

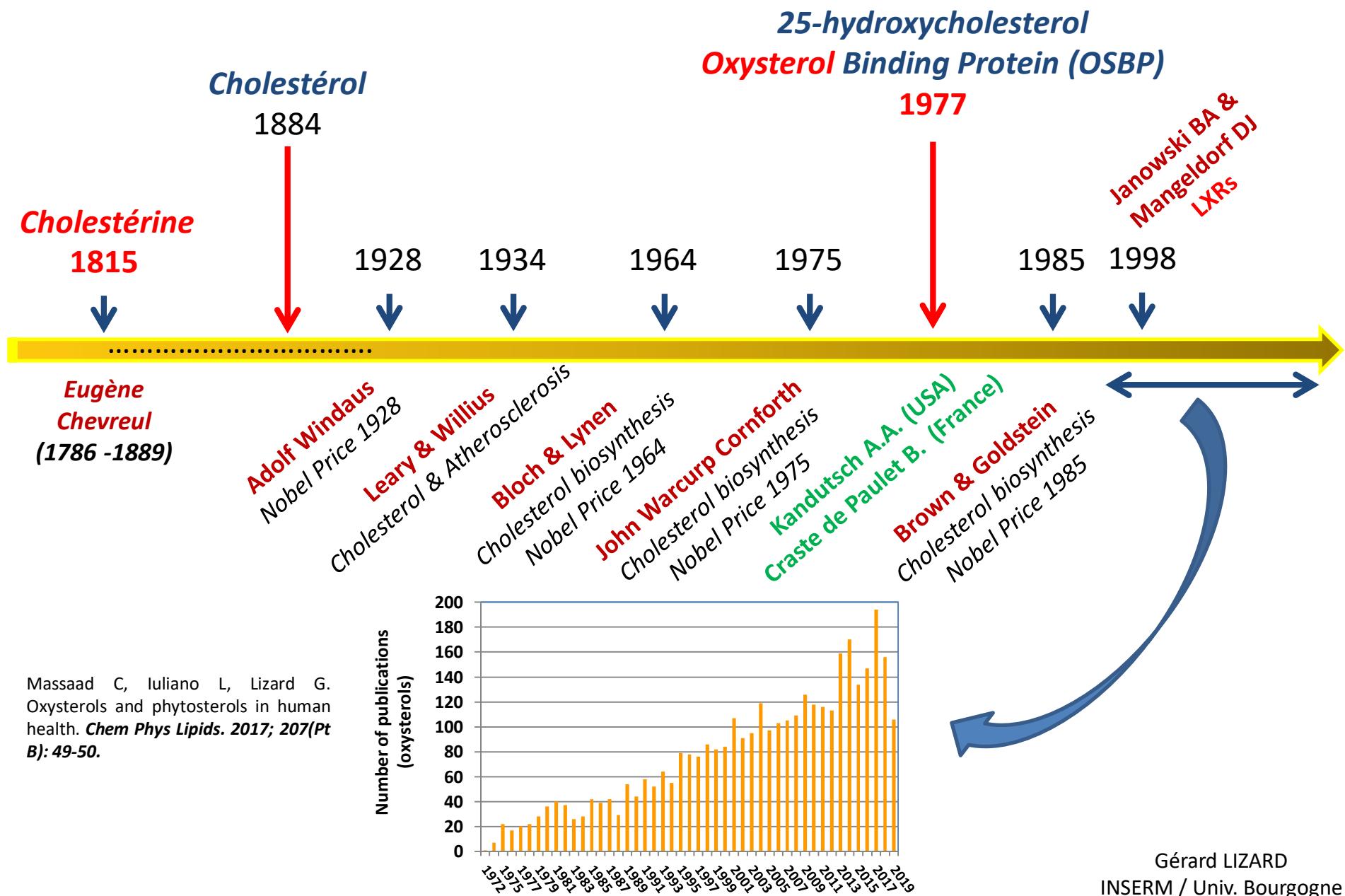
Cytotoxic effects of oxysterols at the mitochondrial and peroxisomal level: implication in age-related diseases



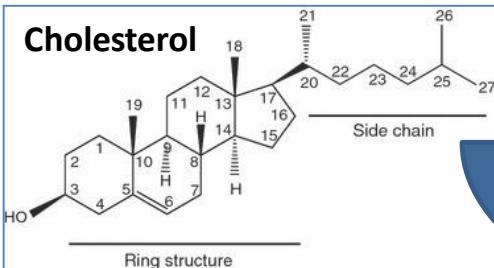
Gérard Lizard

¹ Univ. Bourgogne Franche-Comté, Team 'Biochemistry of the Peroxisome, Inflammation and Lipid Metabolism'
EA 7270 / INSERM, Dijon, France,

From Cholesterol to Oxysterols



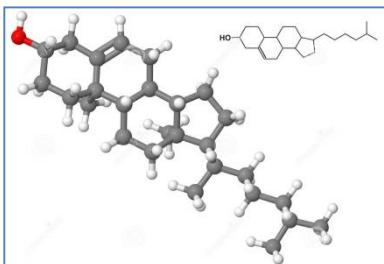
Oxysterols Biogenesis



Cholesterol (C27)

- Steroid backbone is rigid
- The side chain is flexible

OXYSTEROLS
Cholesterol oxide derivatives
One or more oxygen atoms

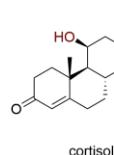


Cholesterol

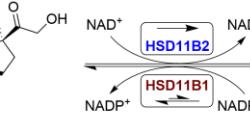


- Auto-oxidation (7KC, 7 β -OHC, ...)
- Enzymes (24S-OHC; 27-OHC; ...)
 - * mainly cytochromes P450 (CYP)
 - * Cholesterol 25-hydroxylase
 $\text{cholesterol} + \text{AH}_2 + \text{O}_2 \rightleftharpoons \text{25-hydroxycholesterol} + \text{A} + \text{H}_2\text{O}$
 - * 11 β -Hydroxysteroid dehydrogenase type 1 et 2

(7 β -OHC)



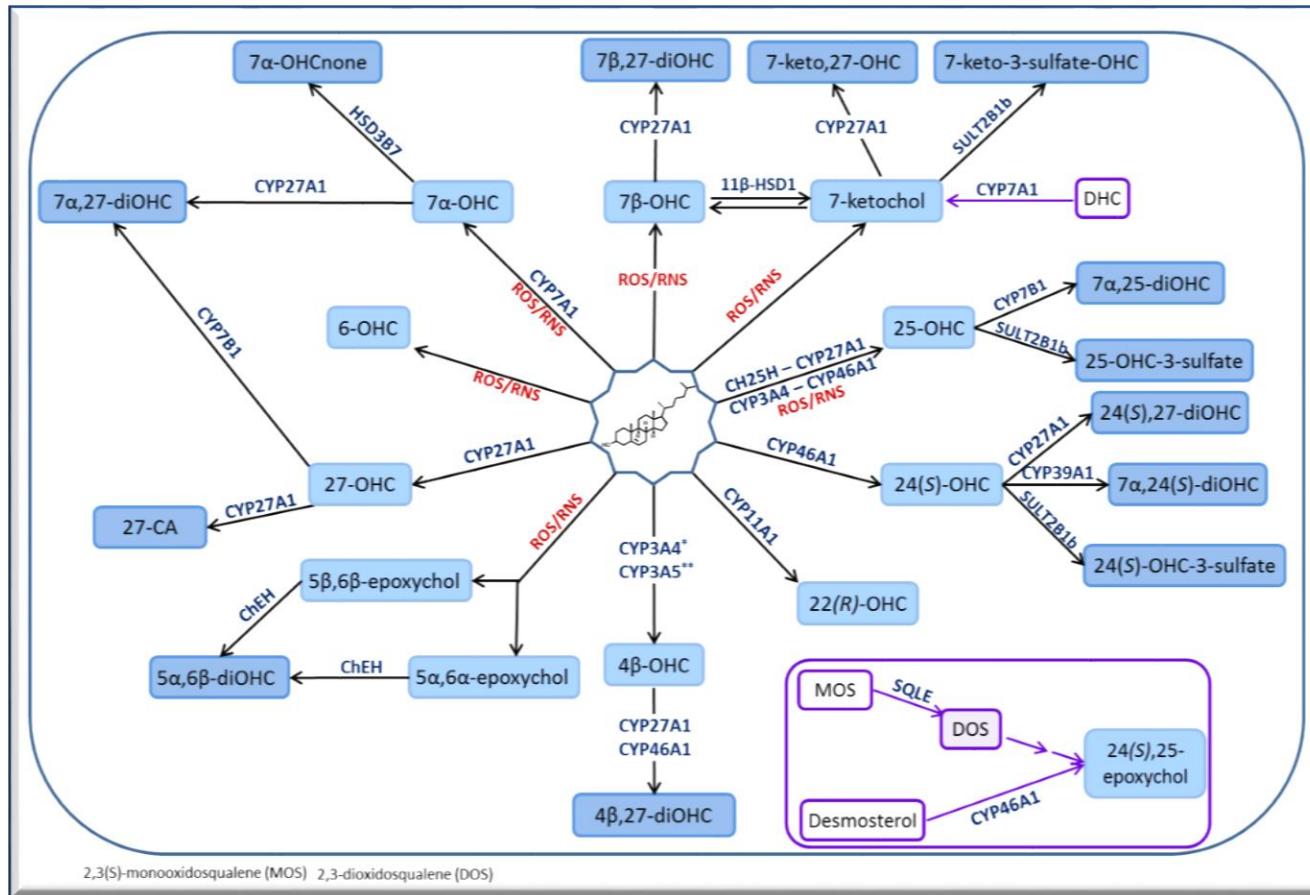
cortisol



(7KC)

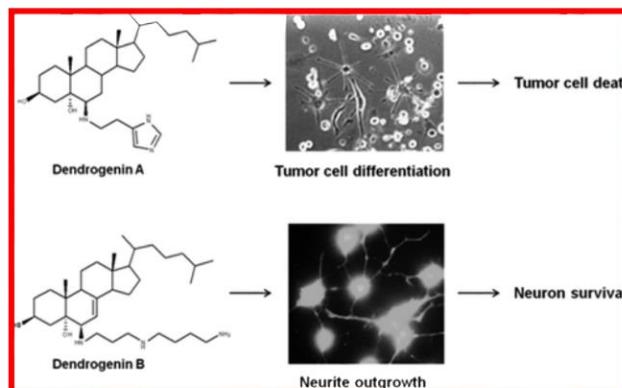
- Both processes (25-OHC, 7KC, 7 β -OHC)

Oxysterol Network / 'oxysterome' / 'oxisome'



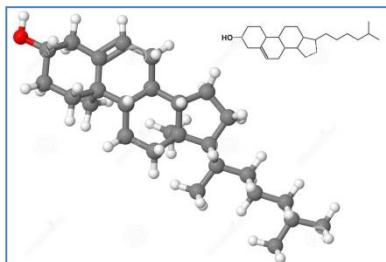
❑ Mutemberezi V. et al.,
Progress in Lipid Research, 2016

❑ de Medina P. et al.,
J Med Chem 2009;52(23):7765-77.



✓ **Aminoalkyoxysterols (dendrogerin A)**
plants, amphibians and ancestral fishes
(dogfish shark *Squalus acanthias*, sea lamprey *Petromyzon marinus*) and
vertebrates (humans)

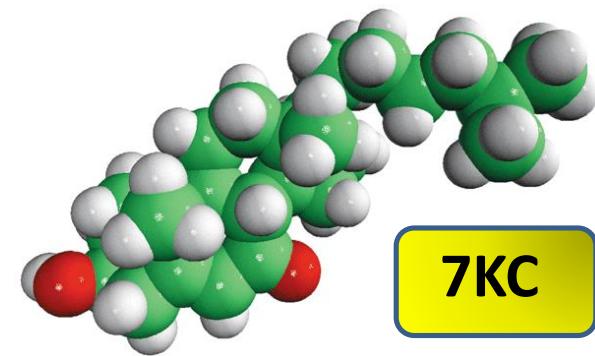
Biogenesis of 7-ketcholesterol (7KC)



Cholesterol

Auto-oxidation

Enzymes



Biogenesis of 7KC

- *Auto-oxidation*

- ✓ Reactive oxygen species (ROS)
- ✓ Fenton reaction (Fe²⁺/Fe³⁺)
- ✓ Reactive nitrogen species (RNS)

- *Enzymes*

✓ CYP7A1 ; 7-dehydrocholesterol + CYP7A1 = 7KC

(Smith-Lemli-Opitz syndrom; cholesterol deficiency)

✓ 11 β -HSD1 ; interconversion of 7 β -hydroxycholesterol in 7KC

Metabolism of 7-ketcholesterol (7KC)

To reduce or to inhibit
7KC-induced cytotoxicity

□ Metabolism of 7KC (eucaryotic cells)

- Reduction

11 β -HSD1 ; interconversion 7KC in 7 β -hydroxycholesterol (*toxicity* : 7 β -OHC > 7KC)

- Oxidation

CYP27A1 ; to reduce 7KC toxicity

- Sulfatation

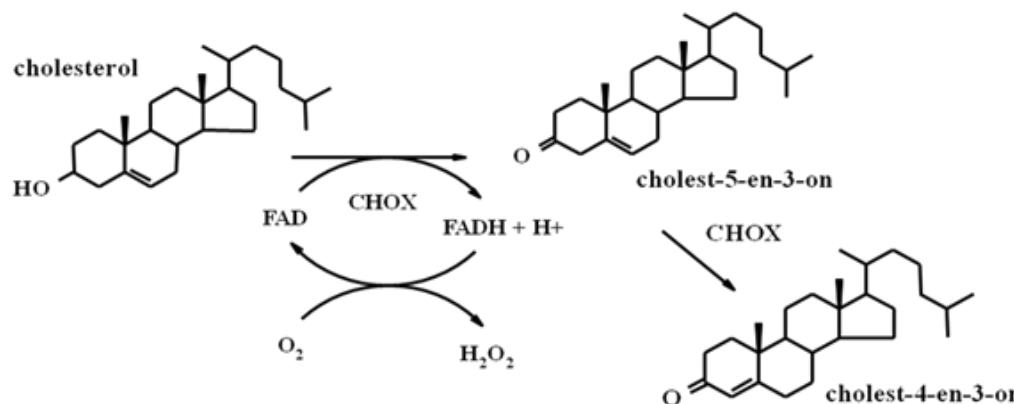
Sult2B1b ; to reduce 7KC toxicity

- Esterification

ACAT; LCAT ; cPLA2 α ; SOAT1; *unstable ester* (7KC release)

□ 7KC metabolism (pro-caryotic cells : bacteria)

- Oxidation : cholesterol oxidase; *inhibition of 7KC-induced toxicity*



Aging and age related diseases : Implication of 7-ketcholesterol

Increase lifespan

- ✓ Aging of the population
- ✓ Age related diseases

(7-ketcholesterol: 7KC)

