

The background of the slide is a light gray gradient with several realistic water droplets of various sizes scattered across it. The droplets have highlights and shadows, giving them a three-dimensional appearance.

SRAGE AND ITS ROLE IN COLORECTAL CANCER PATIENTS

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INTRODUCTION

IMPAIRED AWARENESS OF GLYCATION BIOLOGY IN CANCER INITIATION AND PROGRESSION IS ONE OF THE FUNDAMENTAL REASONS FOR ITS INVESTIGATION OF THE MOLECULES INVOLVED IN SIGNALING PATHWAY.

GLYCATION OF BIOLOGICAL MACROMOLECULES RESULTS IN THE PROGRESSION OF ADVANCED GLYCATION END-PRODUCTS (AGES) THAT PROLIFERATES THE PROCESS OF CARCINOGENESIS BY ACTIVATION OF TRANSCRIPTION FACTORS AND RELEASE OF CYTOKINES.



The receptor for advanced glycation end-products (RAGEs) with the binding of its different ligands like:

1- AGEs

2- HMGB1

3- S100

WHICH activate the signaling arrays.



THE ACTIVATION OF DOWNSTREAM SIGNALING PATHWAY ULTIMATELY LEADS TO THE PATHOPHYSIOLOGICAL CONDITIONS OF

DIABETES,

AGEING,

NEUROLOGICAL DISORDERS

AND CANCERS

HOWEVER,

THERE MIGHT BE A LIKELIHOOD OF THE POSITIVE EFFECT OF THE **HMGB1** AND **S100** PROTEINS IN CANCER.



DEFINITIONS

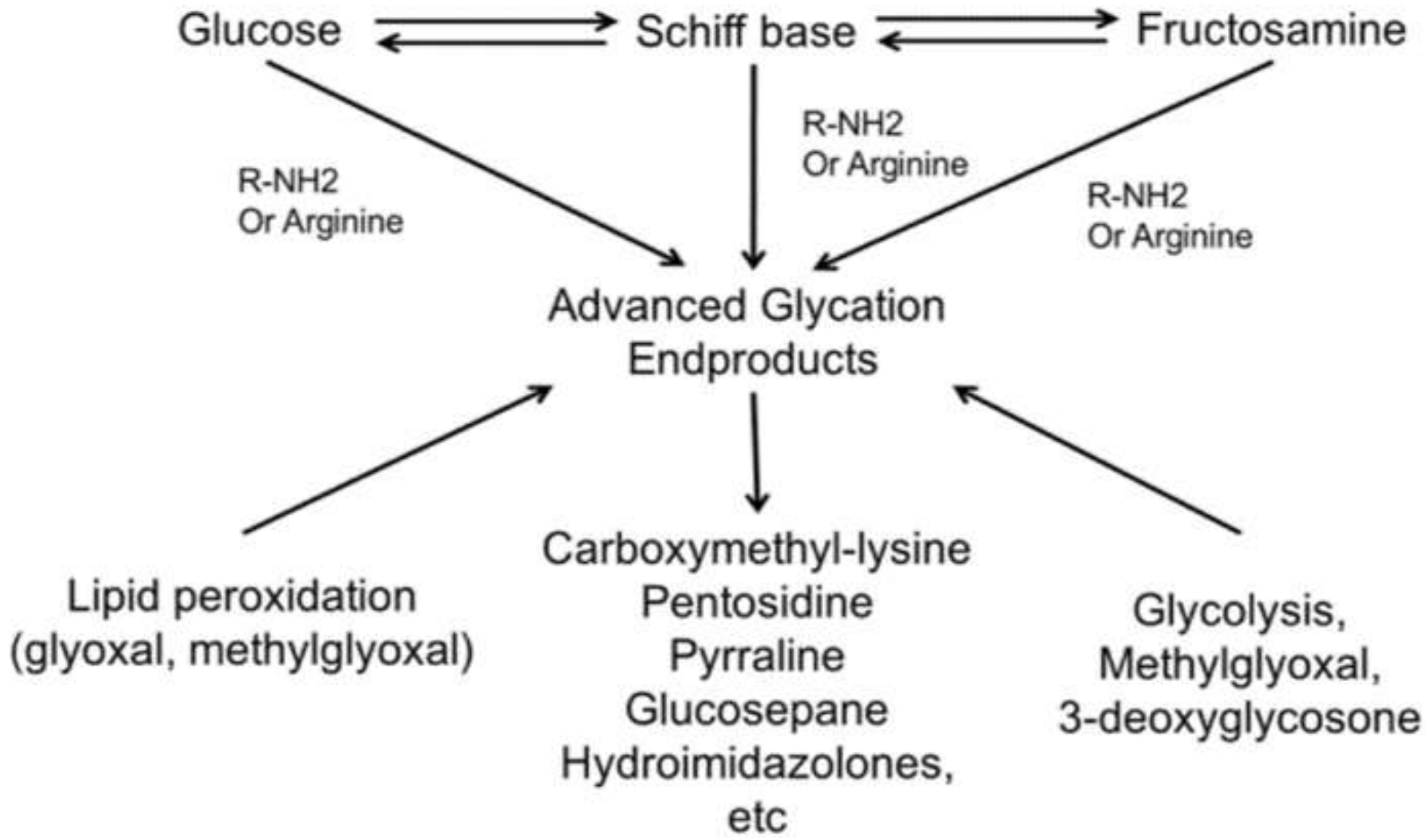
THE RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS (RAGE) IS A MEMBER OF THE IMMUNOGLOBULIN SUPERFAMILY OF CELL SURFACE MOLECULES.

RAGE IS A MULTILIGAND RECEPTOR THAT PROPAGATES CELLULAR DYSFUNCTION IN SEVERAL INFLAMMATORY DISORDERS, IN TUMORS AND IN DIABETES.

RAGE IS EXPRESSED AT LOW LEVELS IN NORMAL TISSUES, BUT BECOMES UPREGULATED AT SITES WHERE ITS LIGANDS ACCUMULATE.

ADVANCED GLYCATION END PRODUCTS (AGES) ARE HARMFUL COMPOUNDS THAT ARE FORMED WHEN PROTEIN OR FAT COMBINE WITH SUGAR IN THE BLOODSTREAM. ... FOODS THAT HAVE BEEN EXPOSED TO HIGH TEMPERATURES, SUCH AS DURING GRILLING, FRYING, OR TOASTING, TEND TO BE VERY HIGH IN THESE COMPOUNDS.

AMONG THE MECHANISMS BY WHICH HYPERGLYCEMIA MAY LEAD TO TISSUE DAMAGE, NONENZYMATIC GLYCOSYLATION INVOLVES EXCESSIVE CHEMICAL ATTACHMENT OF GLUCOSE TO PROTEINS WITHOUT THE INVOLVEMENT OF ENZYMES. THESE PRODUCTS, RESEMBLING **HEMOGLOBIN A1C, SLOWLY GIVE RISE TO COMPLEX IRREVERSIBLE GLYCOSYLATION PRODUCTS.**

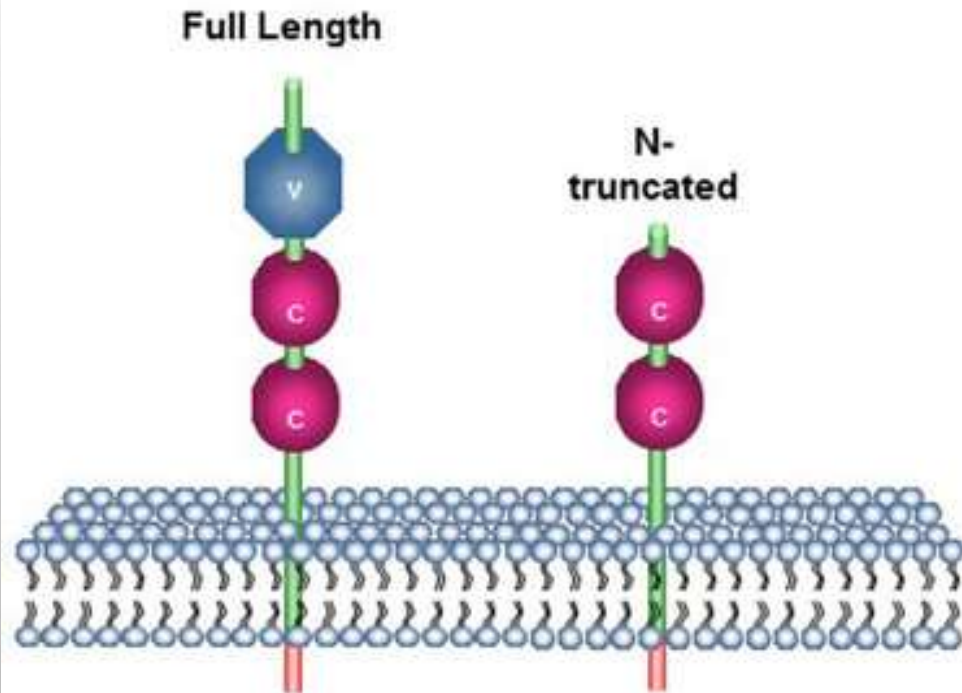


RAGE IS A MEMBER OF THE IMMUNOGLOBULIN SUPER FAMILY, EXISTS IN MANY ISOFORMS AND BINDS DIVERSE LIGANDS INCLUDING PRODUCTS OF METABOLIC STRESS SUCH AS **AGES, HIGH MOBILITY GROUP BOX1 (HMGB1), S100** AND **AMYLOID-B PEPTIDES**.

THE MEMBRANE BOUND FORM, GENERALLY REFERRED TO AS RAGE OR AGER, HAS BEEN SHOWN TO BE A KEY MEDIATOR IN MANY CHRONIC CONDITIONS INCLUDING INFLAMMATION, VASCULAR INJURY AND METABOLIC SYNDROME AS WELL AS SOME CANCERS.

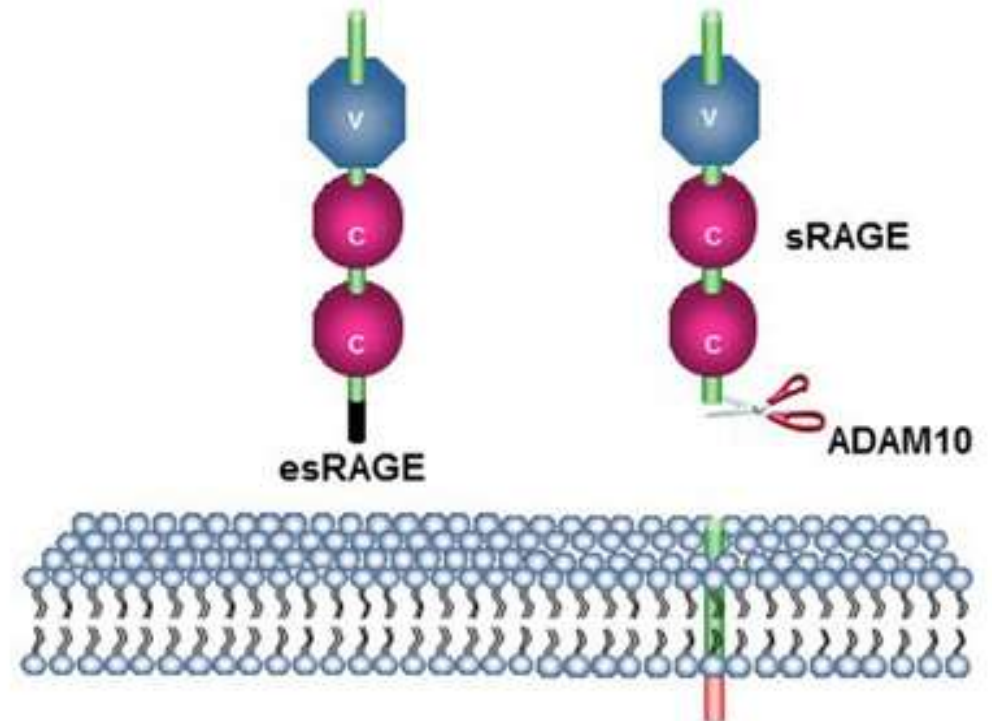
Membrane-bound RAGE

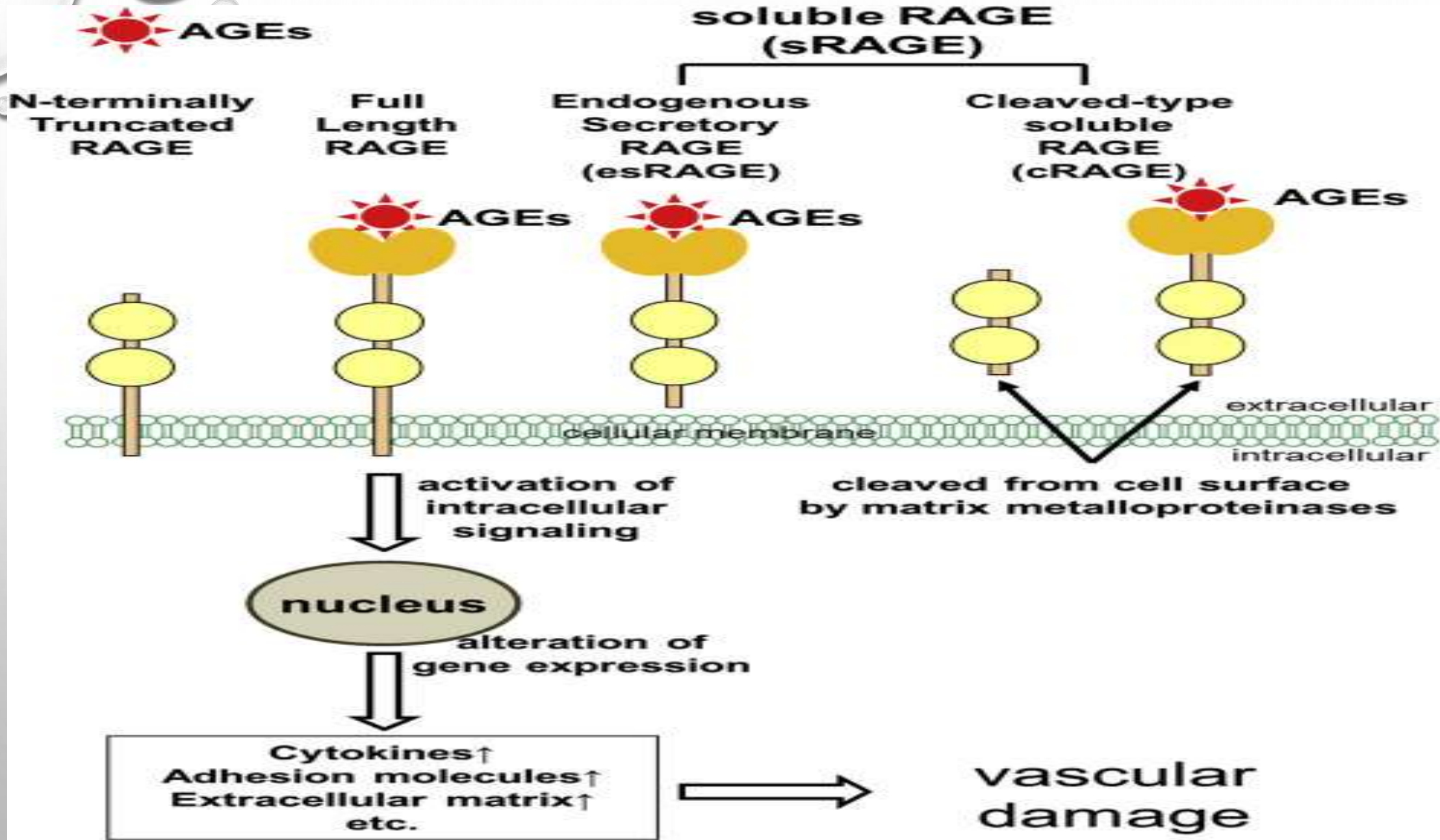
- RAGE Full-Length (FL)
- RAGE N-truncated (Nt)



soluble RAGE

- endogenous secretory, esRAGE
- proteolytic fragment of RAGE







IN MANY PATHOLOGIES RAGE IS THE MAJOR RECEPTOR FOR MOLECULES THAT MEDIATE DISEASE PROGRESSION AND CHRONIC INFLAMMATORY STATE, SUCH AS:

RHEUMATOID ARTHRITIS,

ALZHEIMER'S DISEASE,

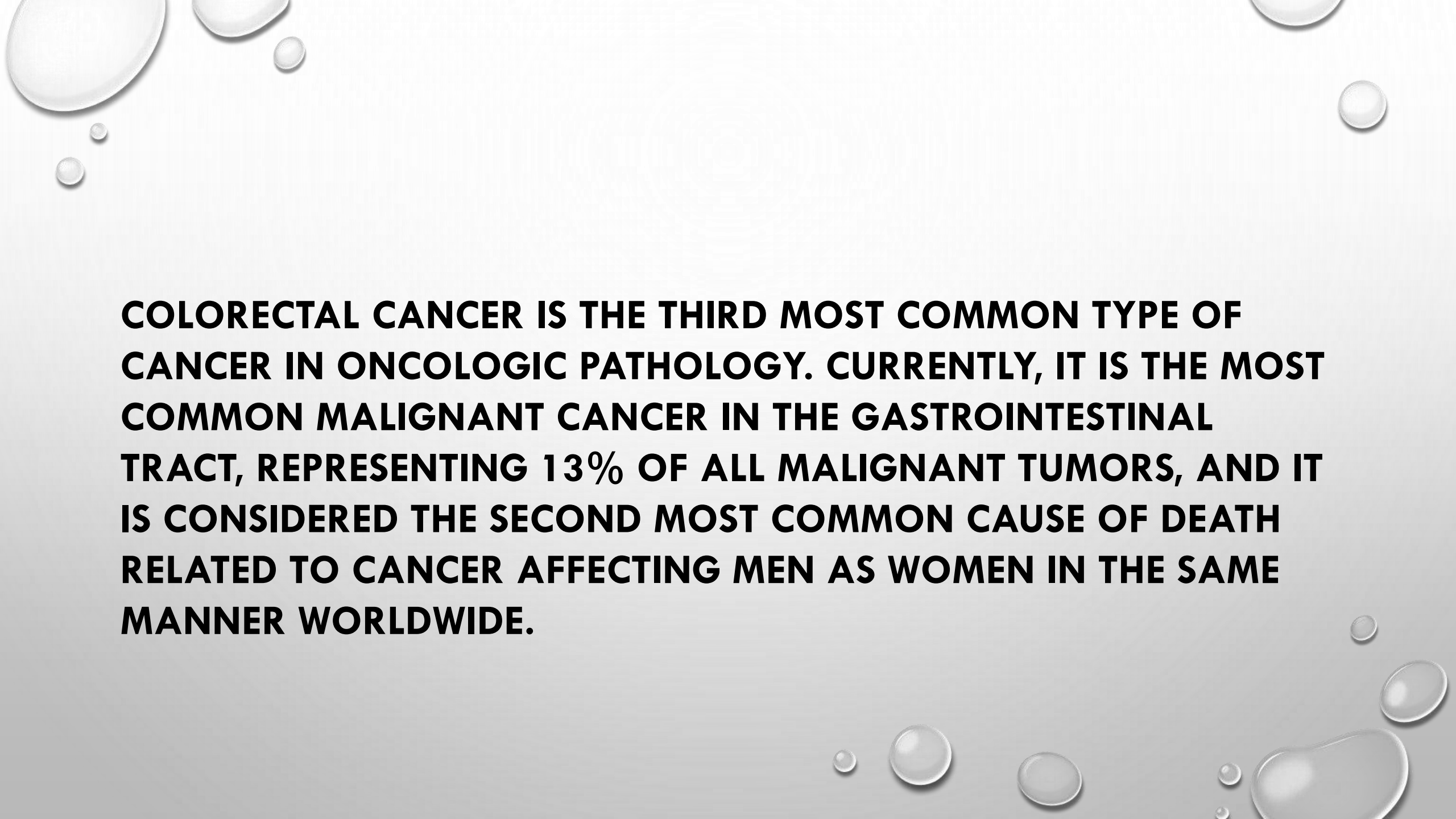
ARTERIOSCLEROSIS,

CHRONIC KIDNEY DISEASE

AND SOME **CANCERS**

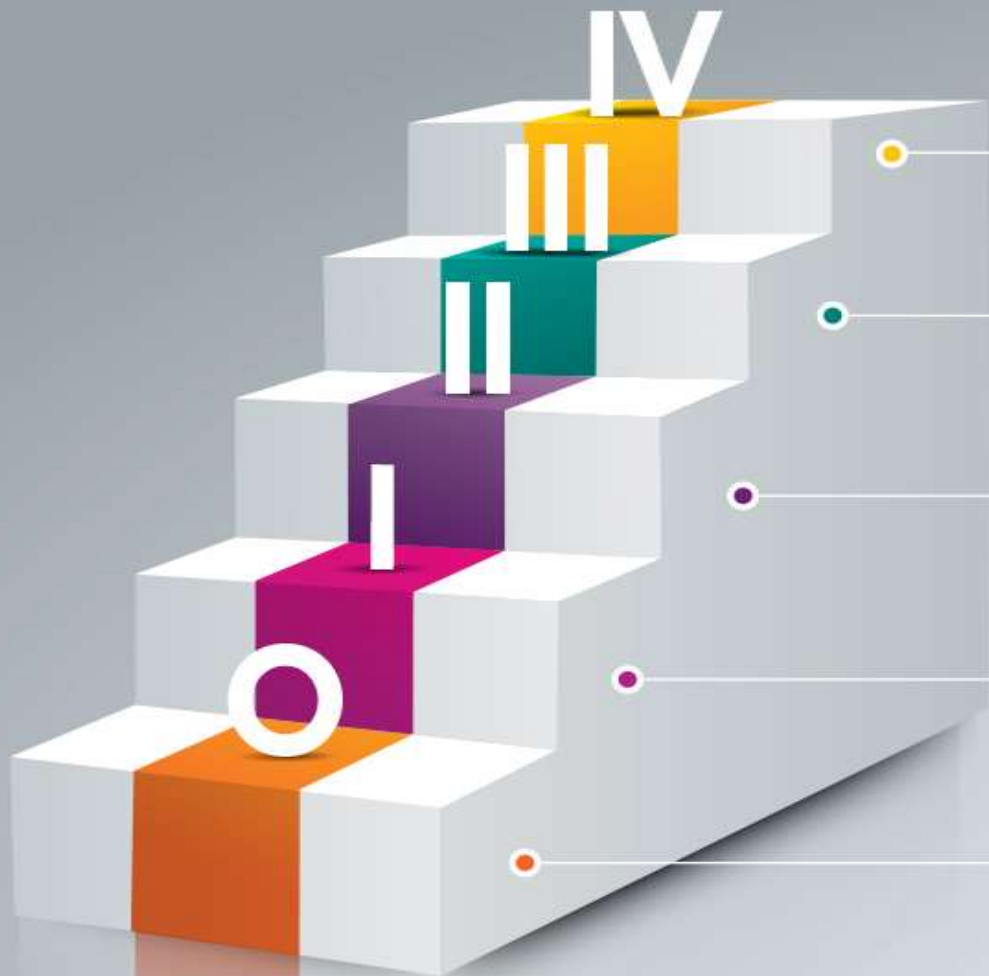
COLORECTAL CANCER:

THE TERM COLORECTAL CANCER REFERS TO A SLOWLY DEVELOPING CANCER THAT BEGINS AS A TUMOR OR TISSUE GROWTH ON THE INNER LINING OF THE RECTUM OR COLON. IF THIS ABNORMAL GROWTH, KNOWN AS A POLYP, EVENTUALLY BECOMES CANCEROUS, IT CAN FORM A TUMOR ON THE WALL OF THE RECTUM OR COLON, AND SUBSEQUENTLY GROW INTO BLOOD VESSELS OR LYMPH VESSELS, INCREASING THE CHANCE OF METASTASIS TO OTHER ANATOMICAL SITES.



COLORECTAL CANCER IS THE THIRD MOST COMMON TYPE OF CANCER IN ONCOLOGIC PATHOLOGY. CURRENTLY, IT IS THE MOST COMMON MALIGNANT CANCER IN THE GASTROINTESTINAL TRACT, REPRESENTING 13% OF ALL MALIGNANT TUMORS, AND IT IS CONSIDERED THE SECOND MOST COMMON CAUSE OF DEATH RELATED TO CANCER AFFECTING MEN AS WOMEN IN THE SAME MANNER WORLDWIDE.

THE STAGES OF COLON CANCER



IV. Cancer has spread to other parts of the body.

III. Cancer has grown outside the colon and has spread to the lymph nodes.

II. Cancer has grown outside the colon, but has not spread to the lymph nodes.

I. The tumor has spread beyond the inner layer but remains within the colon.

0. Cancer cells are found only in the innermost lining of the colon and have not spread.

SRAGE ROLE IN COLORECTAL CANCER

THE PRINCIPAL MECHANISM BY WHICH AGES ELICIT BIOLOGICAL FUNCTION IS THROUGH THEIR RECEPTORS. THE LIGATION OF AGES AND MEMBRANE-BOUND FULL-LENGTH RAGE CAN TRIGGER AN ARRAY OF SIGNALING PATHWAYS THAT ARE INVOLVED IN INFLAMMATION AND TUMORIGENESIS .

Sources

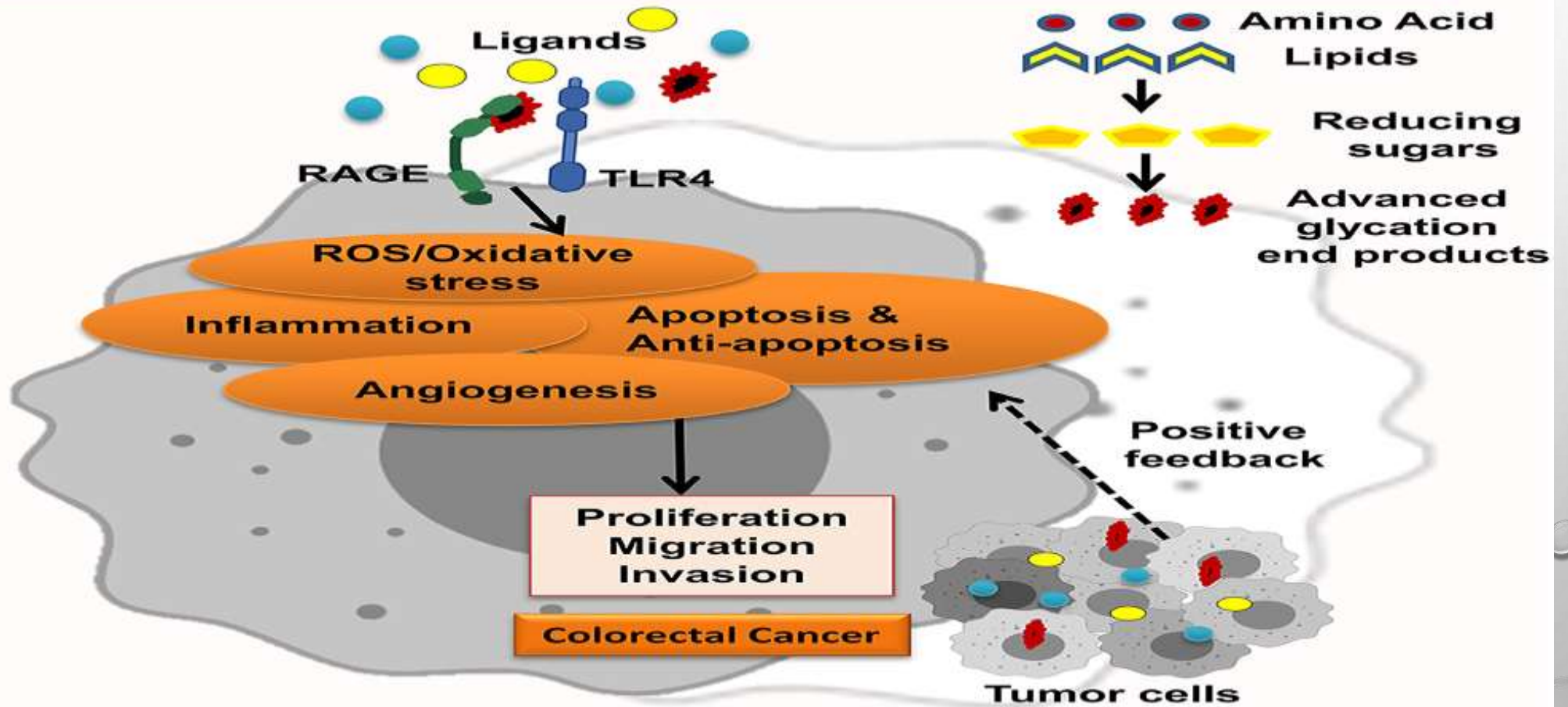
Tumor cells Necrotic cells Inflammatory cells Diet Smoking

Ligands

HMGB1 S100A8/A9 S100A4 S100P AGEs

Targets

Tumor cells Myofibroblasts Endothelial cells immune cells



SOLUBLE FORM OF RAGE (SRAGE) IS FOUND IN THE CIRCULATION IN HUMANS ,BY BINDING AGES OR OTHER LIGANDS AND ACTING AS A “RECEPTOR DECOY”, SRAGE REPRESENTS A NATURALLY OCCURRING COMPETITIVE INHIBITOR OF RAGE-MEDIATED SIGNALING PATHWAYS.



The AGEs-RAGE axis plays a critical role in the pathological interplay between hyperglycemia and vascular homeostasis. However, the role of AGEs in cancer development is largely unknown.

Several hospital-based studies found decreased sRAGE levels in patients with breast cancer, lung cancer, and pancreatic cancer, compared to healthy controls In.

We hypothesized that higher levels of RAGE and lower levels of sRAGE are associated with a greater risk of colorectal cancer.



Thank You!

