CORE RESOLVE SCIENCE

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Inflammatory SPM Support

Specialized Pro-Resolving Mediators (SPMs)

Nature's Key to Resolving Inflammation

Specialized pro-resolving mediators (SPMs) are molecules naturally produced by the body as part of its response to inflammation and proinflammatory cytokine storms. They are specialized compounds derived from essential fatty acids, such as omega-3 fatty acids.

SPMs play a crucial role in the body's resolution phase of inflammation, where they help to actively switch off and resolve the inflammatory response once it has served its purpose. These mediators help to regulate the immune system, reduce excessive inflammation, promote tissue repair, and support the body's return to a state of normalcy after an inflammatory event.

In essence, SPMs act as "**peacekeepers**" in the body, helping to resolve inflammation and restore tissues to their healthy state, contributing to overall wellness and maintaining a balanced immune response.

Inflammation, our body's natural response to injury or infection, is a vital defense mechanism that helps combat harmful pathogens and initiate tissue repair. However, the inflammatory process needs to be tightly regulated to prevent excessive or prolonged inflammation, which can lead to tissue damage and chronic diseases. Here's where Specialized Pro-Resolving Mediators (SPMs) step in, serving as the body's resolution specialists to effectively conclude the inflammatory response and restore tissue homeostasis.

Understanding SPMs

SPMs are a group of bioactive lipid mediators derived from essential fatty acids, notably omega-3 fatty acids like eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid. They are not only essential in initiating the resolution phase of inflammation but also pivotal in orchestrating the immune response to restore tissue integrity.

The Resolution Phase

In contrast to the traditional view that inflammation is merely a response that should be suppressed, the resolution phase is an active and dynamic process mediated by SPMs. They act as "**resolution agonists**," promoting the active resolution of inflammation by dampening excessive immune responses while promoting tissue repair and healing.

SPMs' Mechanisms of Action

SPMs exert their effects through binding to specific receptors on immune cells, triggering intracellular signaling pathways that orchestrate the resolution of inflammation. They promote the clearance of inflammatory cells, regulate cytokine production, enhance phagocytosis of cellular debris, and accelerate tissue regeneration.

Types of SPMs

Several well-known SPMs include **lipoxins** derived from arachidonic acid, **resolvins** from omega-3 EPA and DHA, **protectins**, and **maresins**. Each type of SPM exhibits distinct biological actions and contributes uniquely to resolving inflammation in various tissues and organ systems.

- Lipoxins
- Resolvins
- Protectins
- Maresins

Clinical Implications

Research into SPMs has unveiled promising therapeutic potential in treating chronic inflammatory diseases, such as arthritis, cardiovascular diseases, inflammatory bowel disease (IBD), and periodontitis. By harnessing the power of SPMs, novel therapeutic interventions targeting the resolution of inflammation are being explored, aiming for more effective and targeted treatment approaches.

Enhancing SPM Production

Dietary interventions rich in omega-3 fatty acids, such as **algal oil**, can augment the body's production of SPM precursors. This dietary approach can potentially

enhance the resolution of inflammation and aid in maintaining a healthy immune response.

Specialized pro-resolving mediators represent an emerging frontier in inflammation research, showcasing their pivotal role in actively resolving inflammation and promoting tissue repair. Understanding the mechanisms and therapeutic potential of SPMs provides exciting opportunities for developing novel treatments to manage chronic inflammatory conditions and improve overall health.

Harnessing the natural power of SPMs holds significant promise for developing innovative therapies that target the resolution of inflammation, fostering a new era in healthcare focusing on resolving inflammation, not merely suppressing it.

The Role of Polyunsaturated Fatty Acids in SPMs

Polyunsaturated fatty acids (PUFAs) play a pivotal role in the production of Specialized Pro-Resolving Mediators (SPMs). These bioactive lipid compounds, including resolvins, protectins, and maresins, are derived from specific PUFAs, primarily omega-3 and omega-6 fatty acids.

Here is a list of some key polyunsaturated fatty acids along with their sources:

Omega-3 Fatty Acids

1. **Alpha-Linolenic Acid (ALA):** Found in flaxseed oil.

2. **Eicosapentaenoic Acid (EPA):** Sourced from algal oil.

3. **Docosahexaenoic Acid (DHA):** Found in algal oil and certain types of algae.

Omega-6 Fatty Acids

1. **Linoleic Acid (LA):** Found in High Oleic Sunflower Oil, and Black Seed Oil.

2. **Gamma-Linolenic Acid (GLA):** Sourced from Borage Oil.

3. **Arachidonic Acid (AA):** Present in Cupuaçu Butter.

Omega-9 Fatty Acids

Omega-9 fatty acids, while not strictly classified as essential, are monounsaturated fats and are beneficial for health.

1. **Oleic Acid:** Found abundantly in olive oil

Mechanisms

During the inflammatory response, PUFAs, particularly EPA and DHA, are enzymatically converted into SPMs. Enzymes like **lipoxygenases** and **cytochrome P450 enzymes** act on these fatty acids, leading to the formation of SPMs. These SPMs, such as resolvins, protectins, maresins, and lipoxins, actively engage in signaling pathways that promote the resolution of inflammation, modulate immune responses, and facilitate tissue repair and regeneration.

Polyunsaturated Fatty Acids (PUFA) & SPM Enzymatic Conversions

The enzymatic conversions of Polyunsaturated Fatty Acids (PUFAs) involve several steps that transform these fatty acids into bioactive lipid mediators, including Specialized Pro-Resolving Mediators (SPMs).

Here's an overview of the enzymatic conversions:

Lipoxygenases (LOX): PUFAs, such as omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are acted upon by specific enzymes known as **lipoxygenases**. These enzymes introduce oxygen atoms into the PUFA molecules, leading to the creation of hydroperoxyeicosatetraenoic acids (HPETEs) from EPA and DHA. In addition, Lipoxygenases are enzymes that convert PUFAs into **leukotrienes**, another group of eicosanoids. Leukotrienes are involved in inflammatory and immune responses.

Therapeutics for LOX Gene: [R]

- Vitamin C
- Glycosaminoglycans (Sea Algae)
- Salicylic acid (White willow bark)
- Curcumin
- Galactose (Flax, Sunflower, Licorice, Cherry, Ginger, Olive) [R]
- Linoleic acid (Flax)
- Quercetin (Sophora japonica)
- Baicalein (Skullcap)
- Resveratrol (Japanese knotweed)

Therapeutics for Leukotrienes:

- DHA/EPA [R]
- Butterbur [R]
- Boswellia serrata [R]
- Nigella sativa (Black seed oil) [R]
- Licorice [R]
- Curcumin [R]
- Panax ginseng [R]
- Clove [R]
- Withania somnifera (Ashwagandha) [R]
- Aloe vera [R]
- Capsaicin [R]
- Ginger [R]
- Skullcap [R]
- Quercetin [R]
- Resveratrol [R]

Subsequent Enzymatic Actions: HPETEs are further processed by additional enzymes, including specialized enzymes like **5-lipoxygenase (5-LOX)** and **15-lipoxygenase (15-LOX)**. These enzymes catalyze the transformation of HPETEs into intermediate compounds, such as epoxyeicosatrienoic acids (EETs) and **lipoxins**. **Epoxide hydrolases** also perform enzymatic actions resulting in the generation of specialized lipid mediators.

Therapeutics for 5-LOX Gene: [R]

- Omega-3 fatty acid
- Omega-6 fatty acid
- Linoleic acid (Flax)
- Baicalein (Skullcap)
- Resveratrol (Japanese knotweed)

- Boswellic Acid (Boswellia serrata)
- Honokiol (Magnolia bark)
- Salicylic acid (White willow bark)
- Curcumin
- Heparin (Nattokinase)
- L-Arginine
- Eugenol (Clove oil)
- Ursolic acid (Holy Basil)
- Quercetin (Sophora japonica)

Therapeutics for 15-LOX Gene: [R]

- Linoleic acid (Flax)
- Alpha-Linolenic Acid (Flax)
- Arachidonic Acid (Cupuaçu Butter)
- Myricetin (Berries)
- Apigenin (Parsley)
- Luteolin (Parsley, Olive oil)
- Fisetin (Strawberry)
- Quercetin (Sophora japonica)
- Baicalein (Skullcap)
- Resveratrol (Japanese knotweed)
- Phosphatidylethanolamine (Sunflower Lecithin)

Therapeutics for Epoxide Hydrolases: [R, R]

- Resveratrol (Japanese knotweed)
- Aloe Emodin (Aloe vera, Rhubarb)
- Eugenol (Clove oil)
- L-Arginine
- Vitamin C
- Arachidonic Acid (Cupuaçu Butter)

The **enzymatic conversions of PUFAs** involve a series of transformations catalyzed by various enzymes, ultimately leading to the formation of specialized lipid mediators, such as SPMs, which are crucial in resolving inflammation and maintaining tissue health.

In addition to lipoxygenases and epoxide hydrolases, SPMs are also formed in cells by the metabolism of polyunsaturated fatty acids (PUFA) by one or a combination of **cyclooxygenase**, and **cytochrome P450** monooxygenase enzymes.

Cyclooxygenase (COX): COX enzymes are involved in the conversion of arachidonic acid (a type of PUFA) into various eicosanoids, including **prostaglandins** and **thromboxanes**. These compounds play essential roles in inflammation, blood clotting, and other physiological processes.

Therapeutics for COX-2 (Prostaglandin-Endoperoxide Synthase 2): [R]

- Salicylic acid (White willow bark)
- Curcumin
- Capsaicin (Cayenne)
- Omega-3 fatty acid
- Hesperidin (Citrus)
- Ursolic acid (Holy Basil)
- Resveratrol (Japanese knotweed)
- Panax Ginseng
- Rosmarinic acid (Holy Basil)
- 6-Shogaol (Ginger)
- 8-Gingerol (Ginger)
- Diosgenin (Fenugreek)
- Luteolin (Parsley, Olive oil)
- Narirutin (Orange)
- Quercetin (Sophora japonica)

- Punicalin (Pomegranate)
- Saikosaponins (Bupleurum)
- Tectoridin (Kudzu)
- Wogonin (Skullcap)
- Sulforaphane
- TUDCA
- Nobiletin (Citrus peels)

Other COX-2 Antagonist:

- Andrographis/Andrographolide (R)
- Danshen (R)
- Black Cumin (R)
- Resveratrol (R, R, R)
- Honokiol (R)
- Olive leaf (R)
- Aloe vera (R)
- Pycnogenol (R)
- Glucosamine (R, R)
- Grape seed extract (R)
- White Tea/EGCG (R).
- Bromelain (R)
- Boswellia (R)
- Anthocyanins (from red raspberries) (R)
- Flaxseed (R)
- Emodin (R)

Therapeutics for Thromboxane A2:

- Luteolin [R]
- Curcumin [R]
- Magnolol, Honokiol [R]
- Ginger [R]
- Baicalin [R]
- Resveratrol [R]
- Licorice [R]

Cytochrome P450 Enzymes

Some cytochrome P450 enzymes are responsible for metabolizing PUFAs, particularly in the liver. These enzymes are involved in the breakdown of various fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Efficiency in the breakdown of PUFAs is crucial for maintaining overall health and regulating inflammation and other physiological processes. The efficiency of this process can vary between individuals and may be influenced by factors such as genetics, diet, and overall health.

Cytochrome P450 (CYP) enzymes are a family of enzymes involved in the metabolism of a wide range of compounds, including polyunsaturated fatty acids (PUFAs). The specific CYP enzyme that breaks down PUFAs can vary depending on the type of PUFA and the specific metabolic pathway.

Here are a few examples:

Arachidonic Acid (AA) Metabolism: Arachidonic acid, an omega-6 PUFA, is metabolized by several CYP enzymes, including **CYP2C8**, **CYP2C9**, and **CYP2J2**. These enzymes are involved in the conversion of arachidonic acid into various eicosanoids, including prostaglandins, epoxyeicosatrienoic acids (EETs), and hydroxyeicosatetraenoic acids (HETEs).

- **CYP2C8 Compounds**: [R]

  Salvianolic acid (Dan shen), Birch bark, Salicylic acid (White willow bark), Quercetin/Rutin (Sophora japonica), CoQ10 (Liver extract).

- **CYP2C9 Compounds**: [R]

  Salicylic acid (White willow bark), Curcumin, Glycyrrhizic acid (Licorice), Quercetin/Rutin (Sophora japonica), Rhein (Chinese rhubarb), Daidzein (Kudzu), Hesperetin (Citrus), Fisetin (Strawberry), Resveratrol (Japanese knotweed), Baicalein (Skullcap), Emodin (Japanese knotweed/Rhubarb), Capsaicin (Cayenne).

- **CYP2J2 Compounds**: [R]

  Formic acid (Stinging nettle).

Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) Metabolism: Omega-3 PUFAs, such as EPA and DHA, can also be metabolized by various CYP enzymes. For example, CYP2C9, **CYP2C19**, and CYP2J2 are involved in the metabolism of EPA and DHA into bioactive compounds like epoxyeicosapentaenoic acids (EEQs) and epoxydocosapentaenoic acids (EDPs).

- **CYP2C19 Compounds**: [R]

  Limonene (Citrus), Salicylic acid (White willow bark), Capsaicin (Cayenne), Curcumin, Quercetin/Rutin (Sophora japonica), Daidzein (Kudzu), Isoliquiritigenin (Licorice), Baicalein (Skullcap), Naringenin (Citrus), Formic acid (Stinging nettle), Resveratrol (Japanese knotweed), Emodin (Japanese knotweed, Rhubarb), Ellagic acid (Pomegranate).

Omega-6 and Omega-3 Pathways: Different CYP enzymes are responsible for metabolizing omega-6 and omega-3 PUFAs through their respective metabolic pathways. The metabolism of omega-6 and omega-3 fatty acids involves various enzymatic pathways, including those mediated by cytochrome P450 (CYP450) enzymes. While multiple enzymes contribute to these pathways, specific CYP450 enzymes play a role in metabolizing fatty acids and generating bioactive lipid mediators. Here is a detailed list of some CYP450 enzymes involved in omega-6 and omega-3 fatty acid metabolism:

Omega-6 Fatty Acid Metabolism

CYP1A1, CYP1A2: These enzymes are involved in metabolizing arachidonic acid (AA) into various epoxyeicosatrienoic acids (EETs) and hydroxyeicosatetraenoic acids (HETEs), which play roles in inflammation and vascular regulation.

- **CYP1A1 & CYP1A2 Compounds**: [R, R]

  Diosmin (Citrus), Naringenin (Citrus), Hesperetin (Citrus), Quercetin/Rutin (Sophora japonica), Formic acid (Stinging nettle), Resveratrol (Japanese knotweed), Ellagic acid (Pomegranate), Curcumin, Vitamin C, Sulforaphane/Indole-3-carbinol (Broccoli sprouts), Capsaicin (Cayenne), Salicylic acid (White willow bark), Rhein (Rhubarb), Daidzein (Kudzu), Luteolin (Parsley, Olive oil), Baicalein (Skullcap).

CYP2C8, CYP2C9, CYP2C19: These enzymes contribute to the metabolism of AA into EETs, affecting vascular tone and inflammation.

- **CYP2C8, CYP2C9, & CYP2C19 Compounds**: [R, R, R]

  Salvianolic acid (Dan shen), Limonene (Citrus), Diosmin (Citrus), Birch bark, Salicylic acid (White willow bark), Quercetin/Rutin (Sophora japonica), Formic acid (Stinging nettle), Rhein (Rhubarb), Curcumin, Glycyrrhizic acid (Licorice), Daidzein (Kudzu), Fisetin (Strawberry), Ellagic

acid (Pomegranate), Resveratrol (Japanese knotweed), Baicalein (Skullcap), Emodin (Japanese knotweed, Rhubarb).

CYP2J2: Involved in the metabolism of AA into EETs, which have vasodilatory and anti-inflammatory effects.

- **CYP2J2 Compounds**: [R]

  Formic acid (Stinging nettle)

Omega-3 Fatty Acid Metabolism

CYP2C8, CYP2C9, CYP2C19: These enzymes contribute to the metabolism of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into epoxyeicosatetraenoic acids (EEQs) and epoxydocosapentaenoic acids (EDPs), which may have anti-inflammatory properties.

- **CYP2C8, CYP2C9, & CYP2C19 Compounds**: [R, R, R]

  Salvianolic acid (Dan shen), Limonene (Citrus), Diosmin (Citrus), Birch bark, Salicylic acid (White willow bark), Quercetin/Rutin (Sophora japonica), Formic acid (Stinging nettle), Rhein (Rhubarb), Curcumin, Glycyrrhizic acid (Licorice), Daidzein (Kudzu), Fisetin (Strawberry), Ellagic acid (Pomegranate), Resveratrol (Japanese knotweed), Baicalein (Skullcap), Emodin (Japanese knotweed, Rhubarb).

CYP4A, CYP4F: These enzymes catalyze the conversion of EPA and DHA into omega-3 hydroxyeicosapentaenoic acids (HEPEs) and omega-3 hydroxydocosahexaenoic acids (HDHAs), respectively, which are precursors to various bioactive lipid mediators, including some specialized pro-resolving mediators (SPMs).

- **CYP4A & CYP4F Compounds**: [R, R]

  Lauric acid (Coconut), Coumarin (Cinnamon), NADPH/CoQ10 (Liver Extract)

Additional Notes:

- While CYP450 enzymes are involved in the metabolism of omega-6 and omega-3 fatty acids, the pathways are complex and involve multiple enzymatic reactions.

- Other enzymes such as lipoxygenases (LOX) and cyclooxygenases (COX) are also critical in metabolizing these fatty acids into various bioactive lipid mediators, including prostaglandins, leukotrienes, and SPMs.

The exact CYP enzymes involved in PUFA metabolism may vary depending on the specific biological process and tissue type. It's important to note that CYP enzymes are part of a complex network of enzymes responsible for the metabolism of various compounds in the body.

The metabolism of PUFAs and the production of bioactive lipid mediators play critical roles in inflammation, blood clotting, and other physiological processes. The balance between omega-6 and omega-3 PUFAs and their respective metabolic pathways can influence overall health and inflammation regulation.

Enzymes in Peroxisomes

Some PUFAs, especially very-long-chain PUFAs, may be metabolized in **peroxisomes (PPARG)**, specialized cell organelles involved in fatty acid oxidation.

The Role of PPARG in Inflammation through Polyunsaturated Fatty Acids & SPMs

PPARG is the **MASTER REGULATOR OF FAT CELLS** [R]. Many naturally occurring agents directly bind with and activate PPAR gamma. These agents include various polyunsaturated fatty acids like arachidonic acid and arachidonic acid metabolites.

Peroxisome proliferator-activated receptor gamma (PPARγ) is implicated in regulating inflammation through its interaction with polyunsaturated fatty acids (PUFAs) and their derivatives, specialized pro-resolving mediators (SPMs).

1. **Modulation of Inflammation:** PPARγ activation can regulate the expression of genes involved in inflammation. By doing so, it may help to suppress the production of pro-inflammatory cytokines, reduce the activation of inflammatory signaling pathways, and promote anti-inflammatory responses.

2. **Impact on PUFA Metabolism:** PPARγ is involved in regulating the metabolism of PUFAs, including omega-3 and omega-6 fatty acids. It modulates the expression of enzymes responsible for PUFA metabolism, influencing the availability of fatty acid substrates for the synthesis of SPMs.

3. **SPM Biosynthesis:** PPARγ activation can potentially influence the biosynthesis of SPMs derived from PUFAs. SPMs, such as resolvins, protectins, and maresins, are bioactive lipid mediators with potent anti-inflammatory and pro-resolving properties. PPARγ activity may impact the

production of these mediators by regulating enzymes involved in their biosynthetic pathways.

4. **Resolution of Inflammation:** SPMs are crucial for the resolution of inflammation, promoting the clearance of inflammatory cells, reducing pro-inflammatory signals, and facilitating tissue repair. PPARγ activation might contribute to the resolution phase of inflammation by supporting the generation of SPMs.

5. **Anti-inflammatory Effects:** PPARγ activation may lead to decreased inflammation by indirectly promoting the synthesis of SPMs, which, in turn, facilitate the resolution of inflammatory processes, promoting tissue homeostasis.

- **Therapeutics for Peroxisome proliferator-activated receptor gamma (PPARγ)**: [R]

  Abietic acid (Pine), Curcumin, Salicylic acid (White willow bark), Linoleic acid (Flax), Oleic Acid (Olive), Alpha-Linolenic Acid (Borage), Omega-3 fatty acid (Algal oil), Palmitic Acid (Red Palm Oil), Stearic acid (Coconut), Capric acid (Coconut), Daidzein (Kudzu), Hesperetin (Citrus), Butyric Acid (Inulin FOS), Myristic acid (Coconut), Arachidonic Acid (Cupuaçu Butter), Resveratrol (Japanese knotweed), Glabridin (Licorice), Oleuropein (Olive oil), Phosphatidylcholine (Sunflower Lecithin).

The breakdown of polyunsaturated fatty acids (PUFAs) in peroxisomes primarily involves a family of enzymes called **acyl-CoA oxidases**, which are responsible for the initial steps of fatty acid oxidation.

Acetyl Coenzyme A is the condensation product of coenzyme A and acetic acid which participates in the **biosynthesis of fatty acids and sterols**, in the oxidation of fatty acids and in the metabolism of many amino acids.

Coenzyme A (CoA) was discovered by Fritz Lipmann and his colleagues in the early 1950s. The coenzyme was first isolated from **liver extracts** [R]

The Role of Coenzyme A in Fatty Acid Metabolism & SPMs

Coenzyme A (CoA) is an essential molecule involved in various metabolic processes within the body, including **fatty acid metabolism** and the biosynthesis of **specialized pro-resolving mediators (SPMs)**.

1. **Fatty Acid Metabolism:** Coenzyme A plays a pivotal role in fatty acid metabolism. It acts as a carrier molecule, **facilitating the transport of fatty acids into the mitochondria for β-oxidation**, a process where fatty acids are broken down to generate energy. During β-oxidation, CoA helps in the formation of acetyl-CoA, which subsequently enters the citric acid cycle (also known as the Krebs cycle) to produce energy in the form of ATP.

2. **SPM Biosynthesis:** Specialized pro-resolving mediators (SPMs) are crucial in resolving inflammation and promoting tissue repair. Coenzyme A indirectly participates in the biosynthesis of SPMs by aiding in the metabolism of fatty acids. Precursors such as EPA and DHA undergo enzymatic transformations involving lipoxygenase and cyclooxygenase enzymes to produce SPMs like resolvins, protectins, and maresins.

While Coenzyme A is not directly involved in the synthesis of SPMs, its role in fatty acid metabolism indirectly contributes to the availability of essential fatty acids that serve as precursors for the production of these specialized lipid mediators.

Understanding the interplay between Coenzyme A, fatty acid metabolism, and the biosynthesis of SPMs provides insights into the intricate metabolic processes that support the resolution of inflammation and overall cellular health.

Beta-Oxidation

PUFAs can also undergo beta-oxidation, a metabolic process that breaks down fatty acids to produce energy. This process occurs in the **mitochondria** of cells.

The primary genes and pathways involved in beta-oxidation, the metabolic process responsible for breaking down fatty acids, are coordinated by various enzymes and proteins within specific cellular compartments. The process occurs in multiple steps, and several genes encode enzymes that facilitate these steps:

1. **Acyl-CoA Dehydrogenases:** Genes such as **ACADM**, **ACADL**, **ACADS**, and **ACADVL** encode different forms of acyl-CoA dehydrogenases. These enzymes catalyze the initial step of beta-oxidation by oxidizing fatty acyl-CoA molecules to produce trans-enoyl-CoA.

    - **Compounds for Acyl-CoA Dehydrogenases**: [R, R, R, R]

        - Riboflavin/Flavin adenine dinucleotide (**Liver Extract**), Pantothenic Acid (**Liver Extract**), Pristanic acid (**Liver Extract**), Acetyl L-Carnitine, Butyrate (Inulin FOS).

2. **Enoyl-CoA Hydratases: EHHADH** and **ECHS1** are genes that code for enoyl-CoA hydratases. These enzymes act to hydrate the trans-enoyl-CoA molecules produced in the previous step, forming L-3-hydroxyacyl-CoA.

- **Compounds Enoyl-CoA Hydratases**: [R, R]

    - Coenzyme A (**Liver Extract**), Vitamin B3 (**Liver Extract**), Salicylic acid (White willow bark).

3. **3-Hydroxyacyl-CoA Dehydrogenases: HADHA** and **HADHB** genes encode 3-hydroxyacyl-CoA dehydrogenase enzymes. These enzymes catalyze the oxidation of L-3-hydroxyacyl-CoA to produce 3-ketoacyl-CoA.

    - **Compounds for 3-Hydroxyacyl-CoA Dehydrogenases**: [R, R]

        - Citric acid (Garcinia Cambogia), Coenzyme A (Liver Extract), Vitamin B3 (Liver Extract), Salicylic acid (White willow bark), Calcium D-Pantothenate, Phosphatidylcholine (Sunflower Lecithin), Adenosine (Cordyceps).

4. **Beta-Ketothiolase:** The **ACAA1** gene encodes the beta-ketothiolase enzyme, which is responsible for cleaving 3-ketoacyl-CoA into acetyl-CoA and a shorter acyl-CoA chain.

    - **Compounds for Beta-Ketothiolase**: [R]

        - Coenzyme A (Liver Extract), Vitamin B3 (Liver Extract), Phosphatidylcholine (Sunflower Lecithin), Anthranilic Acid (White willow bark), Phytanic acid (Chlorophyll/Chlorella), Jasmonic acid (Jasmine).

5. **Carnitine Shuttle System:** Genes including **CPT1A**, **CPT2**, and **SLC25A20** encode proteins involved in the carnitine shuttle system. This system transports long-chain fatty acids into the mitochondria for beta-oxidation.

    - Compounds for Carnitine Shuttle System & Fatty Acid Metabolism: [R, R, R, R, R]

        - Polysaccharides, Hyaluronic acid, Heparin (Natto), Acetyl L-Carnitine, Coenzyme A (Liver Extract), Phytanic acid (Chlorophyll/Chlorella), Citric acid (Garcinia Cambogia), Alpha-lipoic acid (Liver Extract, Broccoli Sprouts), Indole-3-carbinol (Broccoli Sprouts), Silibinin (Milk Thistle), Quercetin (Sophora Japonica), Guanine (Pine), Lycopene (Tomato), Lutein, Zeaxanthin, TUDCA, Vitamin C (Acerola), Curcumin, Acetylcholine (Sunflower Lecithin), Taurine, Arginine, Glutamic acid (Alpha-Ketoglutarate), Pristanic acid (Liver Extract).

These genes and their encoded proteins participate in the sequential enzymatic reactions that occur during beta-oxidation. This process involves the repetitive removal of two-carbon units from fatty acyl-CoA molecules, producing **acetyl-CoA, which subsequently enters the citric acid cycle for energy production**.

The pathways involved in beta-oxidation are essential for energy production, especially during periods of increased energy demand or when glucose availability is limited, such as during fasting or prolonged exercise. Dysfunction or mutations in these genes can lead to various metabolic disorders impacting fatty acid metabolism.

The Role of The NLRP3 Inflammasome with SPMs

The NLRP3 inflammasome is a multi-protein complex that plays a **significant role in the innate immune response by promoting the maturation and release of pro-inflammatory cytokines**, particularly **interleukin-1 beta (IL-1β) and interleukin-18 (IL-18)**. Specialized pro-resolving mediators (SPMs) act as resolution mediators in the immune system and have been shown to modulate the NLRP3 inflammasome.

Therapeutics that Target the NLRP3 Inflammasome: [R]

- Andrographis
- Licorice
- Panax Ginseng
- Resveratrol
- Quercetin

Therapeutics for Interleukin-1 beta (IL-1β) and Interleukin-18 (IL-18): [R, R]

- Hyaluronic acid, Glucosamine, Salicylic acid (White willow bark), Resveratrol (Japanese knotweed), Ginsenoside (Panax Ginseng), Curcumin, Rhein (Rhubarb), Quercetin (Sophora japonica), Taurine, Acetylcholine (Sunflower Lecithin), White tea extract.

SPMs, such as resolvins, protectins, and maresins, derived from omega-3 fatty acids, exhibit potent anti-inflammatory and pro-resolving actions. They exert their effects by promoting the resolution of inflammation, clearing cellular debris, and facilitating tissue repair after an inflammatory response. Specifically, SPMs can regulate the NLRP3 inflammasome through various mechanisms:

1. **Inhibition of NLRP3 Activation:** SPMs have been observed to inhibit the activation of the NLRP3 inflammasome. By downregulating the NLRP3

signaling pathway, SPMs help suppress the release of pro-inflammatory cytokines, thereby dampening excessive inflammation.

2. **Reduced Pro-inflammatory Cytokine Production:** SPMs modulate the production and release of pro-inflammatory cytokines, such as IL-1β and IL-18, which are regulated by the NLRP3 inflammasome. By limiting the production of these cytokines, SPMs contribute to resolving inflammation.

3. **Enhanced Resolution of Inflammation:** SPMs promote the active resolution of inflammation by stimulating the clearance of inflammatory cells and debris, facilitating tissue repair and regeneration.

The interaction between SPMs and the NLRP3 inflammasome represents a key mechanism through which resolution of inflammation is achieved. SPMs exert their anti-inflammatory and pro-resolving effects by modulating the NLRP3 inflammasome, contributing to the restoration of tissue homeostasis and promoting the resolution of inflammatory processes.

The Role of SPMs in Cytokine Storms

Specialized pro-resolving mediators (SPMs) play a critical role in mitigating and regulating cytokine storms, which are characterized by an overwhelming and dysregulated release of pro-inflammatory cytokines. These storms are often observed in severe inflammatory conditions, such as certain infections, autoimmune diseases, and acute respiratory distress syndrome (ARDS), including cases seen in severe COVID-19 infections.

Here's how SPMs contribute to managing cytokine storms:

1. **Anti-inflammatory Effects:** SPMs exhibit potent anti-inflammatory properties by inhibiting the production and release of pro-inflammatory cytokines, including **tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6)**, and previously mentioned interleukin-1 beta (IL-1β). These are the primary cytokines involved with proinflammatory cytokine storms.

2. **Resolution of Inflammation:** These mediators actively facilitate the resolution of inflammation by enhancing the clearance of inflammatory cells, debris, and apoptotic cells, thereby promoting tissue repair and regeneration.

3. **Balancing the Immune Response:** SPMs help regulate the immune response by promoting the transition from the inflammatory phase to the resolution phase, preventing excessive and sustained inflammation.

4. **Restoring Tissue Homeostasis:** By modulating the inflammatory response, SPMs aid in restoring tissue homeostasis, which is crucial in controlling the severity and duration of cytokine storms.

In situations where cytokine storms contribute to severe tissue damage and complications, the administration or enhancement of SPMs could potentially offer therapeutic benefits by promoting the resolution of excessive inflammation.

Cytokine storms involve a complex interplay of various genes, signaling pathways, and immune responses. While multiple genes and pathways contribute to cytokine storms, here are some key components:

1. **Cytokines and Chemokines:** Genes related to the production of pro-inflammatory cytokines storms are primarily **tumor necrosis factor-alpha (TNF-α)**, **interleukin-6 (IL-6), interleukin-8 (IL-8),** and previously mentioned **interleukin-1 beta (IL-1β)**.

- **Therapeutics for TNF-α, IL-6, and IL-8**: [R, R, R]

    - Curcumin, Glycyrrhizic acid (Licorice), Rutin (Sophora japonica), Glucosamine, Hyaluronic acid, Butyric Acid (Inulin FOS), Andrographolide (Andrographis), Ginsenoside (Panax Ginseng), Magnolol (Magnolia Bark), Tanshinone IIA (Dan Shen), White Tea Extract, Salicylic Acid (White Willow Bark), Heparin (Natto), Vitamin C (Acerola), Taurine, 4,5-Dicaffeoylquinic acid (Garcinia cambogia), Heparin (Natto), Emodin (Japanese knotweed/Rhubarb), Echinacea.

2. **NF-κB (Nuclear Factor-kappa B) Pathway:** This signaling pathway regulates the expression of genes involved in inflammation, immunity, and cell survival. Activation of NF-κB induces the production of pro-inflammatory cytokines and chemokines, contributing to cytokine storms.

    - **Therapeutics for NF-κB**: [R]

        - Andrographolide (Andrographis), Tanshinone IIA (Dan Shen), Glycyrrhizic acid (Licorice), Fish oil (Algal oil), TUDCA, Rutin/Quercetin (Sophora japonica), Luteolin (Parsley, Olive oil), Diosmetin (Citrus), Emodin (Japanese knotweed/Rhubarb), White tea extract, Resveratrol (Japanese knotweed), Ginsenoside (Panax Ginseng), Honokiol (Magnolia Bark), Schisantherin A (Schisandra Berry), Withaferin A (Ashwagandha).

3. **JAK-STAT (Janus Kinase-Signal Transducer and Activator of Transcription) Pathway:** The JAK-STAT pathway is crucial for signal transduction of many cytokines. Dysregulated activation of this pathway can lead to the uncontrolled production of inflammatory mediators.

    - **JAK/STAT Inhibitors**:

- Grape Seed Extract (R)
- Broccoli sprouts/Cruciferous veggies/Sulforaphane (R)
- Boswellia/Boswellic Acid (R)
- Capsaicin/Chili (R)
- Curcumin (R)
- Black Seed Oil/Nigella sativa (R)
- Resveratrol (R)
- Quercetin (R)

4. **NLRP3 Inflammasome:** Genes associated with the NLRP3 inflammasome, a multiprotein complex that triggers the maturation and release of IL-1β and IL-18, can contribute to cytokine storms when activated excessively.

    - Natural Products that Target the NLRP3 Inflammasome [R]
        - Andrographis
        - Licorice
        - Panax Ginseng
        - Resveratrol
        - Quercetin

5. **Complement System Genes:** Components of the complement system, including **C3a** and **C5a**, can stimulate the release of pro-inflammatory cytokines and exacerbate immune responses.

    - **Therapeutics for C3a and C5a**: [R, R]
        - Oleic Acid (Olive oil), Mannose, Polysaccharides, Heparin (Natto), Lecithin, NADPH (Liver Extract), Adenosine (Cordyceps).

6. **Genes Involved in Adaptive Immune Response:** Genes related to T-cell activation, proliferation, and differentiation can also influence the severity of cytokine storms by contributing to an exaggerated immune response. **SRC Family Kinases and SYK Kinase** are the primary targets.

    - **SRC and Spleen Tyrosine Kinase Compounds**: [R]

        - Resveratrol (Japanese knotweed), Nattokinase (Heparin), Capsaicin (Cayenne), Pycnogenol (Pine bark), Piceatannol (Japanese knotweed), Hesperadin (Citrus), Curcumin, Acetylcholine (Sunflower Lecithin), Butyric acid (Inulin FOS), Tanshinone I (Dan Shen), Ginger, Licorice, Chinese skullcap, Ellagic acid (Pomegranate), Epigallocatechin gallate (White tea extract). [R]

During a cytokine storm, a cascade of events involving these genes and pathways leads to an amplified and dysregulated immune response, resulting in an excessive release of pro-inflammatory cytokines, tissue damage, and potential multi-organ failure. The intricate interactions between these genetic elements and signaling pathways contribute to the pathogenesis and severity of cytokine storms in various inflammatory conditions and infectious diseases.