Casual Friday Series

Atherosclerosis: The Beginning and the End

A BIOGENETIX CLINICAL PRESENTATION

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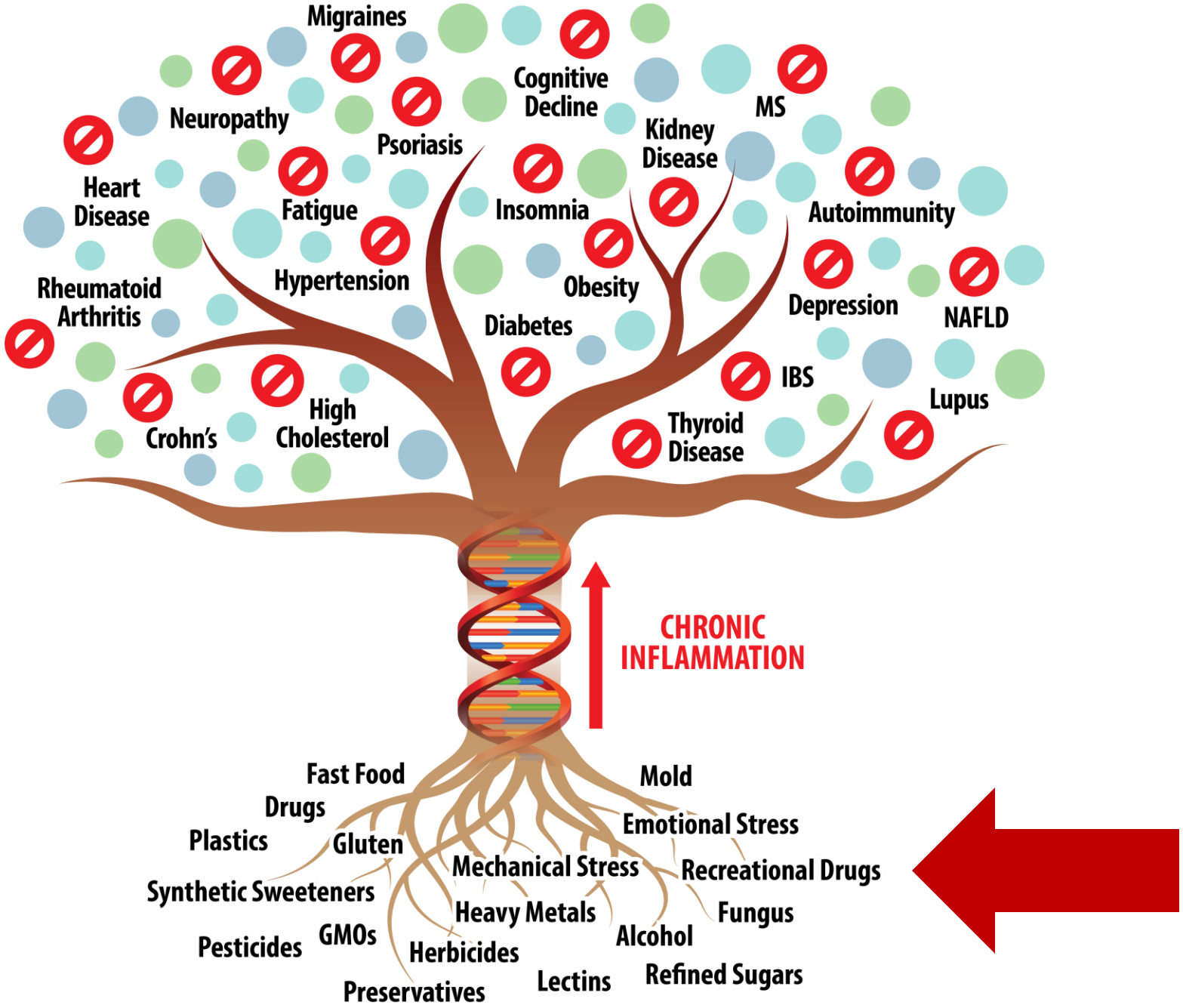
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Mold
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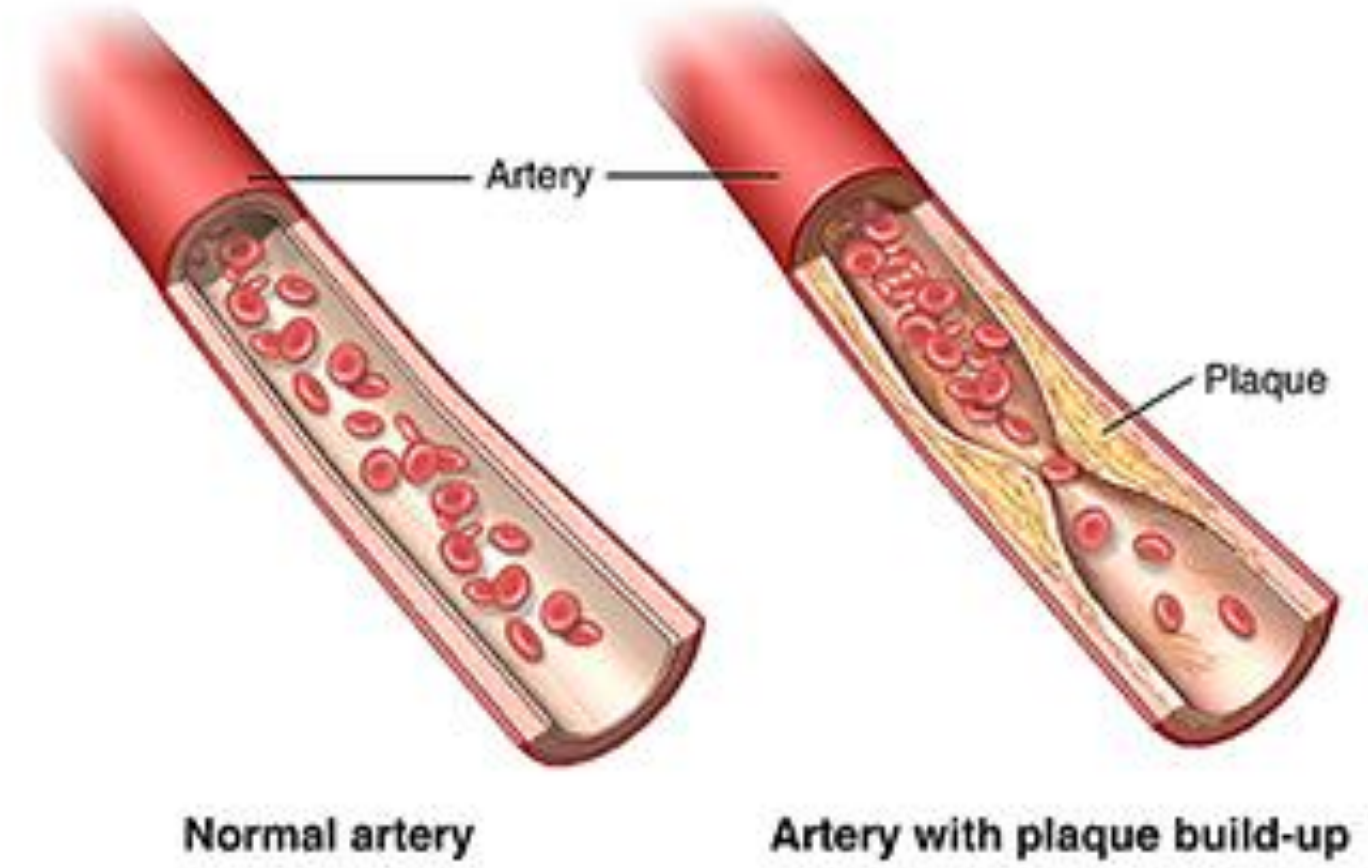
Atherosclerosis



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Atherosclerosis

In the United States, about 610,000 people die of heart disease every year. That is 1 of every 4 deaths. Coronary heart disease is the leading cause of death in the Western world killing over 370,000 people annually. On an average, about 735,000 Americans have a heart attack every year. Out of these, 525,000 have an initial attack, and 210,000 have a recurrent attack. It has been reported that 75% of acute myocardial infarctions occur from plaque rupture and the highest incidence of plaque rupture was observed in men over 45 years; whereas, in women, the incidence increases beyond age 50 years. This higher prevalence of atherosclerosis in men compared to women is attributed to the protective function of female sex hormones but is lost after menopause.

Stroke from any cause represents the fifth leading cause of death and the major cause of serious long-term disability in adults in the United States. It is reported that nearly 795,000 people suffer from stroke every year in the US resulting in about 140,323 deaths. The major form of stroke, ischemic stroke is due to ASCVD.

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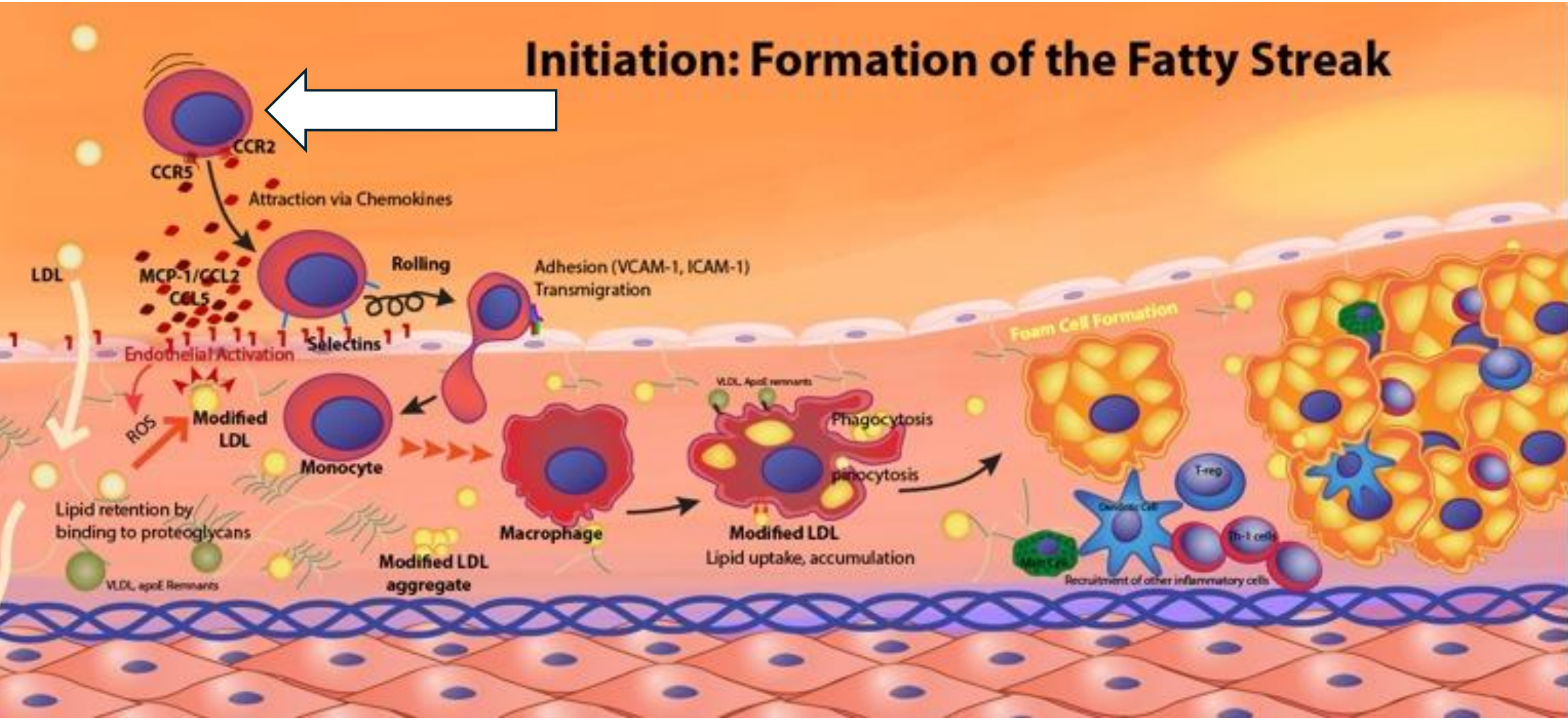

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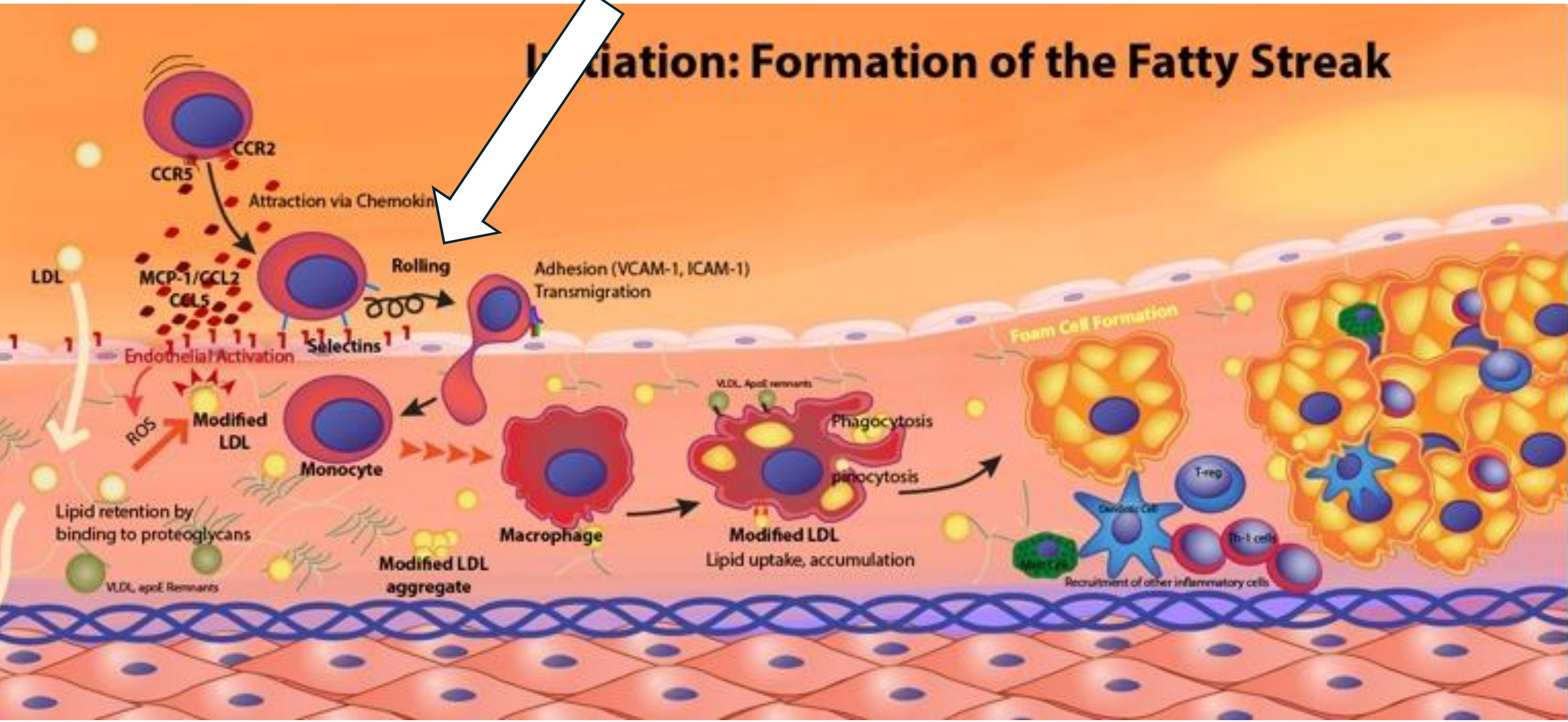

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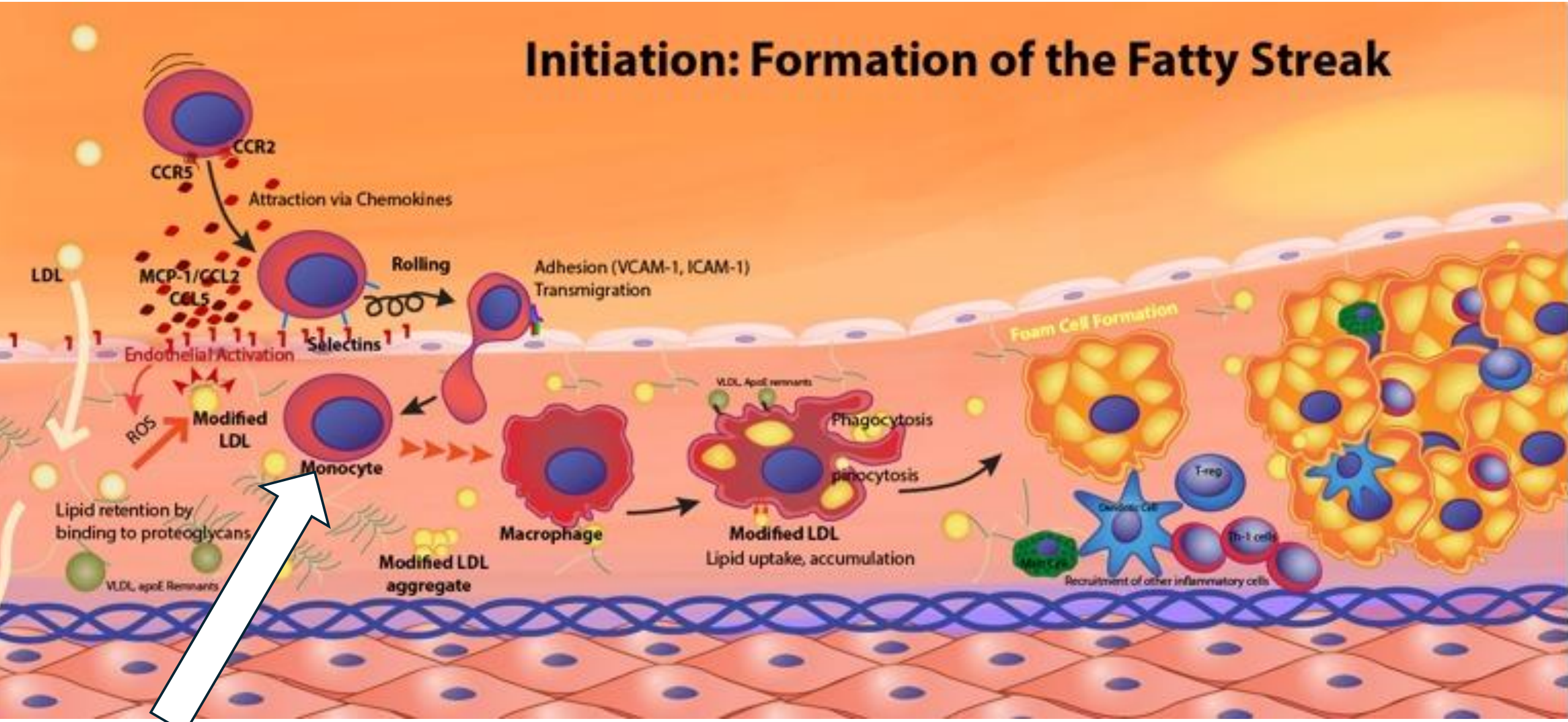

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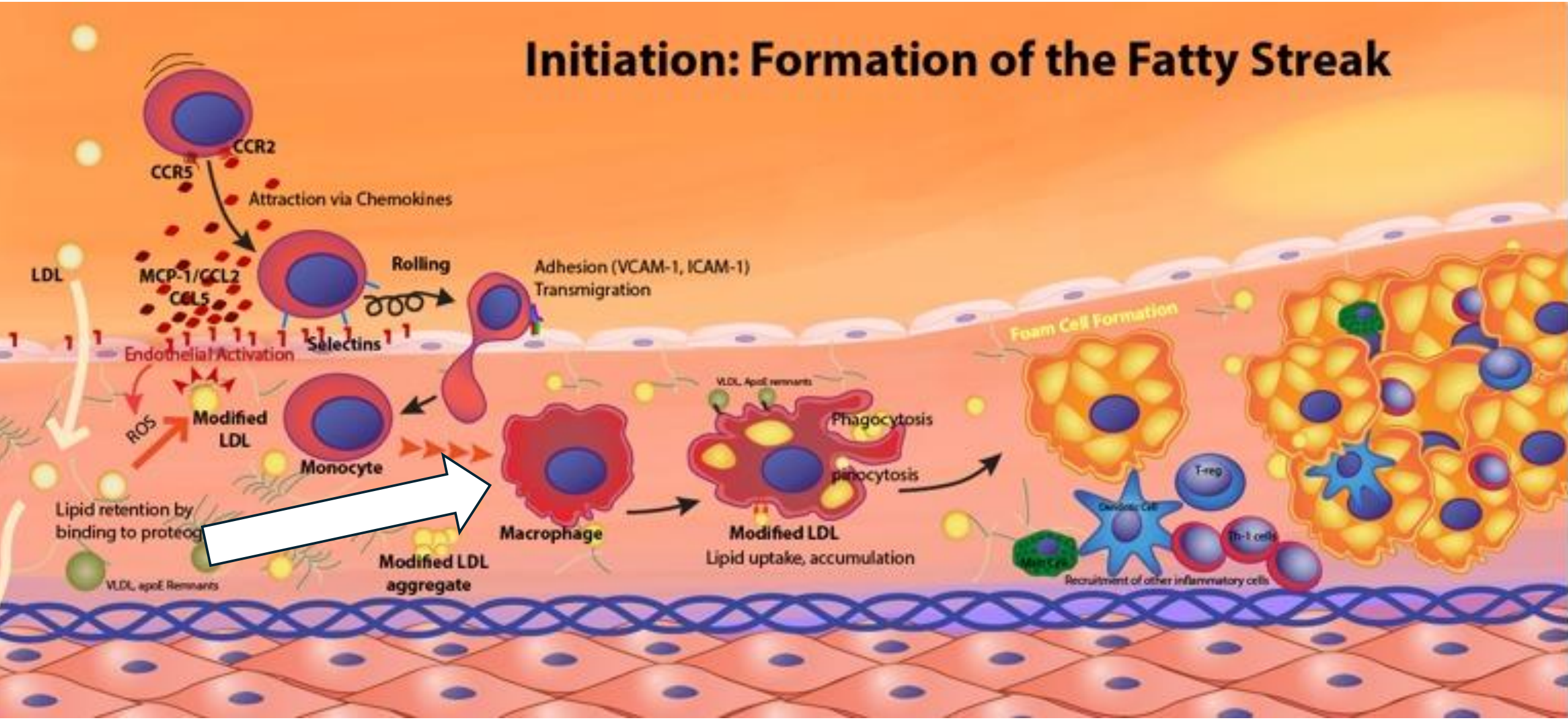

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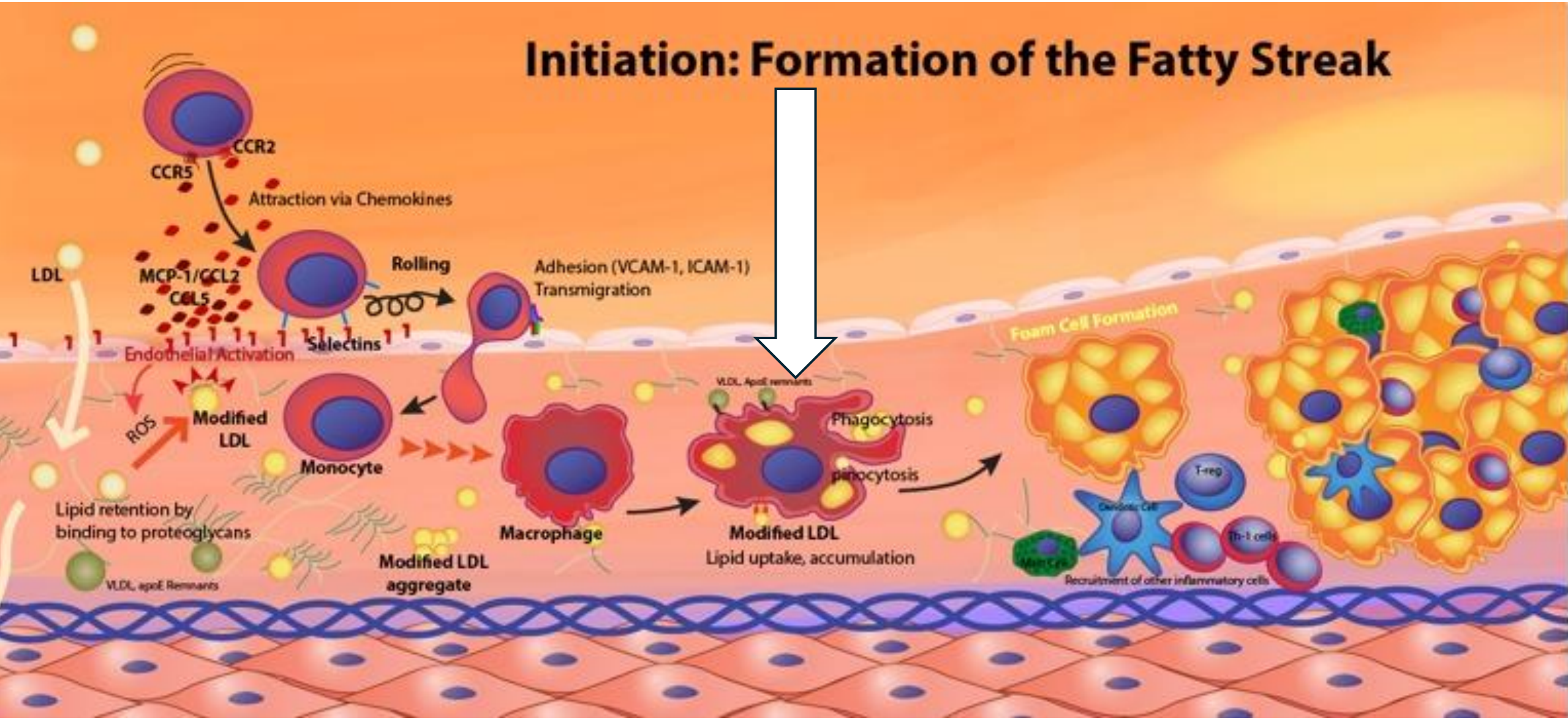

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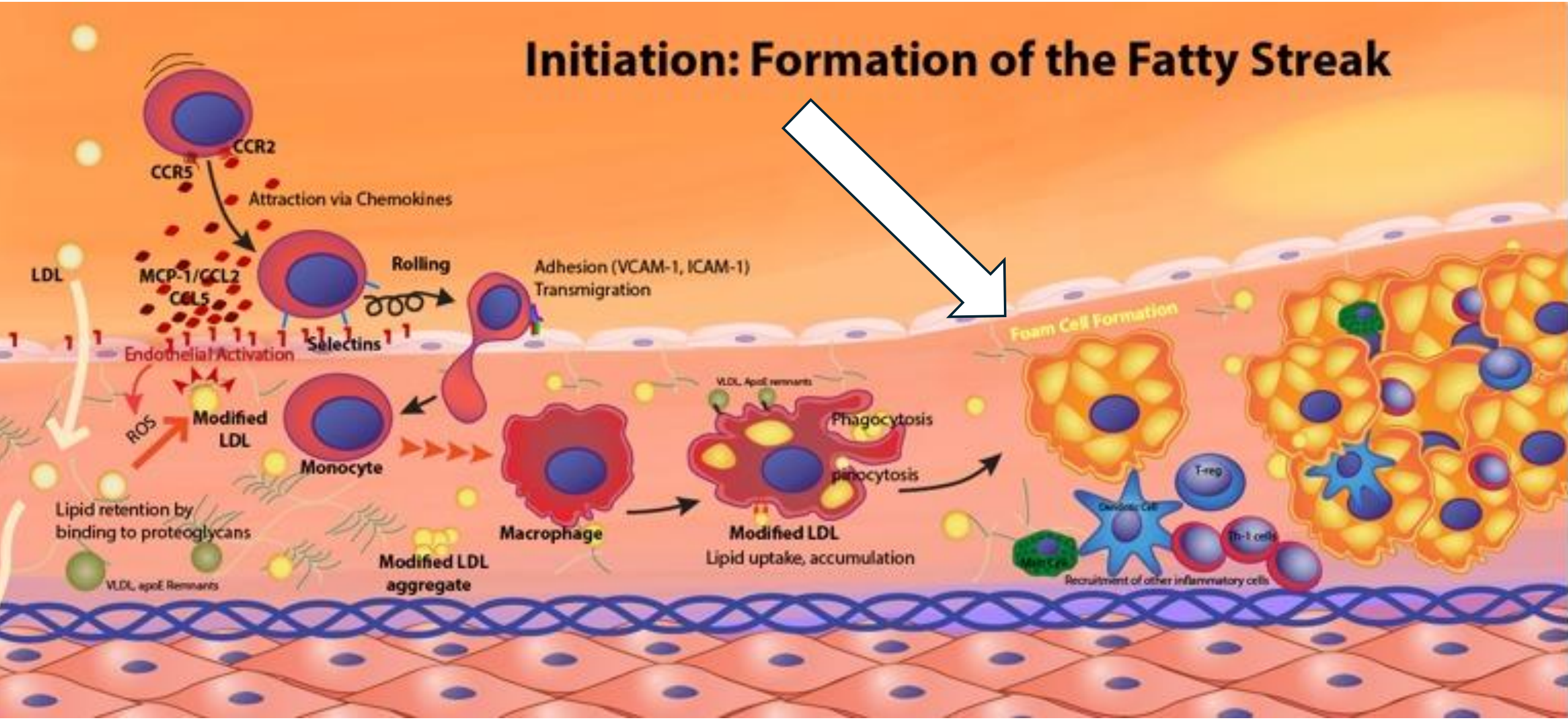

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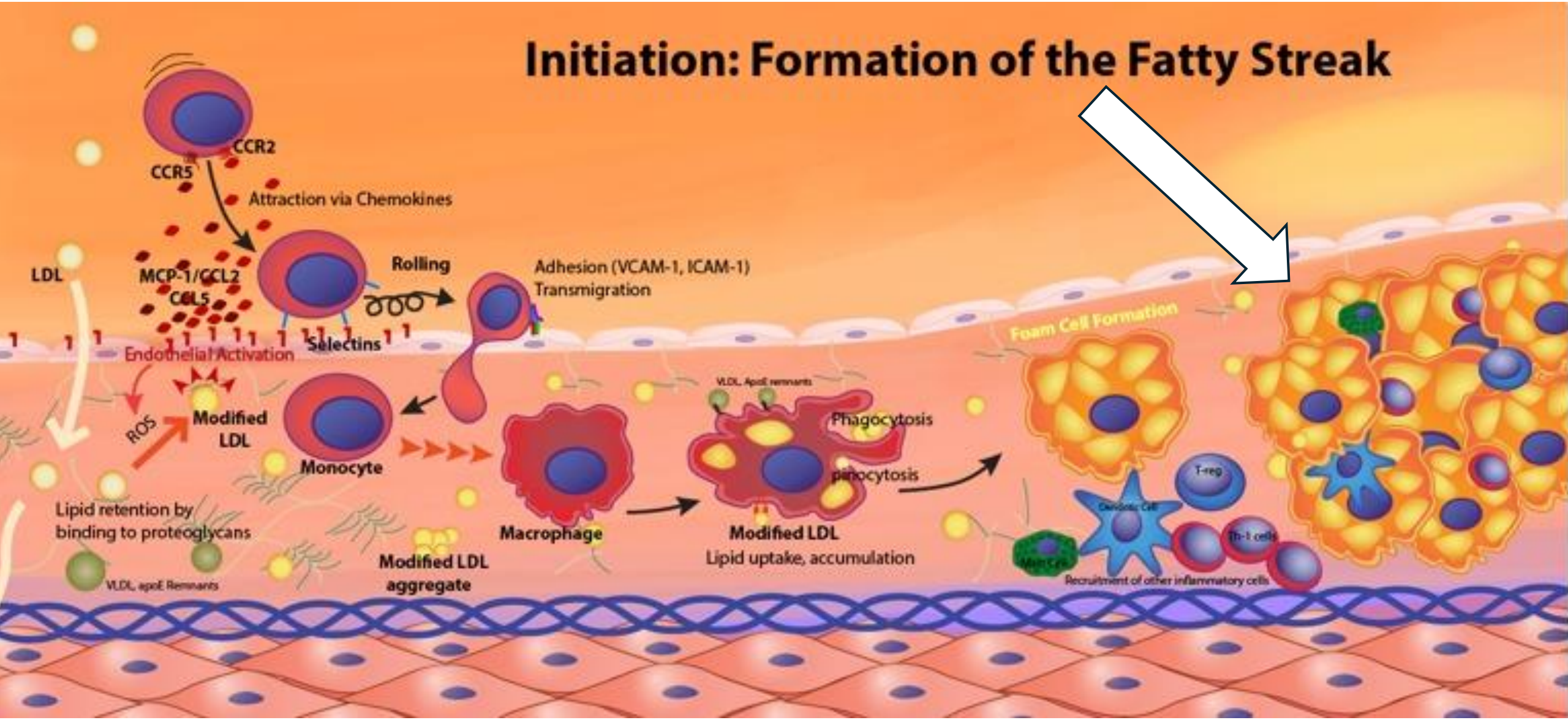

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The Early Fatty Streak Phase

Early fatty streak lesions begin in childhood. The adaptive intimal thickening is present from birth and grows in areas of a high oscillatory shear index where it is characterized by retention of modified lipoproteins in the intima. A characteristic of atherosclerosis-prone areas is an upregulation of nuclear factor-kappaB (NF-kB), a pivot in the inflammatory cascade. Areas of uniform laminar flow trigger an upregulation of Kruppel-like factor (KLF)-2 and 4 in endothelium resulting in athero-protective endothelium typified by anti-inflammatory and anti-thrombotic phenotype. As the LDL particles leave the blood and enter the arterial intima, they accumulate by being trapped by proteoglycans and are modified. While the modifications of LDL are not elucidated, oxidative modification generating oxidized LDL appears to be an attractive candidate.

Typically, endothelial dysfunction induced by proinflammatory stimuli may disrupt the endothelial barrier or microtubule function leading to increased junctional permeability manifested by transendothelial migration of immune cells and atherogenic lipoproteins into the arterial intima. Further, the monocytes in intima mature into resident macrophages via macrophage colony-stimulating factor (M-CSF), imbibe modified lipids and become foam cells the characteristic feature of the early fatty streak lesion.

Advancing Atheroma: Thin-Cap Fibroatheroma and Its Rupture

Advancing atheroma appear at about age 55 to 65 years. Plaque rupture, for example, vulnerable plaques, are dictated by a thin, fibrous cap with low, smooth, muscle cell (SMC) density, abundant lipid, and macrophages, and enriched in tissue factor in the cells. The thin-cap atheroma is surrounded by a necrotic core heavily infested by cholesterol-enriched macrophages, cholesterol crystals and T lymphocytes and susceptible to rupture. The fibrous cap is weakened due to uncontrolled proteolytic enzyme activity, for example, matrix metalloproteinases (MMPs) which expose the intima and produce a thrombus via tissue-factor activation and platelet aggregation that extends into the arterial lumen. This lesion is most frequently known as a vulnerable plaque because of the risk of rupture and life-threatening thrombosis.

Plaque Rupture

This is the region of fibrous cap rupture in which the overlying thrombus interacts with the original necrotic core and is frequently found in the proximal left anterior descending coronary artery, followed by the left and right circumflex coronary arteries. The causes of plaque rupture are not well studied, but main factors include expression of enzymes like MMPs, Myeloperoxidase produced by inflammatory cells that weaken the fibrous cap, high-shear arterial regions, macrophage calcification, and iron deposition.

Growth and Development of the Necrotic Core

This is an important pathogenic process contributing to plaque vulnerability. Studies have shown that repeat intraplaque hemorrhage is a contributing feature to necrotic core expansion as red blood cells are enriched with lipids and a rich source of free cholesterol, which is an important constituent of ruptured plaques.

Many studies indicate the role of the endoplasmic reticulum stress pathway or unfolded protein response as the chief mechanisms of macrophage cell death in plaques causing accumulation of dead macrophages. Also in comparison to early plaques, microvessel density is increased in advanced plaques by a dysregulated neovascularization. In normal and atherosclerotic arteries microvessels are thin-walled and characterized with poor structural integrity and endothelial junctions. Thus, intraplaque hemorrhage together with the death of macrophages coupled with defective phagocytic clearance is one of the primary reasons behind necrotic core expansion in advance stage. Healed plaque ruptures can be easily detected microscopically by identification of disruptions in the fibrous cap in healed lesions consisting of proteoglycans and/or collagen.

Plaque Erosion

It is widely accepted that thrombi may occur due to plaque rupture, plaque erosion, or, rarely, a calcified nodule. In a study on 20 patients who died of acute myocardial infarction, it was found that 60% of patients had plaque ruptures and the remaining 40% had superficial erosion. Plaque erosion is typically characterized by no endothelium at the site of erosion, minimal inflammation, and the exposed intima mainly composed of smooth muscle cells and proteoglycans.

Effective management of atherosclerosis progress and hyperlipidemia with nattokinase: A clinical study with 1,062 participants

Hongjie Chen [1], Jiepeng Chen [2], Fuping Zhang [3], Yuanhui Li [4], Ronghua Wang [2], Qiang Zheng [2], Xu Zhang [2], Jun Zeng [2], Feng Xu [5,*], Yiguang Lin [1,6,7,*]

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PMCID: PMC9441630 PMID: 36072877

Nattokinase (NK), the most active ingredient in natto with an alkaline protease of 275 amino acid residues, molecular weight approximately 28 kDa, was first discovered by Sumi et al. in 1987 (1). It is a potent fibrinolytic enzyme (2) demonstrating many favorable effects on cardiovascular health (3). The effects of NK include antihypertensive, anti-atherosclerotic, lipid lowering, anti-platelet and neuroprotective effects (3). Natto consumption is believed to be a significant contributor to the longevity of the Japanese population and a high intake of natto is associated with a decreased risk of total cardiovascular disease mortality (4). NK as a health supplement has been distributed throughout the world and has gained popularity among people who want to actively prevent cardiovascular disease.

Previous studies have demonstrated that NK and NK-containing natto have anti-atherosclerotic and lipid lowering effects (3, 5). Dietary natto extract supplementation suppresses intimal thickening in rats when compared to the control group (6, 7). The

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Chang et al. proposed that the natto extract suppressed intimal thickening through a synergistic effect attributed to its antioxidant and anti-apoptotic properties (8). Another study demonstrated that NK prevented arteriosclerosis by direct antioxidation leading to reduced lipid peroxidation and improved lipid metabolism (inhibition of LDL oxidation) (9). When used in combination with red ginseng, NK was found to reduce the area of aortic plaque in rabbits fed a hypercholesterol diet (10). We previously demonstrated that daily NK supplementation was an effective way to suppress the progression of atherosclerosis in patients with atherosclerotic plaques (5). In addition to its anti-atherosclerotic effects, NK or natto extract also has a favorable effect on lipids. Using NK or natto extract containing NK, animal studies from various laboratories confirmed that NK has a hypolipidemic effect and significantly reduces elevated serum triglycerides (TG), total cholesterol (TC) and low-density lipoprotein cholesterol levels (LDL-C) (10–16). Our studies found that in patients with hyperlipidaemia, NK treatment (26 weeks at 6,000 FU) reduced TC, LDL-C and TG, and increased the level of high-density lipoprotein cholesterol (HDL-C) (5).

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In the present study, we retrospectively analyzed data from 1,062 participants who received NK orally for 12 months to examine the safety and efficacy of NK in the treatment of atherosclerosis progression and hyperlipidemia. Multiple factors that may influence the effect of NK were also explored. This is the largest study to date designed to evaluate the clinical effects of NK in human subjects and to advance our understanding of the clinical potential of NK. We also provide novel insights into the optimal dose required for the most beneficial effects.

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Factors that may influence the effects of NK

The effect of NK can be influenced by factors such as gender, NK dosage, participant lifestyle, body mass index, smoking status, alcohol consumption, coadministration of other agents such aspirin and vitamin K2. In the current study, information related to these factors was used to examine whether they influenced the effect of NK.

When considering the amount of exercise, step counting is used as an index to categorize participants as sedentary or not. As described in previous studies (21), 5,000 steps per day were used as the cut-off point to classify participants into two groups: <5,000 steps / day (sedentary / non-exercise group) and >5,000 steps / day (non-sedentary / exercise group).

For most of the participants, the dose used in the study was 10,800 FU daily. A small dose of 3,600 FU per day was used in one group for comparison.

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Alcohol consumption was divided into two categories; consumption of alcohol over 100 g per week on average was categorized in the alcohol group and below 100 g per week was categorized in the non-alcohol group. The use of a threshold of 100 g/week is based on a previous study by Wood et al. (23).

The smoking group referred to subjects who smoked on a daily basis regardless of the number of cigarettes used per day and compared to non-smokers.

Some participants used vitamin K2 (180 µg/day) regularly in addition to NK. Therefore, we collected data to analyze whether vitamin K2 influenced the action of NK.

The use of a low dose of aspirin was relatively common. Therefore, we also analyzed whether co-administration of low doses of aspirin and NK resulted in a different clinical outcome.

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Effects of NK use on the lipid profile

The changes in the blood lipid profile of the participants before and after treatment are shown in Table 2. After 12 months of daily NK consumption at a dose of 10,800 FU, a significant reduction in TG, TC, and LDL-C ($P < 0.01$) was evident compared to the values before treatment. Furthermore, NK also had the effect of increasing HDL-C (15.8% increase, $P < 0.01$). The levels of TC, TG, LDL-C, and HDL-C improved in 95.4, 85.2, 84.3, and 89.1% of the participants, respectively, after 12 months of NK use (Table 3). NK administration for 12 months led to a decrease of 15.9, 15.3, and 18.1% in TC, TG, and LDL-C, respectively. Taking all of the data into account, NK produced a significant and favorable effect on the lipid profile in hyperlipidemic participants.

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NK suppresses atherosclerosis

After 12 months of NK consumption, both the size of CCA-IMT and the size of the carotid artery plaque decreased significantly (from 1.33 to 1.04mm on average, $P < 0.001$). The size of the plaque decreased by up to 36%, suggesting that NK is very effective in improving/reducing carotid atherosclerosis (Table 4). The overall improvement rates in CCA-IMT and CPS are not as high as those in blood lipids, with approximately 2/3 and 77.7% of the participants showing improvement in CPS and CCA-IMT, respectively (Table 3).

In smokers and alcohol-drinking participants, we found that hyperlipidemic conditions and atherosclerotic conditions were generally worse compared to nonsmokers and participants who drank less. We also found that the effects of NK on lipid lowering and antiatherosclerotic action were slightly stronger (Tables 9, 10).

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In summary, our data from this largest clinical study involving 1,062 participants suggest that NK at the daily dose of 10,800 FU, which is higher than the recommended dose of 2,000 FU, is significantly effective in the management of atherosclerosis progression and hyperlipidemia. No adverse effects associated with the use of NK is observed. The study advances our understanding of the action of NK and the importance of the dosage of NK. We also demonstrate that other factors, including lifestyle and co-use of vitamin K2 and aspirin, could contribute positively to the clinical outcome. Our findings provide evidence that promising and positive clinical outcome in the management of atherosclerosis progression and hyperlipidemia can be achieved safely by using NK at a dose of 10,800 FU per day. The outcome of this report warrants further randomized control clinical trials using increased doses of NK.

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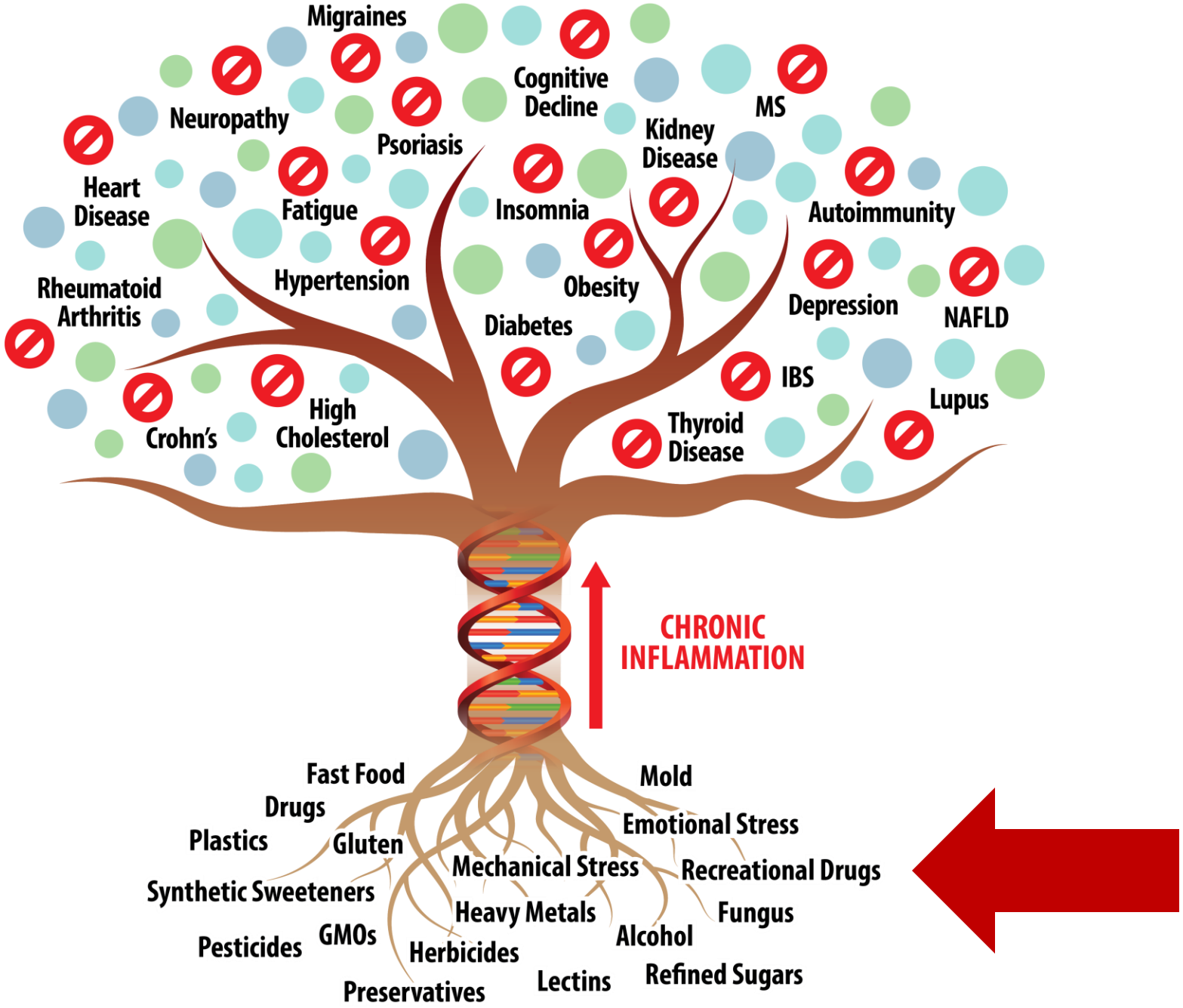
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SUPPLEMENT FACTS

Serving size: 2 capsules Servings per container: 60	Amount Per Serving	% Daily Value
Nattokinase	100 mg (2,000 FU†)	**

** Daily Value (DV) Not Established
† Fibrinolytic Units

Other Ingredients: Microcrystalline cellulose, capsule (hypromellose and water), stearic acid, silica, magnesium stearate, and medium-chain triglyceride oil.
Contains: Soy.
Formulated to Exclude: Wheat, gluten, yeast, animal and dairy products, fish, shellfish, peanuts, tree nuts, egg, sesame, ingredients derived from genetically modified organisms (GMOs), artificial colors, and artificial sweeteners.

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