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Preface

This issue of ANTICANCER RESEARCH presents the Proceedings of the 22nd Annual Meeting of the Society of Biotherapeutic Approaches. It is our great pleasure to introduce this issue expressing my sincere gratitude to the Editors of Anticancer Research for kindly accepting and publishing the proceedings of our regional meeting in Japan in ANTICANCER RESEARCH.

The 22nd meeting was held in Tokyo, Japan on December 8, 2018, chaired by Professor Kazunori Hashimoto, Obstetrics and Gynecology, Tokyo Women's Medical University Medical Center East, Japan and Senior Lecturer Hirohito Kobayashi, Transfusion Medicine and Cell Processing, Tokyo Women's Medical University Hospital, Japan. One of the highlights in this conference was the special lecture on "Cancer immunotherapy using γδ type T cells" presented by Dr. Hirohito Kobayashi, Transfusion Medicine and Cell Processing, Tokyo Women's Medical University Hospital, Japan. In addition, there were two workshops and many oral presentations on a wide range of basic and clinical topics, offering impressive advances in this field.

The main aims of our Society are to facilitate good communication between basic researchers and clinicians, and to perform clinical trials with adequate informed consent in an appropriate and professional manner. These aspects include important issues for the progress of biotherapy as well as for medicine in general. It is our sincere hope that these Proceedings will contribute to further progress in the field of biotherapy and that our members will continue to foster the aims of our Society.

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Review

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Review

Usefulness of Monocytes/macrophages Activated With Low-dose Lipopolysaccharide in Tumor Tissue and Adipose Tissue of Obesity

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Abstract. *Chronic inflammation is involved in the development of cancer, lifestyle-related diseases, and autoimmune diseases. It also influences the severity of these diseases. Macrophages that accumulate in tumor tissues and adipose tissues of obesity have been shown to increase expression of inflammatory cytokines, thereby inducing inflammatory changes in these tissues. The macrophage phenotype is believed to be important in mediating inflammatory changes in tissues. Recently, monocytes/macrophages activated with low-dose lipopolysaccharide (LPS) were demonstrated to suppress increased expression of monocyte chemotactic protein (MCP)-1 and inflammatory cytokines (interleukin (IL)-1 β, IL-8, and tumor necrosis factor (TNF)-α). By suppressing the increased expression of chemotaxis-related and inflammation-related factors, monocytes/macrophages activated with low-dose LPS are considered to suppress the migration of macrophages into tissues and to regulate inflammatory changes in these tissues, respectively. The effects of macrophages activated with low-dose LPS were different from those of macrophages activated with high-dose LPS. In this review, we discuss the usefulness of monocytes/macrophages activation by low-dose LPS.*

In the bone marrow, monocytes differentiate from multipotent myeloid stem cells. They are released into the peripheral circulation, where they circulate for several days. Thereafter they migrate into various tissues and become macrophages. During differentiation of monocytes to macrophages, they are educated by the tissue environment and acquire tissue-specific functions (1, 2). It is believed that macrophages play important roles in the maintenance of homeostasis, host defense mechanisms (such as phagocytosis of cancer cells), and tissue remodeling (3, 4). Reportedly, macrophages accumulate in tumor tissues and adipose tissues of obesity (5, 6). Moreover, it has been demonstrated that macrophages that accumulate in tumor tissues or adipose tissues of obesity differentiate by interacting with cancer cells or adipocytes, thereby inducing inflammatory changes in the tissues by increasing the expression of inflammatory cytokines (7, 8). Inflammatory changes in the tissues are believed to cause chronic inflammation; chronic inflammation has been demonstrated to be involved in the development of cancer, lifestyle-related diseases included in the metabolic syndrome such as diabetes, stroke, and arteriosclerosis diseases, and autoimmune diseases (9, 10). It also influences the severity of these diseases. The macrophage phenotype is therefore important in mediating inflammatory changes in tissues.

Lipopolysaccharide (LPS), an extracellular membrane component of gram-negative bacteria, is known to induce the expression of inflammatory cytokines through toll-like receptor-4 (11). When LPS is intravenously administered at a high concentration, inflammatory cytokines are systemically produced from activated macrophages, causing acute septic shock (12). Recent research has demonstrated differences between the effects of macrophages activated with low-dose LPS and those activated with high-dose LPS, suggesting LPS acts more as an exohormone than as an endotoxin (13). Additionally, LPS has been demonstrated to be non-toxic, when administered orally and dermally (14). Environmental exposure to LPS in childhood has been suggested to play an important role in the development of

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tolerance to ubiquitous allergens, and LPS signal transduction was essential for skin wound healing (15, 16). However, the significance of low-dose LPS has not been fully elucidated. Further investigation in this area may lead to development of novel approaches to prevent cancer and lifestyle-related diseases.

Monocytes/Macrophages Activated with Low-dose LPS Suppress Macrophage Migration into Tissues

In monocyte chemotactic protein (MCP)-1-deficient and MCP-1 receptor, C-C chemokine receptor (CCR)-2-deficient mice, the number of macrophages in adipose tissue of obesity induced by a high fat diet was significantly reduced compared to those in wild type mice (17-19). Alternatively, in transgenic mice overexpressing MCP-1, the number of macrophages to adipose tissue of obesity induced by a high fat diet was significantly increased compared to those in wild type mice (20). The migration of macrophages into adipose tissues was demonstrated to be performed *via* the MCP-1 receptor, CCR-2. MCP-1 is therefore considered to be an important molecule contributing to macrophage migration into adipose tissues. Furthermore, MCP-1 is shown to be involved in the migration of monocytes to the vessel wall at the beginning of arteriosclerosis (21).

Monocytes activated with low-dose LPS (100 pg/ml) were co-cultured with cancer cells or adipocytes using a transwell system. The results revealed that increased expression of MCP-1 was suppressed not only in monocytes but also in cancer cells and adipocytes (22, 23). Furthermore, the expression of MCP-1 was significantly reduced in mouse macrophages after low-dose LPS pre-treatment compared with that after high-dose LPS pre-treatment (24). These results suggest that monocytes/macrophages activated with low-dose LPS suppress increased expression of MCP-1. It is therefore possible that monocytes/macrophages activated with low-dose LPS have a suppressive effect on migration into tissues and the intima of arteriosclerosis.

Monocytes/Macrophages Activated with Low-dose LPS Suppress Inflammatory Changes in Tissues

Macrophages that accumulate in tumor tissues and adipose tissues of obesity have been shown to increase the expression of inflammatory cytokines, thereby inducing inflammatory changes in these tissues, and possibly causing chronic inflammation. The increased expression of inflammatory cytokines (interleukin (IL)-1 β, IL-8, and tumor necrosis factor (TNF)-α) in human monocytes by co-culture with human cancer cells or adipocytes using a transwell system was reportedly suppressed by pre-treatment with low-dose LPS (100 pg/ml) (22, 23). In addition, the increased expression of anti-inflammatory cytokines (IL-10 and transforming growth factor-β) in human monocytes by co-culture with human cancer cells using a transwell system was suppressed by pre-treatment with low-dose LPS (25, 26). Furthermore, mouse macrophages activated with low-dose LPS (50 pg/ml) were shown to suppress the increased expression of IL-6 (27). The induction of MCP-1 suggests to play a role in the early stage of inflammatory changes in tissues (7). MCP-1 is also considered as a key molecule contributing to the inflammatory changes in adipose tissues. In MCP-1-deficient and CCR-2-deficient mice, the expression of TNF-α significantly decreased and that of adiponectin significantly increased in the adipose tissue compared to those in wild type mice, while systemic insulin resistance improved (18, 19). In transgenic mice overexpressing MCP-1, the expression of TNF-α significantly increased in the adipose tissue compared to those in wild type mice, while systemic insulin resistance deteriorated (20). It is therefore possible that monocytes/macrophages activated with low-dose LPS regulate chronic inflammation in tissues by suppressing inflammatory changes.

Moreover, the increased expression of an angiogenesis-related factor, vascular endothelial growth factor-A in human monocytes by co-culture with human cancer cells using a transwell system was suppressed by pre-treatment with low-dose LPS (100 pg/ml) (22). Therefore, monocytes/macrophages activated with low-dose LPS may suppress the invasion and metastasis of cancer by suppressing angiogenesis.

Monocytes/Macrophages Activated with Low-dose LPS Regulate the Expression of Immune Response-related Factors

Macrophages respond to LPS signaling *via* nuclear factor (NF)-κB (3), and upon activation with high-dose LPS, enhance the production of this transcription factor. Mouse macrophages activated with low-dose LPS reportedly exhibited reduced expression of RelB, a member of the NF-κB transcription factor family, and failed to activate the classical NF-κB pathway (24). By both activating and repressing immune response-related factors, RelB is believed to function as a dual transcriptional regulator during LPS tolerance and severe systemic inflammation, respectively (28). The increased expression of RelB in human monocytes by co-culture with human cancer cells using a transwell system was suppressed by pre-treatment with low-dose LPS (100 pg/ml) (25). Monocytes/macrophages activated with low-dose LPS may be attributed to regulating the expression of RelB.

Moreover low-dose LPS was shown opposite effects on IL-1 receptor-associated kinase 1 (IRAK1) and PI3K pathways as compared to high-dose LPS, leading to an opposing regulation of RelB in IRAK1-deficient mice (29). Monocytes/macrophages activated with low-dose LPS thus

appear to regulate the expression of immune response-related factors. It is possible that monocytes/macrophages activated with low-dose LPS restore the original function, such as the maintenance of homeostasis.

Conclusion

Monocytes/macrophages play an important role in the immune system. Educated by the tissue microenvironment, they terminally differentiate into various types of macrophages with tissue-specific characteristics. Monocytes/macrophages activated with low-dose LPS may regulate inflammatory changes in tissues by inducing different functions of macrophages. The effects of monocytes/macrophages activated with low-dose LPS were different from those of monocytes/macrophages activated with high-dose LPS. Moreover, monocytes/macrophages activated with low-dose LPS have been reported to regulate the expression of RelB, which functions as a dual transcriptional regulator during an immune response (28). Low-dose LPS treatment may, therefore, be useful in developing therapies for cancer, lifestyle-related diseases, and autoimmune diseases, by preventing chronic inflammation.

Conflicts of Interest

The Authors have no conflicts of interest for this article.

Authors' Contributions

All Authors have contributed to data collection and interpretation. TH drafted the manuscript, HI contributed to reviewing and editing the manuscript.

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