Development of age spots as a result of accumulation of aged cells in aged skin

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Abstract

Age spots are the brown spots that develop in the skin but change in color and shape with time. To understand the mechanism of development of age spots, characteristics of age spots are analyzed with Misrepair mechanism, a mechanism introduced in Misrepair-accumulation aging theory. An age spot is pathologically a group of aggregated basal cells, which contain lipofuscin bodies. Accumulation of lipofuscin bodies is a sign of aging of a cell. Characteristics of age spots include: in-homogeneity in distribution, growing flatly before becoming protruding, irregularity on shape, in-homogeneity on the color and the protruding degree of a spot, and softness of the protruding spots. Based on these characteristics, we make a hypothesis on the development of age spots. A. Aging of a tissue is the basis for the development of age spots. Deposition of a lipofuscin-containing cell is a consequence of aging of the skin, and it is a manifestation of Misrepair. B. A flat spot results from the accumulation of lipofuscin-containing cells. When an aged cell remains, this cell can accelerate the aging of its neighbor cells by increasing the damage-sensitivity and reducing the repair-efficiency of local tissue. By a viscous circle, more and more neighbor cells become aged and they form a flat spot with irregular shape. C. A protruding spot develops when some of the cells in a flat spot die and release lipofuscin bodies. For the survival of the organism, un-degradable lipofuscin bodies have to be isolated by a capsule composed of fibrotic membrane for maintaining the structural integrity of the local epidermis. Successive deaths of lipofuscin-containing cells make the capsule “grow” in three-dimension with multiple layers of fibrotic membrane, resulting in the protruding of a spot. In conclusion, development of an age spot is a result of accumulation of aged cells in aged skin.

Keywords

Age spots, aging, lipofuscin-containing cells, lipofuscin bodies, flat spot, protruding spot, in-homogeneity, aged cells, basal cells, Misrepair, Misrepair-accumulation theory, neighbor cells, increased damage-sensitivity, reduced repair efficiency, fibrotic capsule, basement membrane

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Introduction

Age spots are the brown spots on the skin, and they are different from melanotic nevi and verrucous nevi. Melanotic nevi are the spots that are flat or mildly protruding with homogenous color: deep brown or black. Melanotic nevi are all round in shape with clear boundary. Melanotic nevi can develop in any age, and they are pathologically a group of melanocytes, which can be a result of cell proliferation. A single verrucous epidermal nevus is a spot that is round and protruding with color of light brown, and it can develop also in any age. Differently, age spots are the spots that are in the beginning flat with light color and irregular shape but later become larger, protruding and darker in color. An age spot is pathologically a group of basal cells, which contain lipofuscin bodies. Lipofuscin bodies are intracellular lysosomes, which contain half-digested cell wastes. Age spots develop also in the liver, cordial wall, and nerve system; therefore they are also called “lipofuscin spots” and “liver spots”. Since accumulation of lipofuscin bodies in a cell is a sign of aging of the cell, age spots is a result of aggregation of aged basal cells. So far, it is unknown why these aged cells cluster together and why the spots are changing with time on size, on shape and on color. To these phenomena, traditional biological theories including damage (fault)-accumulation theory [1] and gene-controlling theory [2, 3] are unfortunately unable to give an interpretation. In the present paper, we will analyze age spots with Misrepair mechanism, and make a hypothesis on the process of development of an age spot. Misrepair mechanism is a mechanism that we have proposed in our novel aging theory, the Misrepair-accumulation theory [4, 5]. Our discussion tackles the following issues:

I. Characteristics of age spots

II. A novel aging theory: Misrepair-accumulation theory

III. Misrepair mechanism in the development of an age spot

3.1 Deposition of lipofuscin-containing cells in a tissue

3.2 Enlargement of a flat spot as a result of accumulation of aged cells

3.3 Protruding of a spot as a result of isolation of lipofuscin bodies in a tissue

IV. Conclusions

I. Characteristics of age spots

Age spots develop mainly on the part of skin where is often exposed to sunlight, including the face and the back sides of hands. The brown color of an age spot is from the color of lipofuscin bodies in cells. Lipofuscin is a mixture of lipids and proteins in lysosomes, in which lipids bind to protein fragments via malondialdehyde. Lipofuscin inclusion bodies are lysosomes that contain half-digested cell wastes, and they appear when a cell has reduced efficiency on functionality or has increased production of wastes. Thus the accumulation of
lipofuscin bodies is an effect but not the cause of aging of a cell. Lipofuscin bodies have also been seen in neuron cells, muscle cells, and hepatocytes. Within a part of the skin, age spots are different from each other on shape, on size, on color and on the degree of protruding. New spots tend to develop close to old ones, resulting in satellite-like distribution of spots. Old spots are permanently larger than new ones. A flat spot is light brown in color and is smoothing like that of normal skin. A protruding spot is a soft spot, dark in color, covered with cuticle-like substance, and filled with lipids. In a protruding spot, basal cells aggregate in columns from the level of basement membrane to that of skin surface, accompanied with the thickening of squamous epithelial layers and keratinocyte layers.

During the development of age spots, some phenomena are characteristic. A. Age spots are inhomogeneous on distribution, size and shape. B. A flat spot can “grow” in two-dimension and rest “flat” for many years before becoming protruding. C. Within one spot, some parts can be flat and some parts can be protruding with deeper color, which makes a spot rough and in-homogenous in color. D. A protruding spot in late stage is soft, lipid-containing but irremovable (Figure 1). A sound aging theory should be able to explain all of these phenomena; however, on the in-homogeneity of the distribution of spots, none of traditional theories has given an interpretation. For example, gene-controlling theory suggests that certain genes control the whole process of aging independently [2, 3]. However, if such genes existed, the locations of age spots should be independent of the locations of damage-exposure, which is not true. Damage (fault)-accumulation theory suggests that aging is a result of accumulation of “faults” as intrinsic damage, which are left unrepaird due to the limitation of repair/maintenance [1]. However, if aging was a direct result of damage, accumulation of random damage should result in a homogenous distribution of spots within the affected area of tissue. For understanding the development of age spots, a distinct view on aging is needed. We demonstrate that our recently raised Misrepair-accumulation theory is useful to explain these issues [4, 5].

**Figure 1. In-homogeneity of age spots on distribution, on size, and on shape**

Age spots on the skin are inhomogeneous on distribution, on size and on shape (A). Even within one spot, some parts can be flat with light color and some parts can be protruding with deeper color, which makes the spot rough and inhomogeneous in color (B).
II. A novel aging theory: Misrepair-accumulation theory

For explaining aging changes, we proposed a generalized concept of Misrepair in our Misrepair-accumulation theory \(^{[4, 5]}\). The new concept of Misrepair is defined as an incorrect reconstruction of an injured living structure, and it is applicable to all living structures including molecules (DNAs), cells, and tissues. Scar formation is a typical example of Misrepair. In situations of severe injuries, when a complete repair is impossible to achieve, Misrepair is a strategy of repair for maintaining the structural integrity and increasing the surviving chance of an organism. However, Misrepair results in alteration of the structure and reduction of the functionality of a living structure. The structural alterations made by Misrepairs are irreversible and irremovable, and they accumulate and disorganize gradually a living structure, leading to aging of it. Aging of an organism is a process of accumulation of Misrepairs. Misrepair mechanism is a surviving mechanism for an organism; and it is essential for the survival of a species. Aging of an individual is a sacrifice for species’ survival.

Misrepairs have a tendency to accumulate to the part of a tissue where an old Misrepair has taken place, since this part of tissue has increased damage-sensitivity and reduced repair-efficiency. Accumulation of Misrepairs is therefore focalized and self-accelerating. Development of aging changes is thus self-accelerating and inhomogeneous \(^{[6]}\). Aging can take place on each level of living structures; however aging of an organism takes place essentially on tissue level. An irreversible change of the spatial relationship between cells/extracellular matrixes in a tissue is essential and sufficient for causing a decline of organ functionality. Aging of a tissue does not always require aging of cells. In contrast, aging of a tissue is often the cause for aging of cells.

III. Misrepair mechanism in the development of an age spot

An age spot is pathologically a group of aggregated basal cells, which contain lipofuscin bodies. It is so far unknown whether or not this cell-aggregation is a result of cell proliferation. In our view, a flat spot cannot be a result of cell proliferation by four reasons. Firstly, if the cells in a spot are the offspring cells of a lipofuscin-containing cell through cell proliferation, these cells should have reduced levels of lipofuscin, and the spot should have reduced color during growing, which is however not true. Secondly, a flat spot can grow flatly for many years, and this cannot be possibly a result of cell proliferation, which should be in three-dimension like that in a tumor. Thirdly, if a spot is a result of cell proliferation, its boundary should be smoothing rather than irregular. Finally, lipofuscin-containing cells are dying cells with reduced potential of cell division, and this does not allow the continuous growing of an age spot for many years. Therefore, the aggregation of cells in an aged spot is probably a result of accumulation of aged cells. But why do these cells in a local area of a tissue undergo aging successively? What is the factor that drives this process of successive aging of cells in a neighborhood? These are the questions that need to be answered.

3.1 Deposition of lipofuscin-containing cells in a tissue

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Lipofuscin bodies are cell wastes, which are half-degraded and isolated in lysosomes in cells. Appearance of lipofuscin bodies is a sign of aging of a cell. For the cells with long lifespan and long process of aging such as neuron cells and muscle cells, intracellular lipofuscin bodies have long time to accumulate. Thus the level of lipofuscin in these cells is high and the bodies can be easily observed. Differently, for the cells with short lifespan such as epithelial cells and hepatocytes, lipofuscin bodies cannot easily accumulate. Normally an aged epithelial cell will be soon removed and replaced by a new cell. However, when a tissue is aged, the maintaining efficiency of the tissue will decrease and some aged cells cannot be removed. Long survival of an aged cell enables the accumulation of lipofuscin bodies. Thus in a regenerable tissue, remaining of a lipofuscin-containing cell is the consequence of aging of the tissue. Deposition of a lipofuscin-containing cell is a kind of Misrepair of the tissue. In return, an aged cell can enhance aging of the tissue by affecting the local substance-transportation and information-communication.

An age spot on the skin is composed of basal cells, which are anchoring to the basement membrane in epidermis. Basal cells are the stem cells that are responsible for producing new epithelial cells for the regeneration and reparation of epidermis. Basal cells can be injured by UV-radiation and chemical substances, and some of them can survive through Misrepairs and become aged. Normally the aged basal cells, which have reduced functionality, will be soon removed by the local langerhans cells and replaced by new basal cells. However, when the local part of the skin has reduced efficiency on functionality, some of the aged cells cannot be removed and they can survive longer. Therefore, deposition of lipofuscin-containing basal cells in epidermis is a result of aging of the skin.

3.2 Enlargement of a flat spot as a result of accumulation of aged cells

A lipofuscin-containing basal cell in skin is actually an invisible age spot, and the focal accumulation of lipofuscin-containing cells results in a visible spot. But what is the factor that causes the focal accumulation of aged cells? In our view, a triggering factor for this process is the deposition of an aged cell in the tissue. Remaining of an aged cell is a kind of Misrepair, and this Misrepair has altered the relationship of this cell with its neighbor cells, and this alteration will affect the functionality of neighbor cells and the local tissue. An aged cell has two effects on its neighbor cells: **A.** the neighbor cells will not be able to make adaptive responses efficiently to the loads from environment changes and become fragile to damage; and **B.** the neighbor cells and the local tissue will have reduced repair-efficiency. Taken together, the neighbor cells of an aged cell have increased risk for injuries and for Misrepairs. By this mechanism, an aged cell promotes the aging of its neighbor cells. Because of the reduced functionality of the local tissue, these aged neighbor cells cannot be completely removed; therefore they can remain and then make more neighbor cells aging (Figure 2). By such a viscous circle, the range of affected cells is gradually enlarged, and the increase of number of aged cells is accelerated with time. Lipofuscin bodies will accumulate in these long-lived aged cells, and more and more neighbor cells will become lipofuscin-containing cells. Accumulation of these cells in a neighborhood results in the development of a visible spot with irregular shape. In this stage, the spot is flat, since the aged cells are in a normal cell.
organization in epidermis. Increase of the number of affected basal cells results in the growing of a spot in two-dimension. A spot can rest flat for many years, and only when some of the aged cells die and release lipofuscin bodies, the spot will become protruding.

Figure 2. Effect of an aged cell on a tissue: promoting the aging of its neighbor cells

An aged cell in a tissue will affect the functionality of its neighbor cells, and makes the neighbor cells and the local tissue have increased damage-sensitivity and reduced repair-efficiency. The neighbor cells then have increased risk for injuries and for Misrepairs. In this way, an aged cell (AC) promotes the aging of its neighbor cells (NAC1 and NAC2).

3.3 Protruding of a spot as a result of isolation of lipofuscin bodies in a tissue

On the skin of old people aged over 70 years old, the age spots can change enormously within one year, a spot or part of a spot can become protruding and darker in color. A protruding spot has some characteristics, which can reveal something. A. A protruding spot is soft and full of lipids, and this implies the death of lipofuscin-containing cells and the release of lipids in the spot; B. A protruding spot cannot drop off from the skin, and this implies that the spot is probably fixed to basement membrane or to derma; C. In a protruding spot, the basal cells are arranged in a column from the level of basement membrane to that of skin surface, and this implies also that the spot is probably fixed to basement membrane. By analyzing these characteristics, we make a hypothesis on the process of development of a protruding spot, which can be described in three steps. 1) Development of a protruding spot is promoted by death of a lipofuscin-containing cell in the flat spot. 2) Isolation of lipofuscin bodies and the dead cells in situ is achieved by constructing a capsule with fibrotic membrane, which is similar to basement membrane. 3) Successive deaths of local lipofuscin-containing cells make the capsule “grow” in three-dimension with multiple layers of fibrotic membrane, resulting in the protruding of a spot.

An aged cell will die from failure of functionality. The released lipofuscin bodies will promote tissue response to remove them. However, lipofuscin bodies are difficult to be digested by langerhans cells, and a solution is to isolate them in situ. Isolation of un-

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degradable substance by a fibrotic capsule is a compromise of a tissue for the sake of survival, and it can be understood as a Misrepair. Such a Misrepair does not only reduce the toxicity of dead substance to local cells but also rebuilds the structural integrity of the tissue. Basal cells are normally anchored to basement membrane. When a basal cell dies, the neighboring basement membrane can be used as a material for isolating the dead substance. A fibrotic capsule is probably made by constructing new basement membrane or similar membrane around the dead cell (Figure 3B). Since basement membrane is invisible in hematoxylin and eosin staining, the fibrotic capsule is difficult to be observed. When more neighbor cells die, enwrapping will take place in a higher level with a new layer of fibrotic membrane, which enwraps both of the newly dead substance and the old capsule. Successive deaths of cells make the capsule bigger and bigger in three-dimension, and the spot becomes protruding. The concentrated lipofuscin bodies in the capsule make a protruding spot soft and fat with deeper color. Multiple layers of fibrotic membrane in the capsule make a spot look to be covered by cuticle-like substance.

Our hypothesis on the process of development of a protruding spot is schematically presented in Figure 3. At first, death of a lipofuscin-containing cell promotes the development of the first-level of capsule made of a layer of fibrotic membrane (Capsule 1, Figure 3B). Reorganization of local basal cells takes place for sealing the local epidermis. Then, death of neighbor cells next to the first one promotes the development of the second-level of capsule with another layer of fibrotic membrane (Capsule 2, Figure 3C), which enwraps the newly dead cells and the capsule 1. In this way, the capsule becomes bigger and bigger by including more and more old capsules, for example, the capsule 1 and the capsule 2 (Capsule 3, Figure 3D). Successive enwrapping of dead cells and lipofuscin bodies in multiple levels of capsules with multiple layers of fibrotic membrane makes part of a spot “grow” in 3D.
Figure 3. A hypothesized process of the development of a protruding spot

Our hypothesis on the process of development of a protruding spot is schematically presented. At first, death of a lipofuscin-containing cell promotes the development of the first-level of capsule made of a layer of fibrotic membrane (Capsule 1, B). Reorganization of local basal cells takes place for sealing the local epidermis (B, C, and D). Then, death of neighbor cells next to the first one promotes the development of the second-level of capsule with another layer of fibrotic membrane (Capsule 2, C), which enwraps the newly dead cells and the capsule 1. In this way, the capsule becomes bigger and bigger, by including more and more old capsules, for example, the capsule 1 and the capsule 2 (Capsule 3, D). Successive enwrapping of dead cells and lipofuscin
bodies in multiple levels of capsules with multiple layers of fibrotic membrane makes part of a spot “grow” in 3D.

IV. Conclusions

Aging of a tissue is the basis for the development of age spots. Development of an age spot proceeds in three stages: A. deposition of a lipofuscin-containing cell in an aged tissue, which determines the location of a spot; B. focal accumulation of aged cells, which results in the development and enlargement of a flat spot; and C. death of lipofuscin-containing cells and isolation of lipofuscin bodies in a fibrotic capsule, which result in the protruding of part of a flat spot in the skin. The in-homogeneity of age spots on distribution is a result of focalized accumulation of aged cells, and this can only be explained by Misrepair mechanism. Thus, development of an age spot is a result of accumulation of aged cells in aged skin.

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