Macular xanthophylls and age-related macular degeneration

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Key References

For details and citations, please see:

<table>
<thead>
<tr>
<th>American Journal of Clinical Nutrition. 96(suppl); 1123S-33S. 2012.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SanGiovanni JP, Neuringer MN. The putative role of lutein and zeaxanthin as protective agents against age-related macular degeneration: promise of molecular genetics for guiding mechanistic and translational research in the field.</td>
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<td>SanGiovanni JP, Chew EY, Johnson EJ. Lutein.</td>
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</table>
SanGiovanni and Neuringer, *AJCN*, 2012

### Putative Relationships of Macular Xanthophylls with AMD

Genetic, dietary, and environmental factors affect concentrations of macular xanthophylls within retinal cell types manifesting AMD pathology.

### Application of Molecular Genetics to Investigate of MX-AMD Relationships

Study of AMD-associated genes encoding enzymes, transporters, ligands, and receptors affecting or affected by macular xanthophylls.
Key Premises

Approach to Study of MX-AMD Relationships

<table>
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<tr>
<th>Humans cannot biosynthesize lutein and zeaxanthin de novo.</th>
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<td>Humans have the capacity for efficient uptake, transport, retention, and repair of MXs in the retina.</td>
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<th>MXs have the capacity to affect processes implicated in AMD pathogenesis</th>
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<td>The biophysical and biochemical properties of MXs provide biologic plausibility for their actions in supporting cytoarchitecture, filtering damaging wavelengths of light, attenuating oxidative stress, and influencing signal transduction cascades.</td>
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<td>Study of AMD-associated genes encoding enzymes, transporters, ligands, and receptors affecting or affected by MXs and their metabolites will meaningfully inform approaches to inquiry and inference.</td>
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Overview of Presentation

1. Age-related Macular Degeneration (AMD)
2. Macular Xanthophylls (MXs: lutein, zeaxanthin, meso-z.)
3. Putative Actions of MXs on Processes Implicated in AMD Pathogenesis and Pathophysiology
4. Findings from Observational Studies and Model Systems
5. Applications in Molecular Genetics
## The Burden of AMD

### Nature and Scope of AMD
- Major cause of vision loss - elderly.
- 3.5 M living with AMD
- 1.7 M living with AMD
- 50% increase from 2004 to 2020.
- Treatments limited in scope/efficacy.

### Economic and Social Impact
- Treatment with intraocular injections with anti-angiogenic drugs.
- AMD-related outpatient services are incurred annually by ~1.4 million people aged ≥ 65.
- ~$570M in Medicare claims per year.
Nature of AMD

Clinical Subtypes
Neural and/or vascular pathology.
Neovascular (NV) AMD: New abnormal blood vessels leak fluid and blood leading to loss of vision.
A. Normal retina

Optic nerve
Macula
Choroid

Bruch’s membrane
Retinal pigment epithelium

New abnormal blood vessels leak fluid and blood leading to loss of vision.

B. Atrophic MD
Geographic Atrophy

C. Neovascular (NV) AMD
KEY POINTS

AMD is neurodegenerative and vasoproliferative disease of public health significance.

The chemical composition of the macula is notable for high content of lutein, zeaxanthin, and meso-zeaxanthin.
Xanthophylls and Macula

Lutein and Zeaxanthin are major diet-based MXs
~40 carotenoids in diet
~15 carotenoids in serum

*Meso*-zeaxanthin (major MX) is a lutein metabolite.

MX concentration is amplified 1,000- to 10,000-fold from circulation to the retina.

Active transport mechanisms.

Specific binding proteins in retina.
Structures of Macular Xanthophylls

Diet-based

Lutein, (3R,3’R,6’R)-β,ε-caroten-3,3’-diol, C_{40}H_{56}O_{2}, MW = 568.871)

Zeaxanthin, (3R,3’R)-β,β-caroten-3,3’-diol)

Lutein Metabolite

Meso-Zeaxanthin, (3R,3’S)-β,β-caroten-3,3’-diol)
Laminar Distribution of Macular Xanthophylls

Snodderly et al. 1984
KEY POINT

MXs are found in retinal photoreceptors, a cell type sustaining damage in AMD.
Putative Actions of MXs

- Interaction with membrane-bound proteins and lipids.
- Attenuation of energy in range of damaging blue light.
- Modulation of oxidative stress and redox balance.
- Interaction with constituents of signal transduction cascades inhibiting cell growth, stimulating differentiation, transactivating/antagonizing nuclear receptors, and influencing adhesion complexes.
MXs and Membrane-bound Molecules

- Rhodopsin
- Xanthophyll
- Phospholipid Membrane Bilayer

ICVNF
International Congress on Vegetarian Nutrition
Attenuation of Blue Light Exposure

Landrum and Bone (2001)

![Graph showing the absorption spectra of Lutein and Zeaxanthin with peaks at different wavelengths.](image)

- Lutein peaks at 445, 451, 477 nm.
- Zeaxanthin peaks at 423, 474 nm.

Absorption rates:
- Lutein absorption *100 = 60%
- Zeaxanthin absorption *100 = 38%
Attenuation of Blue Light Exposure

MXs as blue light filters

Distribution of macular pigment

Absorbance spectrum of macular pigment

Schalch et al. 1999
Attenuation of Blue Light Exposure

![Graph showing the concentration of macular pigment and lutein/zeaxanthin ratio vs. eccentricity in mm.](image_url)
Barker FM, et al., 2011

Adults Rhesus monkeys on a life-long MX-free diet showed reduced amounts of blue light damage after a 6-month MX supplementation program.
Retinal and Serum Response to MXs

Human Studies

Supplement Intake → Status

Dietary Intake → Status
Intake-status-AMD Associations

Dietary Intake → Structure (AMD)

1993 Serum
1994 Serum
1995 MPOD
1997 Serum
1998 Serum
2001 Serum
2002 Plasma
2003 Serum
2005 Serum
2006 Serum
2007 Serum
2008 Serum
2009 Serum

Status → Structure (AMD)
Dietary Intake $\rightarrow$ Structure (AMD)

1993 Serum
1994 Serum
1995 Serum
1997 MPOD
1998 Serum
2001 Serum
2002 Plasma
2003 Serum
2005 Serum
2006 ARDS
2007 Australia
2008 USA
2009 USA

Status $\rightarrow$ Structure (AMD)
KEY POINTS

MX intake associated with retinal MX status.

MX intake & retinal status associated AMD.
### Key Premises

#### Approach to Study of MX-AMD Relationships

<table>
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<tr>
<th>Premise</th>
<th>Details</th>
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<td><strong>Humans cannot biosynthesize lutein and zeaxanthin <em>de novo.</em></strong></td>
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## Molecular Genetics of MX-AMD axis

### Genes influencing retinal MX status – Extant Literature

<table>
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<tr>
<th>Uptake and Transport</th>
<th>Status</th>
<th>AMD</th>
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</thead>
<tbody>
<tr>
<td>CD36 (CH, RPE)</td>
<td>⋄</td>
<td>⋄</td>
</tr>
<tr>
<td>SCARB1 (CH, RPE)</td>
<td>⋄</td>
<td>⋄</td>
</tr>
<tr>
<td>Tubulin genes (OPL)</td>
<td>⋄</td>
<td>⋄</td>
</tr>
<tr>
<td>APOE (circulation)</td>
<td>⋄</td>
<td>⋄</td>
</tr>
<tr>
<td>APOA1 (HDL-C)</td>
<td>⋄</td>
<td>⋄</td>
</tr>
<tr>
<td>ABCA1 (HDL-C)</td>
<td>⋄</td>
<td>⋄</td>
</tr>
<tr>
<td>GSTP1 (retina -- zeaxanthin)</td>
<td>⋄</td>
<td>⋄</td>
</tr>
<tr>
<td>STARD3 (retina – lutein)</td>
<td>⋄</td>
<td>NSF</td>
</tr>
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</table>

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<tr>
<th>Cleavage-Synthesis</th>
<th>Status</th>
<th>AMD</th>
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<tbody>
<tr>
<td>BCMO1</td>
<td>⋄</td>
<td>NSF</td>
</tr>
<tr>
<td>BCO2</td>
<td>⋄</td>
<td>NSF</td>
</tr>
<tr>
<td>LPL</td>
<td>⋄</td>
<td>⋄</td>
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- ⋄ = Findings from studies in humans
- ⋄ = Findings from studies in model systems
- NSF = No significant findings at present
Genes influencing retinal MX status – Extant Literature

<table>
<thead>
<tr>
<th>Interference Growth Factors</th>
<th>Status</th>
<th>Retinopathy</th>
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<td>IGF Genes</td>
<td>●</td>
<td>●</td>
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<th>Disease Low MX Status</th>
<th>Status</th>
<th>AMD</th>
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<tr>
<td>ALDH3A2 (SLS)</td>
<td>●</td>
<td>NSF</td>
</tr>
<tr>
<td>ABCA4 (Stargardt Disease)</td>
<td>●</td>
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Expression of MX-related Genes

SanGiovanni and Neuringer, AJCN, 2012

Sequence Variation in Genes:

- Uptake and transport
- Binding in the retina
- Cleavage
- Cellular response to stress
- Growth factors
- Low MX status in retina
# Summary of Key Points

## Bases for examining AMD-MX relationships

1. **AMD is primary cause of vision loss in elderly of European ancestry.**
2. **Macula contains high concentrations of lutein, zeaxanthin, meso-z.**
3. **Humans cannot synthesize lutein and zeaxanthin de novo.**
4. **MX capacity to influence processes implicated in AMD pathogenesis**
5. **Dietary, environmental, genetic factors affect retinal response to MX**
6. **Gene-MX-AMD relationships for genes encoding MX transporters, zeaxanthin binding protein, and gene associated with low MX status in people with a monogeneic retinal degeneration.**
7. **Next steps.**
Next Steps

Research Opportunities

1. Ultra-structural localization (cell types) of MX binding protein.
2. Broader analysis of genetic variation and regulation.
3. Model systems.
4. Integrated systems-based approaches.
Thank you

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