THE RELATIONSHIPS BETWEEN EICOSANOID PRODUCTION AND PRO-INFLAMMATORY CYTOKINES

by

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ABBREVIATIONS

The following abbreviations are used in this thesis.

$1\alpha,25\text{-(OH)}D_3$	1α,25-dihydroxyvitamin D_3
AA	arachidonic acid (20:4 n-6)
Abs	antibodies
α-LNA	α-linolenic acid (18:3 n-3)
A	amp (s)
BCA	bicinchoninic acid
BSA	bovine serum albumin
cAMP	cyclic 3', 5'-adenosine monophosphate
^oC	degrees Celsius
Ca^{++}	calcium
CI	carboxyheptyl imidazole
COX	cyclooxygenase
$cPLA_2$	cytosolic phospholipase A_2
CSF	colony stimulating factor
d	day (s)
Da	Dalton
DAG	diacylglycerol (s)

DHA	docosahexaenoic acid
DPBS	Dulbecco's PBS
DTT	dithiothreitol
ELISA	enzyme linked immuno assay
EP	prostaglandin E receptor
EPA	eicosapentaenoic acid
ERK	extracellular regulated kinases
ETrA	eicosatrienoic acid
FA	fatty acid (s)
FCS	fetal calf serum
g	gram
GSH	glutathione
h	hour (s)
H_2O_2	hydrogen peroxide
IBMX	1-methyl-3-isobutylxanthine
I-BOP	5-heptenoic acid, 7-{3-{3-hydroxy-4-(4-iodophenoxy)-1-{2.2.1}hept-2-yl}-,{1S-1α,2α{Z},3β(1E,3S*),4α}
IFN	interferon
IL-1	interleukin-1
IL-1R	interleukin-1 receptor
IL-1Ra	interleukin-1 receptor antagonist
Ig	immunoglobulin(s)
IP_3	inositol triphosphate
JNK	c-Jun NH_2-terminal kinase,

k	kilo
l	litre
LA	linoleic acid
LPS	lipopolysaccharide
m	milli
M	molar
MAP	mitogen activated protein
MeOH	methanol
min	minute (s)
n	nano
NSAID	non-steroidal anti-inflammatory drug
O_2	oxygen
OA	oleic acid
p	pico
PBS	phosphate-buffered saline
PGA_2	prostaglandin A_2
PGE_2	prostaglandin E_2
$PGF_{2\alpha}$	prostaglandin $F_{2\alpha}$
PGG_2	prostaglandin G_2
PGH_2	prostaglandin H_2
PGI_2	prostacyclin I_2
PKA	protein kinase A
PKC	protein kinase C
PLA_2	phospholipase A_2
PLC	phospholipase C

PUFA	polyunsaturated fatty acid (s)
PMA	phorbol myristol acetate
RA	rheumatoid arthritis
RIA	radioimmunoassay
s	second (s)
SD	standard deviation
SKF86002	[5-(4-Pyridyl)-6 (4-fluorophenyl)-2,3-dihydroimidazo (2,1-b) thiazole]
$sPLA_2$	secretory phospholipase A_2
sTNFR	secretory tumour necrosis factor receptor
STZ	serum-treated zymosan
TNF	tumour necrosis factor
TNFR	tumour necrosis factor receptor
TXA_2	thromboxane A_2
TXB_2	thromboxane B_2

SUMMARY

Rheumatoid arthritis is an inflammatory disease of unknown cause associated with progressive joint damage and functional disability. Current therapy for rheumatoid arthritis is toxic and is associated with a high incidence of side effects.

Recently, the inflammatory cytokine tumour necrosis factor α has been reported to be an important, proximal mediator of rheumatoid arthritis. Antibodies or receptor antagonists for this molecule have been shown to be effective therapy for rheumatoid arthritis. However, such therapy remains expensive, inaccessible for the majority of patients and associated with adverse effects.

The aim of this thesis was to explore alternate strategies that may alter inflammatory cytokine production, particularly tumour necrosis factor α, and therefore provide a possible treatment for rheumatoid arthritis. The focus of the alternate strategies as described in this thesis are the eicosanoids, thromboxane A_2 and prostaglandin E_2. These strategies are safe, accessible and not associated with significant adverse events. Alteration of these eicosanoids was shown to modulate tumour necrosis factor α both *in vitro* and *in vivo*. The significance of this alteration of tumour necrosis factor α by these strategies as it might apply to rheumatoid arthritis remains to be tested.

AUTHORS DECLARATION

31/12/01

This work contains no material which has been accepted for the award of any degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Peter Savas Penglis

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