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Zurich<sup>UZH</sup>

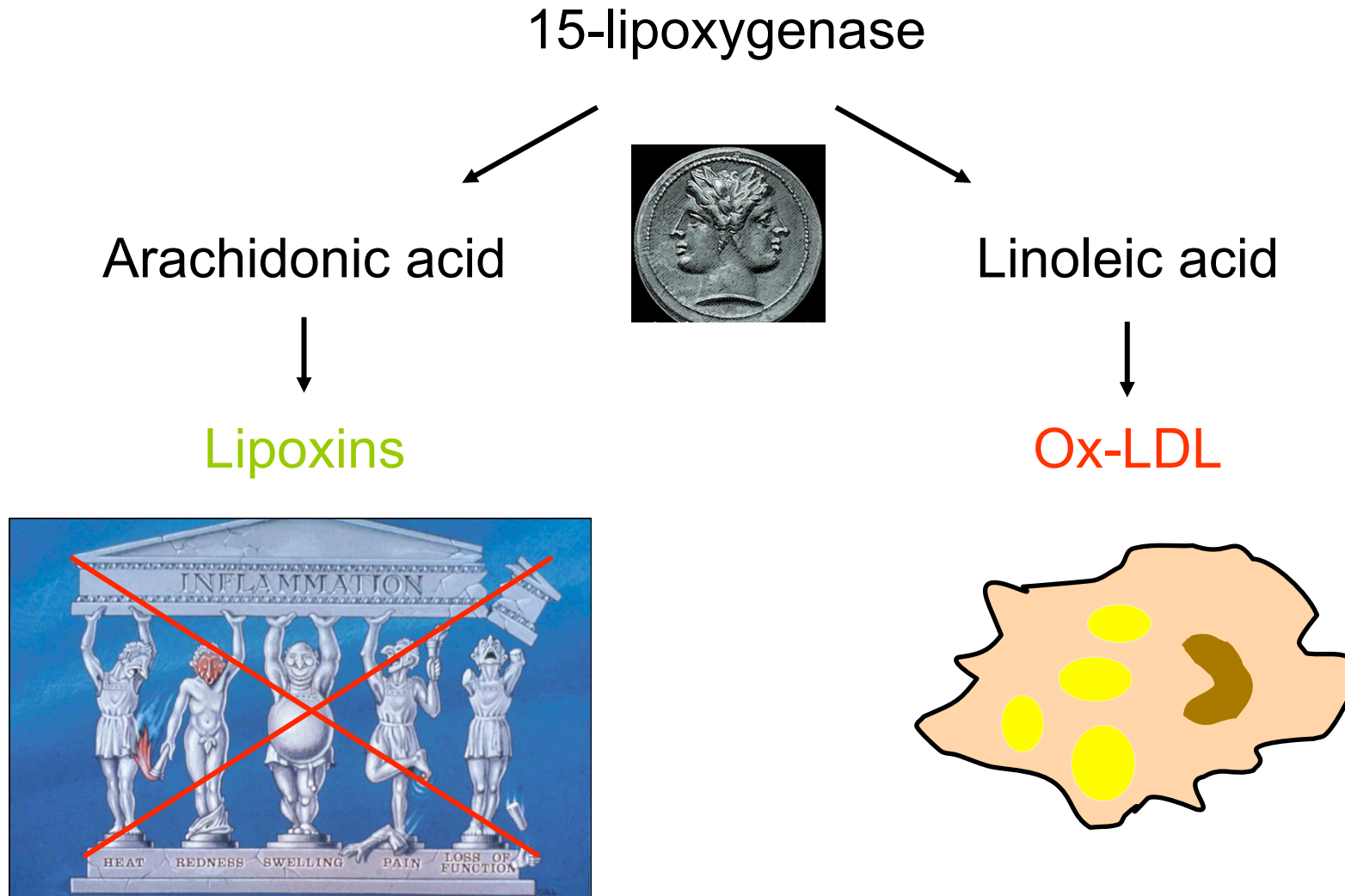
# Regulation of the second 15-lipoxygenase, ALOX15B in human macrophages

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Swiss MedLab Congress, Bern

14.06.2012

# 15-lipoxygenase: A janus enzyme



# Role of 15-lipoxygenase activity in atherosclerosis - animal models

## Pro-atherogenic activity



apoE<sup>-/-</sup> mice with 12/15-LOX knockout → atherosclerotic lesion formation ↓

(J Clin Invest. 1999 Jun;103(11):1597-604)

## Anti-atherogenic activity



New Zealand and WHHL Rabbits overexpressing 15-LOX in macrophages → reduced number of atherosclerotic lesions

(J Clin Invest. 1996 Nov 15;98(10):2201-8)

## - human: clinical studies

- c.-292C>T in 15-lipoxygenase gene → trend toward an atheroprotective effect for CAD but no effect on the risk for MI

(Clin Chem Lab Med.2007;45(4):487-92.; Atherosclerosis. 2009 Jul;205(1):192-6. Epub 2008 Nov 27. )

- T560M → associated with a significantly increased risk for CAD and showed a trend to be associated with MI

(Atherosclerosis, 198 (2008), pp. 136–144; Atherosclerosis. 2009 Jul;205(1):192-6. Epub 2008 Nov 27)

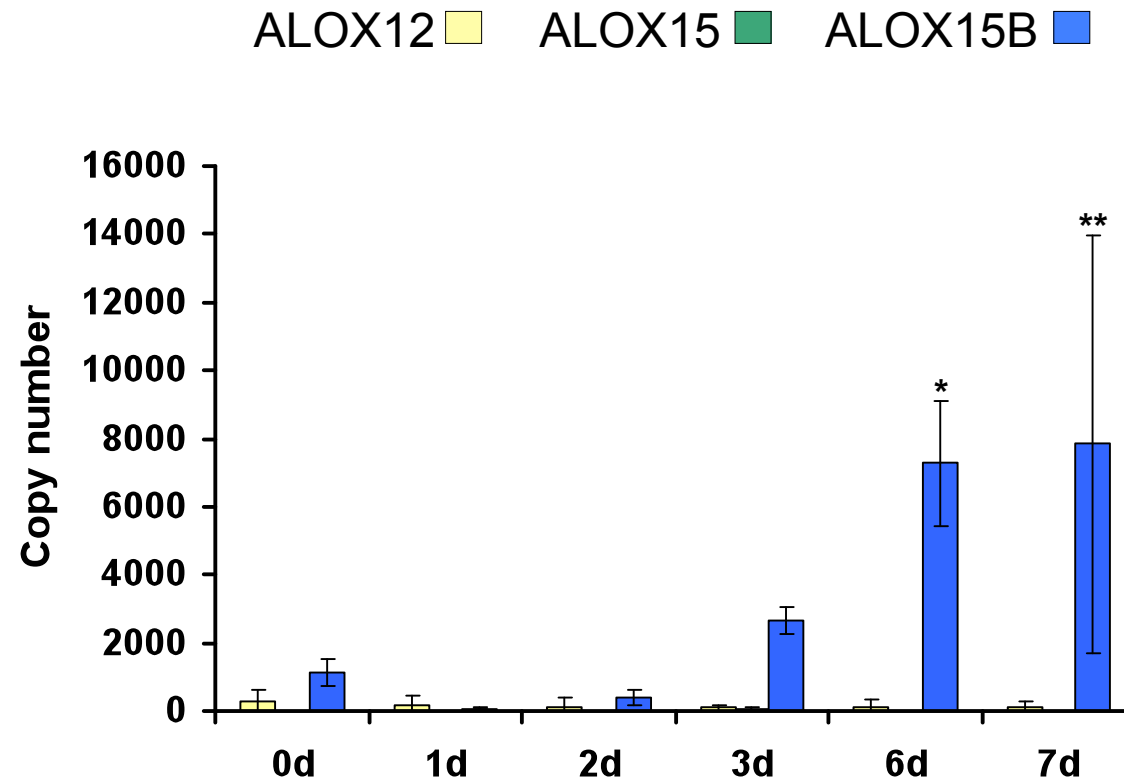
## Several 12/15-LOX isoforms with variable enzyme activity in human

<b>LOX sub-families</b>	<b>Isoenzymes</b>	<b>Main substrates</b>	<b>Main products</b>
Reticulocyte-type 12/15-LOXs	ALOX15	Arachidonic acid  Linoleic acid Ester lipids	15-HpETE 12-HpETE 13-HpODE
Platelet-type 12-LOXs	ALOX12	Arachidonic acid	12-HpETE
Epidermis-type LOXs	ALOX12B	Arachidonic acid	12(R)-HpETE
	ALOX15B	Arachidonic acid	15-HpETE

(Prostaglandins Leukot Essent Fatty Acids. 2007 Aug;77(2):67-77)

# ALOX12, ALOX15 and ALOX15B mRNA expression during macrophages differentiation

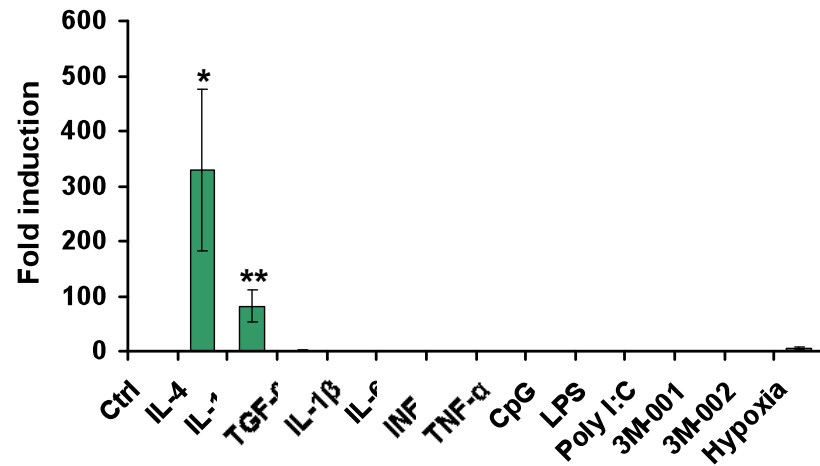
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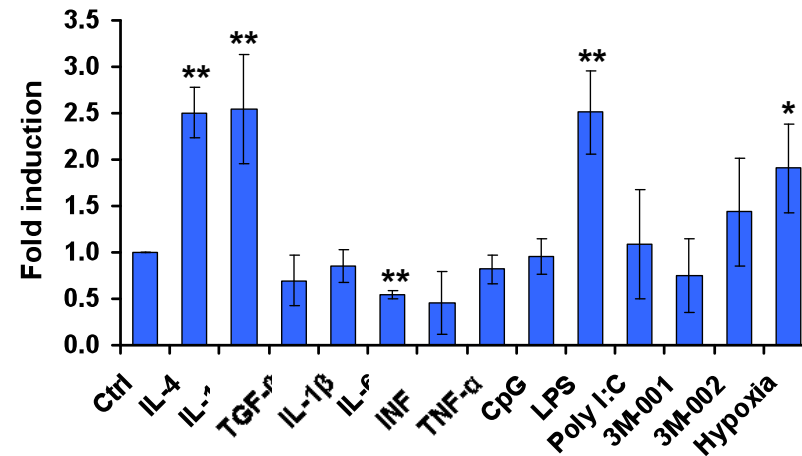
# ALOX15 and ALOX15B mRNA expression in human macrophages after stimulation

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ALOX15

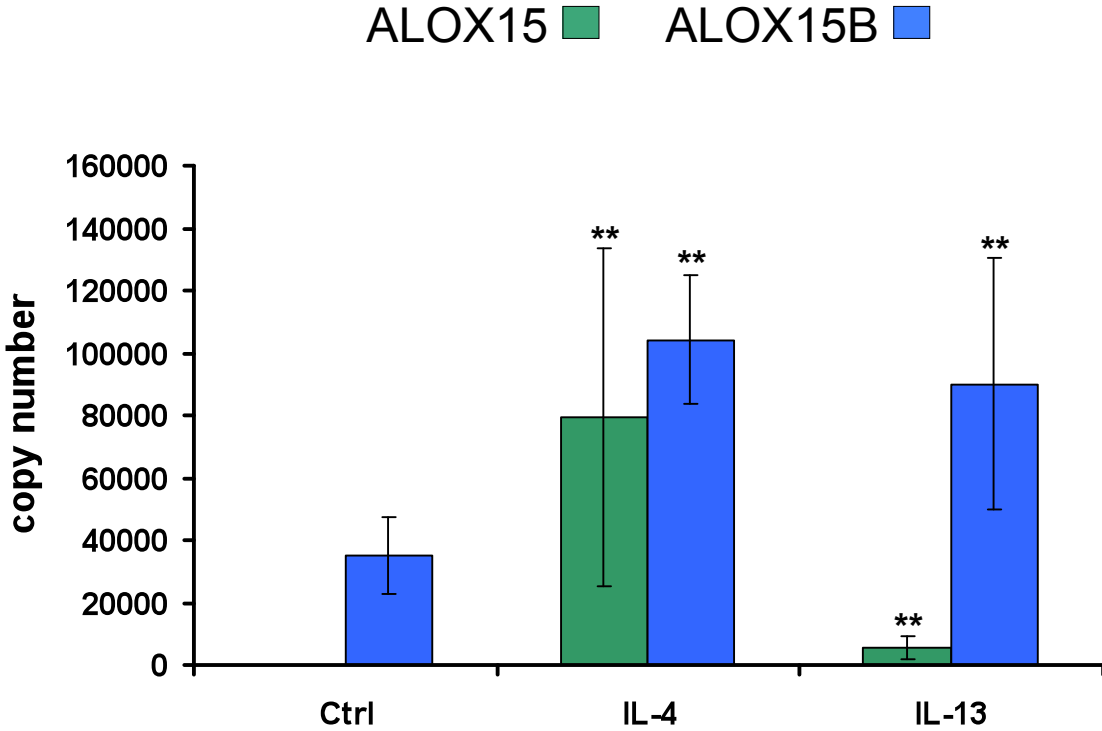


ALOX15B



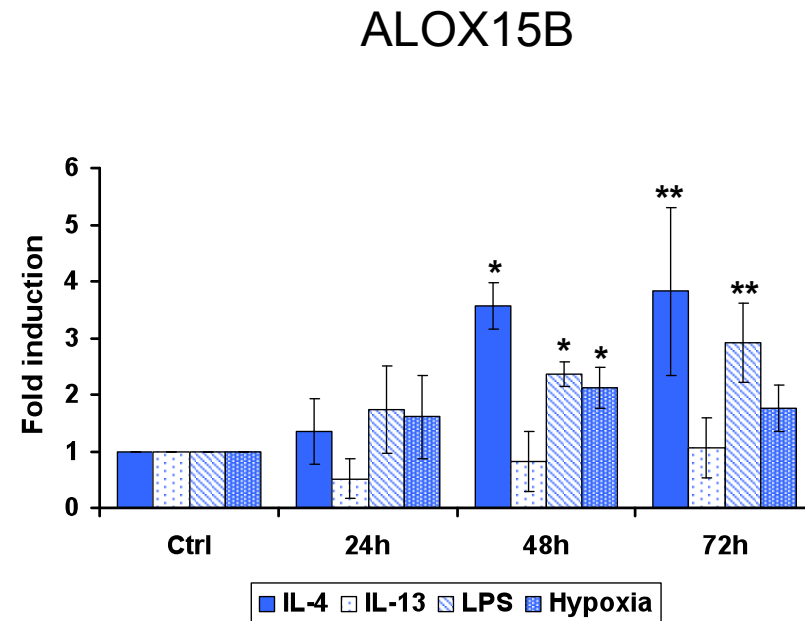
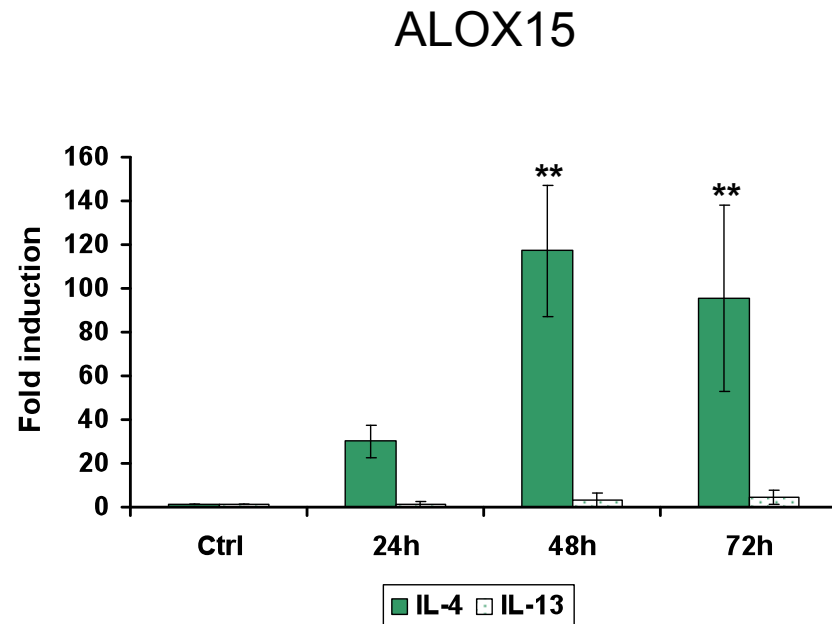
# Absolute quantification of ALOX15 versus ALOX15B mRNA expression

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# ALOX15 and ALOX15B protein expression after stimulation over 3 days

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# Summary and conclusion

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- ALOX15B is expressed in resident macrophages while ALOX15 and ALOX12 are not
  - Stimulation with IL-4, LPS and Hypoxia induced ALOX15B protein expression, while ALOX15 protein expression was mainly observed following IL-4 stimulation
  - 15-lipoxygenase activity results from ALOX15 and ALOX15B following IL-4 stimulation under normoxic conditions
  - Under hypoxic conditions and in LPS-stimulated macrophages only ALOX15B is expressed and therefore, represents the sole 15-lipoxygenase activity
- We suggest that ALOX15B may play a more important role in human atherosclerosis than ALOX15



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## Acknowledgments

Martin Hersberger  
Margot Crucet  
Claudio Gemperle



FONDS NATIONAL SUISSE  
SCHWEIZERISCHER NATIONALFONDS  
FONDO NAZIONALE SVIZZERO  
SWISS NATIONAL SCIENCE FOUNDATION