79]. T ••• ce ••• ce ••• f h ••• ce
a ••• a h a a ce a ••• AP-1 a ce a h [57,
60, 102]. T ••• ce ••• ••• a ••• h ••• ce a ••• ab-
••• ••• h ••• ce a ••• a ••• a h ••• ••• a ••• a
••• ce ••• h ••• a ••• a - ce ••• b ••• ••• a
••• ••• ce ••• ce ••• f γ -GCS a ••• ce a GSH ••• •••
h A ••• ce ••• NF- κ B ••• ••• a ••• ce ••• f γ -GCS-HS •••
••• ••• ••• a a ••• ce h ••• ••• [91, 103, 104]. I a
••• ••• h a b ce ••• ce a ••• ce ••• f NF- κ B, h •••
h ••• a h ••• a ••• ce h a ••• ce ••• f γ -GCS-HS
••• ••• ••• b h a ••• a ••• ce ••• ••• h ••• a ••• ce •••
e- ce ce ce a γ -GCS-HS a ce ••• ••• •••
h ••• a ce a ••• a ce ••• [91, 103]. H ••• •••
a h a ••• ••• ce h ••• ••• a ••• ce ••• f γ -GCS-
HS ••• ••• ••• h ••• ce ••• h ••• ••• h ••• b •••
••• ••• ce ••• f NF- κ B h ••• a ce ••• a h ••• a •••
ce ••• f γ -GCS-HS ••• h a ••• a ••• ce a ••• a
••• h ce ••• ••• ••• ••• ••• TNF- α a h a ••• •••
[29, 30, 68, 85 87].

At post-transcriptional and translational levels

Re a ••• ce ••• f GSH a γ -GCS a a ••• ce ••• ce •••
a ••• ••• - a ce ••• a a ••• h a a a ••• ••• a
h *in vivo* a ••• ce ••• [105, 106]. Va ••• -
f a a ••• a ••• ce h a ce ce ca ••• ••• ••• ce •••
a ••• (cAMP) a h ce a ce ce ••• ce h a •••
h a ••• ••• f a a ••• a ••• b GSH h h •••
a ••• a a ••• a ••• ce (ab ••• 3) [107]. I a ••• ce h •••
a h γ -GCS ce ••• b ••• b a ••• h ••• ce ••• h •••
h a a ••• ce a h a a ••• ce ••• [107],
••• a ••• ce f h a h a h a h

ac a GSH () .
 T of ac a GSH a e , a , b
 h a of b c a a b a a .
 h e b a a c [136, 137]. I e a
 h e b a a c a GSH h
 h ELF. T f c . of c a GSH a .
 h f c h b . / b a of c c ,
 e b a e a h h c of c a h e
 h ac a e . [138, 139]. GSH- e a b-
 a c . , c a a e -S- c a e a
 GSH e . , b c a h GSH a e f
 [137, 138]. F h a , a e z h ac a
 e e c e a c a a GSH, e a a
 e e c e a c a a f a c a e GSH off
 [137, 140]. H e . , e e f f a e c c a
 e a h in vivo, c e c e a e
 e h a h b e e b a h e e e
 e a e e f a a c c a e
 c e a a GSH, a e a e e ELF.
 T c a h h a GSH a e h c e of
 h a a e e e h GSH h h
 ELF h h b c . a h a e a e h f
 e . h

Regulation of glutathione in oxidant-mediated susceptibility/tolerance

Effect of pro- and anti-inflammatory mediators

TNF- α a b , e - f a a c e a
 e z a a , e a e a of f a a
 e . I c e c c f a a
 c a e a c a e a c e a h a a of f e c c
 h c a c h a [141]. TNF- α
 a h a f a a e a COPD a ARDS
 a e c e a e b c a e -
 a a a f (BALF) a h COPD h a
 [142]. R e , a e a [86, 143] a
 e a e e of ac a GSH b TNF- α
 h e e e a a e a c e in vitro, e
 a a of GSH GSSG. Th f e b a e -
 b e c a a GSH e b a a e e a
 c e a a a e e e h a , c c h
 a a e of e a of e γ -GCS-HS a ac-
 a of AP-1 [85, 87]. Sh a , e e of
 f b b a e a a E₂, a f a a e a
 c a a b of e a f b b a c e f e a a
 a e c . , e c e a GSH
 e h e a [111]. F e e , GSH c e a a
 e h a b e h c . a b e e a a a
 e h of f a h a a a b e e c e -
 e a e f c . a e CF [144].
 T a h e e b f a a h e a
 h ac e e e GSH f a a a e e
 c e c e b e e a f c a of f a a
 e . h
 G c c c . , c a e a e a e , a e
 e a a - f a a h a e d e f a a
 e a . A a e e of e e -
 e a a e f a e h c c c c h e a e
 [145]. E e e th e a A549 c e e e -
 h

a e a e e c e a e b e b a a a a e GSH
 e e h (TNF- α - e a e) h e e c e [71, 86]. De a -
 e a e a e c e a e γ -GCS-HS e e e e
 a h a e e a c e in vitro b a a c e a
 c c a h b e of AP-1 a c e
 f a c [86]. T h b b h a e e of e -
 a e a e h a e f a h a h e a e
 a h e e of h c c e a a GSH.
 h h

Effects of oxidants

E e e of a e e a e e in vitro e e a ,
 c a H₂O₂, e e a a h e e c c c e
 h e a e b , c a e a a e e of GSH,
 a c a e c e a f e a of GSSG, f e e b
 a b b c h a e GSH e a 24 [29, 70 72]. T
 c c a c e a e h e of e h
 b e c c a c (RNA) f e γ -GCS e e [30, 70, 72].
 E e a c e a e a e h a e b a e e - e
 e h c a [137]. T a h e e a ac
 e a e h ac a a h e e e e e -
 e e of e c e e h e e e a h a
 e e e [138]. T , e h - e e f a
 e a a e a h e a h e a e a b e e
 e a e e e f a e e e , b
 e a h c c / a a h c c a h a a b -
 e e a e e (a b e 2). h
 O a e e c e b e z e [77], a e /
 a e e a e [71], e e a e c h (4-
 h -2- e e a) [76], e z a a e [91, 92],
 h a [146] a e a c [101] a e a e - e
 h a ac a h GSH h e , f e e b d e a e
 GSH e e e a e of γ -GCS-HS RNA
 a e a e e a c e , e e a c e in vitro a
 e e c e h e a e a in vivo a . NO a
 h e , c a S- e e e c a e De aNONO a e,
 a c a h a e e e of GSH f e e b
 c e of GSH e b e a c e e e of
 e γ -GCS-HS a γ -GCS-LS h a a c a c a
 h e c c c e [90], e a f b b a [89] a
 b e h a c e e e a c e [88]. T e c e a e GSH
 e e c a e b NO e e a f h e e a c -
 a f e c c a a e h a e e a
 h b e e f a a e . O a e e e b
 e a e a c a e e [93], e [94], e
 h c c [96], a h c a [95] a e c e GSH
 e e a e a b e a a c e . O e
 c h b c c e e a ac h e e e a h of
 ROS c a e c e b e a h c a h h c a [66,
 97] a h e h a [98] h c e a e GSH
 c a c e c e h e . T e e a a c c e h e e
 e a e e e a c e a e e (MRP) e a h
 e a e e e a e - e e e a e , -
 h e c c a e h (GS-X) , c e [147
 150]. T e f c e a e e of MRP c e e e
 c e h c e e . I e b e a e
 c e e e of MRP a GS-X e a e e b c b
 a a e f a a e e e a e e f c a of
 e b b k a e e e e e e e e [151].
 T e c e of GSH e a b e a c a e
 a h a of e e -ac h e e e a e , a c h
 a c-JNK, e e e e a , h a e a a
 NO [37]. γ -GCS-LS a e c c c h a c e

• • • • • a a • • • • • a a
 • • • • • a L2 • • • • • a h He G2 • • • • • a
 • • • • • a • • • • • of b • • • • • a b e a • • • • • h a
 • • • • • a f • • • • • a c • • • • • h a GSH • • • • • a
 • • • • • h • • • • • c e a h • • • • • a c e • • • • • a e h [28, 73].
 E • • • • • • • • • • • b e a • • • • • of • • • • • a a • • • • • a -
 • • • • • a • • • • • h a • • • • • a a a a a • • • • • a c e • • • • • a
 a • • • • • a • • • • • e, • • • • • c e • • • • • f • • • • • b e -
 • • • • • e • • • • • e • • • • • h a • • • • • e • • • • • [74, 152]. I
 • • • • • b e a • • • • • GSH • • • • • a • • • • • a c e • • • • • c e a
 • • • • • c e c d h • • • • • e • • • • • h b a • • • • • e c h b e
 a h • • • • • c e • • • • • a f f e • • • • • c e • • • • • .

Effect of growth factors

T a f • • • • • f a c • • • • • (TGF)-β1 a f c -
 • • • • • a • • • • • f a c • • • • • h a • • • • • a e c e a • • • • • f e a • • • • •
 a • • • • • c e h f f e • • • • • h a • • • • • e • • • • • of e a c e a
 a • • • • • e • • • • • c • • • • • a e h a f b e c • • • • • ,
 a • • • • • e • • • • • of c e [153]. R e c e • • • • • e a e • • • • •
 c e a e • • • • • e • • • • • TGF-β1 b e d h a h a
 a • • • • • a e • • • • • IPF a COPD a e • • • • • h a • • • • •
 • • • • • h BALF of a c a a c a c e • • • • • a h e h • • • • •
 e a b e c [154, 155]. TGFβ1 a • • • • • e a e
 h-GCS-HS RNA a a • • • • • e • • • • • a
 a • • • • • a e a c e a h • • • • • a h e • • • • • h e a
 c e in vitro [109, 110]. I • • • • • e • • • • • e c e • • • • • a b
 FACTOR et al. [156] • • • • • e c e a e • • • • • a • • • • •
 • • • • • h a • • • • • a TGF a h e c (• • • • • e • • • • •) h e • • • • •
 • • • • • h a • • • • • c e a e c e b • • • • • a - e a e
 • • • • • . V a • • • • • e • • • • • a e • • • • • a γ-GCS-HS
 RNA • • • • • e • • • • • h e h e c e h h of AP-1
 a c • • • • • f a c [31, 67, 68, 86], a a TGFβ1 a
 c e e a e γ-GCS-HS • • • • • e • • • • • h via a AP-1
 c e a [157]. T • • • • • e • • • • • of TGF-β1 a
 • • • • • h e a e a h e h h • • • • • a
 a e f a h a e h a e c h a IPF a
 COPD. M e b e • • • • • e c e a e GSH • • • • • h a a a a e
 c e f c e a c e • • • • • e c e . In vitro h e
 a GSH (• • • • • c e c e a a a e a f e h
 HLF) • • • • • h e f b e b a • • • • • f e a • • • • • [158]. T e
 • • • • • a c e of GSH e a a b e • • • • • e e a c h /
 c e b • • • • • e • • • • • e a c e • • • • • e • • • • • e • • • • •
 a - f a a • • • • • a h a • • • • • / • • • • • a
 c e • • • • • of f c • • • • • c f a a • • • • • in vivo • • • • • .
 D f f e a h a • • • • • of a • • • • • a γ-GCS • • • • •
 • • • • • e • • • • • a b e e • • • • • e a b • • • • •
 f a c • • • • • c h a • • • • • e • • • • • f a c [99] a h a c e h
 a a • • • • • c h e [103, 159, 160]. I a c e a GSH
 • • • • • e a e a b e e • • • • • e b e e e a e • • • • • e • • • • •
 • • • • • h c • • • • • a • • • • • h a c e • • • • • f • • • • • e c e
 a e a c e • • • • • a e a e c e a h a f a e
 [161 165]. E a c e h a a c f b e b a • • • • • f a c • • • • •
 (FGF-1) a b e e • • • • • e • • • • • c a e a f h a • • • • •
 a a h e • • • • • c e • • • • • e • • • • • b • • • • • c
 f b e b a . R e c e • • • • • a a f • • • • • h Choi et al. [100] a e
 • • • • • a e • • • • • e • • • • • of a c • • • • • c a FGF-1 h e
 c b a h a a e • • • • • e h e c h f e c e • • • • • (/
 KS0FGF-1) a e b • • • • • c f b e b a c e c e a h e
 c e a e • • • • • e • • • • • of b e γ-GCS b
 a c e a e c e a e γ-GCS a c h • • • • • e • • • • • a -
 • • • • • of a c h a GSH • • • • • [100]. T e h • • • • •
 a a c e a e GSH c e • • • • • per se b e i e f e

a • • • • • c e • • • • • h • • • • • c e a e • • • • • e • • • • • of γ-GCS
 a γ-GCS a c h h a b c a e a c e • • • • • e • • • • •
 • • • • • f a c • • • • • . h

Role of γ-glutamylcysteine synthetase in genetic susceptibility to disease

R e c e • • • • • e a e • • • • • a GSH • • • • • a • • • • • / • • • • •
 GSH • • • • • e h • • • • • h e • • • • • of f a c • • • • • e • • • • • h
 • • • • • c e b h • • • • • a - / h a - e a e
 c e a a e . F o e a • • • • • e c c e b • • • • • c a e e
 • • • • • a b e e • • • • • e a a f a c • • • • • f o • • • • • e -
 • • • • • h of COPD [166, 167]. F h e • • • • • e • • • • • a h b e e
 • • • • • a • • • • • e • • • • • c e • • • • • e h e f e e a h f f e
 b • • • • • e b , c h • • • • • e c e c e c e a h f f e
 P-450
 1A1 (CYP1A1), a h e - S - a f e a e (GST) (GST -
 M1 a GST -) a h c • • • • • a e • • • • • e a e , a
 e a • • • • • - f a a • • • • • e c a T N F - α , a • • • • •
 c a e a c e a e • • • • • of c h c f a a
 e a h [168 172] a h f a h a • • • • • e • • • • • [173,
 174]. T e • • • • • e • • • • • of e e c e c e • • • • • -
 c e h e a e • • • • • h a • • • • • of e z e of • • • • • -
 a • • • • • e • • • • • h e a γ-GCS [85 87, 102, 166].
 V a h a • • • • • e • • • • • of γ-GCS • • • • • a
 a • • • • • h a e c e h b f a c • • • • • h a -
 c e • • • • • , c • • • • • e c c a a of e
 a • • • • • e • • • • • COPD. I h a b e e • • • • • e a a G A G
 h c e e e e a • • • • • h • • • • • e c c b 5 ' - c e
 a a c e • • • • • e • • • • • h e γ-GCS-HS h e • • • • • [175].
 G e e c a a of 50 h a C a c a a e f e
 e e a e e a f o • • • • • : A1 (• • • • • e a , 35% f e • • • • •
 c h) , A2 (e • • • • • e a , 11% f e • • • • • c) , a A3 (• • • • •
 e e a , 54% f e • • • • • c) . A • • • • • c e a c e • • • • •
 e e a a b e e a c e a e h h c e b a e • • • • • ,
 of c h a f c a c e of h a c a a e c e -
 h a • • • • • , f a • • • • • h D e • • • • • of GSH e e
 a h e a c e a e h a e c e c e • • • • • e a
 h of c e c of γ-GCS a c h a a e h e c
 a a e a [176]. G e e c a a e e a e h h γ-GCS
 • • • • • a a c e a e a A h T h a • • • • • /
 a e b a c e e 1109 a h e c e b • • • • •
 of h e e c e a a h a c 370, a a e c
 • • • • • h • • • • • h c e e +206 of a • • • • • a a -
 • • • • • h • • • • • a c e of a c a of
 CAGC a c e h e h a DNA (cDNA) c e • • • • •
 1972 1975 e 3' - a a e e of γ-GCS
 c a a c b h T a • • • • • a • • • • • h e γ-
 GCS DNA of 38 h a b e c [176]. T • • • • • e • • • • • of
 c a • • • • • a h h b a c e a e h e c • • • • • -
 h h e c c e a / • • • • • e • • • • • of γ-
 GCS h c a a h e a b b e a c h a e
 a h h c e b • • • • • of GSH e f a h a e • • • • •
 • • • • • c e c e c h a a e e a e .
 T e γ-GCS b h e e a e c a e • • • • • e a a e
 c h • • • • • e a e • • • • • of e RNA a e
 c b e a b b e e e f f e h [175, 177, 178].
 H a γ-GCS-HS c a e c e • • • • • e 6 (6 12) a
 γ-GCS-LS c e • • • • • e 1 (1 21) [177 179]. G e e c
 a a e e a h a a f e • • • • • e • • • • • of γ-GCS-LS
 c • • • • • e , 1 22 → 21 , c c c h a a a
 h e • • • • • a . T e • • • • • e • • • • • h c e e • • • • •
 e h e a h a • • • • • e • • • • • of e e e -
 • • • • • a [180]. R e c e • • • • • a a h e • • • • • a e a AP-1
 a A R E , c a e • • • • • h • • • • • e • • • • • h of h
 h h h h h h h h

a c a e e a c e e o / e e a a e o
 [206]. A h a h c a e o a b o f GSH h o -
 c e a e e h a e o e o e o a c e o v i a
 e a o f ICAM-1 h VCAM-1 [207, 208], a
 c e a a c e a c e c e a e NAC
 a e a e e a - h c e - e a e h o
 a e o b o a c e [208]. T e f o e , a c a h
 h a c e a GSH b a a c e h b e a h o a
 c e a e o a e o o , c h o e
 c h c f a a h . h h h
 h M o a o f o f a c o c e o a a e e
 c e a a a h e o c c o o a a e -
 T a e c c a a f a a a h c e .
 T e e h a a o f e o a a f a c o
 (EGF) c c h h e o f h a c e b H₂O₂ h
 o f e c e f a a a h c e e [209] h₂O₂
 o e a o o a c e c
 e h a c e , a e o e b e b -
 a h e [3, 9, 210, 211]. I a o , h a c e a e
 h a c e a GSH e e a o a a c o a e c a e
 b o a , h o a a c a e e h e c e
 o a a h o f a c a e o a h o f a c o
 (VEGF) a f c o a c e h [212, 213] h D o -
 e a o f VEGF a c e o a b e a c a e
 a o o , c a b e e a o e e
 o f h f a a o h h e a e h c a h h e a a
 COPD. GSH a o e o c h NAC h b TNF-
 α- c e h h h h , c e a h e e e a-
 a GSH a a a o c h e e o a b
 b o o f h o a a f e e a c a [214]. h
 HO-1 a e b e o f e e a c f a o f e e ,
 c a a a a h h h f a a o . A o o f o
 GSH h e e a o f e a c f a c a a c a o
 o f e a h c e o e h b o b h e o [215]. T e
 h a h o f GSH f b o b a a e o h -
 a - c e e o f HO-1 [216]. T e f f e c a
 e e c e e e o f AP-1 (J h J) b
 [192]. S h a , e a - c e e o f e e e a
 o o e e h s p 7 2 a e a e b a h b e ,
 h h a o c e e o o f GSH a c e f a h a o
 [217]. H e c e , c e a a a e a c e o f a c e a
 GSH e e o a h e c e o f f a a o
 e o e o h e a o c o o .

Oxidant-mediated mitochondrial damage

M e o a o a o c e a b a a a o f
 ROS (e.g. H₂O₂ a O₂·), c a e o a b o e
 b GSH- e e o h h e c a a e a c b .
 M e o a c e a 15 20% o f e e a c e a GSH.
 T e h c e o a GSH o o h e e e f o
 a d o f h a c e o a a o e a a c a b
 GSH f o e c h o e e c h a a a , a
 c e o d h o o h e e z h e γ-GCS γ-GT
 [218]. h M c c a GSH d a b e c e b e o e
 o a e h o o b TNF-α, a a e b
 e o e o a a [10, 219]. PNF-α
 e o e o c c o h c GSH e e a e
 h e a a e e e a c e [86, 143, 220]. T
 e h o b TNF-α h o b e o o o a h e
 e f o c o a h e a d o f O₂· v i a e e c o
 a o c a [143, 221]. o a o f GSH a c e -

a e a c a o f NF-κB a a a e o c o -
 a DNA e a o a o o f b o b a i n v i t r o h a
 a c e f c o e o [219, 221, 222]. I
 o a c c o a GSH h a a e o e a -
 h o e a a h o a e f e c e , a h c e
 o a a f c o , e a o c o o h f c o -
 a e o [221, 223]. CHEN et al. [220] a e c c o
 o o a e a o o o f c c o h a GSH
 a b c h e e o o e a c e h (HUVEC) -
 e a h TNF-α- c e a h o o c e o (VCAM-1)
 e e o b o ICAM-1 h e o a o o c e a
 e o c a e o HUVEC , e a o -
 c h a GSH o e o e o a c e h f c o
 [220]. R e c e a e o h a e e e o f
 a o e e c a e b o c h d a e e e o
 o f G P h a o c e e h o e c c o a a
 o a e e [224, 225]. T f e o a e e
 o a c e o f c c o h GSH o o a h e
 e a o f c e f c h o . I o b h a a b a e
 c c o a GSH e o a h e o e -
 e a e h f a a o c e . h

Oxidant-mediated extracellular matrix remodelling

I a c e a o o GSH e e a e b o o e o b e
 o e e e e o o f ECM h o a -
 o a e h [226, 227]. T o e b o
 o b a o : 1) o a - c e h a a e -
 a e b e e c a e a o e e a (MMP)
 b o B h o c (BB)-3103 [228]; a 2) e-
 b o f a b e a GSH a a c a e a c a -
 o o f MMP , e o b c e a e a a h o f o
 a o a ECM h [227]. T b e a o f h
 ECM b MMP-9 a MMP-2 a c h a h a b o c e b
 c e a a a o e e e e [227]. I a b o e
 h a a o e e h e b o z e h c e a e
 h h a o e e e a c a e a e ECM o-
 e e I d h a e e e e o [229]. O e f o f
 o a e e c a e e e f o t-h o -
 o o e a o h a o f c o a e h e ,
 b a c a e a b o a e o h o /
 c e o [226, 230]. TYAGI a c o e o [11, 226] e-
 o a e a i n v i t r o e o o f a c a
 o GSSG e d o e a o o f MMP , c a a
 a c a e o h a o f e a c e c e b b e
 e e MMP . GSSG a h b e e b o f
 e a o e e a (TIMP) h b o b a [226]. T o
 a o a c a GSH a NAC a e o e c h a -
 o a P D T C h a b o e o o h h a c a o
 o f MMP-2 a MMP-1 a h c a e h c h a e TIMP
 o e c o f b o b a c e [220].

Immune effector response

T e c c e f o f PETERSON et al. [231] e a
 h o a c e o f GSH e a e - e e c e
 h o a T- e e (T) c e 1 v e r s u s T 2 c e o
 e o a e h h e o e o e h a h o f
 e a e , a e c e a e a c e a h e o f GSH
 h e e a b o h o c o f C F a HIV- o -
 o h a e [144, 232], e o e a o a
 o a e e e h a b e o e h e
 h h h

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 e a a h h a α -1- o o a e b o. *Chem
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 e a o f e o f h a o e c o a o
 e ab e b c a e h i n h v i v o a i n
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 a o e o e i n v i t r o , e a o e II
 e h c . *Eur Respir J* 1997; 10: 1392 1400.

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 e f c e c e e e a f f h e h
 e a a c h h a c o a f b o h. *Am Rev
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 a c o a h f b o . *Thorax* 1995; 50: S53 S58.

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 e a o a f h o f a e h e a e a o
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 1178.

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 a h o e b o c o a a a a f f o a e
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 a o o a e d h f c o a e e o f
 a o e . *Am J Physiol* 1987; 63: 152 157.

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 e e ab , f a a a a a a h e
 a a c e o f c o c o o . *Am J Respir Crit Care Med*
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 h f (ELF) a o o e c a e HIV+
 e e e a h e o a . *Am J Respir Crit
 Care Med* 1999; 159: A885.

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 h o a a e e o a c o a
 f b o . *Free Radic Biol Med* 1999; 27: 60 68.

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 R e a o o f h a γ - a h e e e a e c o -
 o a e c h o f c a a c a e a h b
 H o G2 c e . *Biochem J* 1997; 328: 99 104.

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 C o h e a β - a f a e e - c e e o o
 o f e a γ - a e h e e a e o a b -
 h h e e a e b a a a h a h e o o
 e e e /TRE e e c e . *J Biol Chem* 1997; 272: 7445
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 b c a e e o a c a e AP-1 h a
 a o a o e a c e . *FEBS Lett* 1996; 396: 21 25.

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 h h

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 e e o o a a f a e . *Am J
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 o h c o f e a c h o e a e e c e b
 a a e o a c e i n v i t r o . *Free Radic Biol Med* 1998;
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 N e e B. I o o o o f a NAD(P)H o a e -
 e z e o o e a o a o o o h o
 e e a o b a e II c e . *Thorax* 1997; 52: 465 471.

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 N o c a o o a o DNA a a e a o o a
 e o a h c e . *Free Radic Biol Med* 1999; 27: 234 240.

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 GJ. O a o a a o o h o o f b o c o a o a
 a a e f a e a c e e a h e
 o e : e c e f o h o - e a e -
 a o , a o , a c o a o h. *Crit Care Med* 1999;
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 O h a T. Ac h a b o f e a a h a b o
 e o c o f o o a o . *J Biol Chem* 1999; 274:
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 o z h o e a e c o e , o a f c o h a
 c e h o a a a a c b o c . *Thorax*
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 e o o b a a e o o e e c e b
 o z o o h e . *Am Rev Respir Dis* 1984; 130:
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 o f a e a h h e e a c a e e o e:
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 effec of c a e e o e o c h
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 c a h c o c o o h a . *Eur Respir J* 1999; 14:
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 e a c e a e a c h o o e e a e b e e a
 a e a o a . *Am J Physiol* 1997; 273: L 265
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 C, M d a o RJ. T o effec of o o o o z o e a h
 o o o o h e a a e o o o f a o c
 a a c o a e a h e : o e - a e - e e e
 effec . *Am J Respir Crit Care Med* 1999; 160: 33 39.

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 R e a c e o o e c h a h e e a o
 e a o a c : e h o o e a o a a o b o o h c
 h h

- of a γ -a c e e e a e. *J Biol Chem* 1993; 268: 19675-19680.
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