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MAPK IS IMPLICATED IN SEPSIS, IMMUNITY, AND INFLAMMATION

Raoul Saggini[1*] and Raffaele Pellegrino[2]

[1] Physical Medicine and Rehabilitation, University "G. D'Annunzio" of Chieti-Pescara, Chieti, Italy;
[2] Physiatrist and Pain Therapy, Lecce-Castromediano/Cavallino, Lecce, Italy.

**Correspondence to*:
Prof. Raoul Saggini,
Physical Medicine and Rehabilitation,
University "G. D'Annunzio" of Chieti-Pescara,
Chieti, Italy.
e-mail: raoulsaggini@gmail.com

ABSTRACT

The mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway is a chain of cellular proteins that communicate from the receptor to the cellular DNA. The receptor binds effector molecules and transmits the signal to the DNA that induces protein kinases and generates a protein. Protein kinases are produced by the cells themselves through the process of gene expression. Innate immunity and adaptive immunity are activated during infections with activation of the mitogen-activated protein kinase (MAPK) and receptor-interacting kinase (RIPK) pathways that regulate the balance between cell survival and death, as well as the production of pro-inflammatory molecules. In sepsis, this balance fails. Serine-threonine kinase, or kinase 1, is responsible for the activation of multiple MAPKs. MAPK activation appears in many cellular processes, including differentiation, proliferation, and apoptosis, and leads to activation of transcription proteins with production of inflammatory cytokines. MAPKs, which can be stimulated by cytokines and microorganisms, mediate extracellular signal-regulated kinases (ERKs) involved in cell growth and survival and c-Jum N-terminal kinases (JNKs) linked to apoptosis. These protein kinases are produced in all eukaryotic and prokaryotic cells and play a crucial role in signal transduction, cell cycle regulation, and many other biological processes.

KEYWORDS: *MAPK, pathway, sepsis, immunity, inflammation, cell signaling, receptor*

INTRODUCTION

The Ras-Raf-MEK-ERK pathway, also known as the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway, is a chain of cellular proteins that communicate a signal from a receptor on the cell surface to the DNA in the cell nucleus (1). The signaling molecule binds to the cell receptor to initiate the signal which results in the DNA in the nucleus expressing a protein to cause a change in the cell, such as cell division and metabolism, for example (2).

The MAPK/ERK pathway includes many proteins, such as mitogen-activated protein kinases (MAPKs). MAPKs communicate by adding phosphate groups to a neighboring protein (phosphorylating it), thus acting as an "on" or "off" switch. The immune system uses various signaling pathways to defend itself from infections. Both nonspecific, innate immunity and specific, long-term adaptive immunity are activated during infections. Once the immune system is activated by infection, pathways such as MAPK and receptor interacting protein kinase (RIPK) are also activated (3). These pathways orchestrate the balance between cell survival, cell death, and the production of pro-inflammatory molecules (4).

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Sepsis occurs when this balance fails, and the body's immune response becomes overwhelming. Both excessive activation of MAPK-driven cytokine release and RIPK-mediated cell death can drive the uncontrolled inflammation and organ damage that characterize sepsis (5).

Serine-threonine kinase, or kinase 1, is ubiquitous in cells and is responsible for activating multiple MAPKs to regulate biological processes, including infections (6). Activation of MAPKs leads to downstream signaling and activation of transcription proteins with the production of inflammatory cytokines (7) (Fig.1). MAPK signaling and integrins play an important role in microbial-induced infections. MAPK activation occurs in many cellular processes, including differentiation, proliferation, apoptosis, and both innate and adaptive immune responses, and MAPK stimulators include both cytokines and microorganisms (8). MAPK mediates various cellular pathways, such as ERKs that are involved in cell growth and survival, and c-Jum N-terminal kinases (JNKs) that are associated with apoptosis and pathogen-induced inflammatory responses (9). When cells are infected by pathogens, MAPK pathways are activated to defend the host from infection, and this creates an inflammatory response.

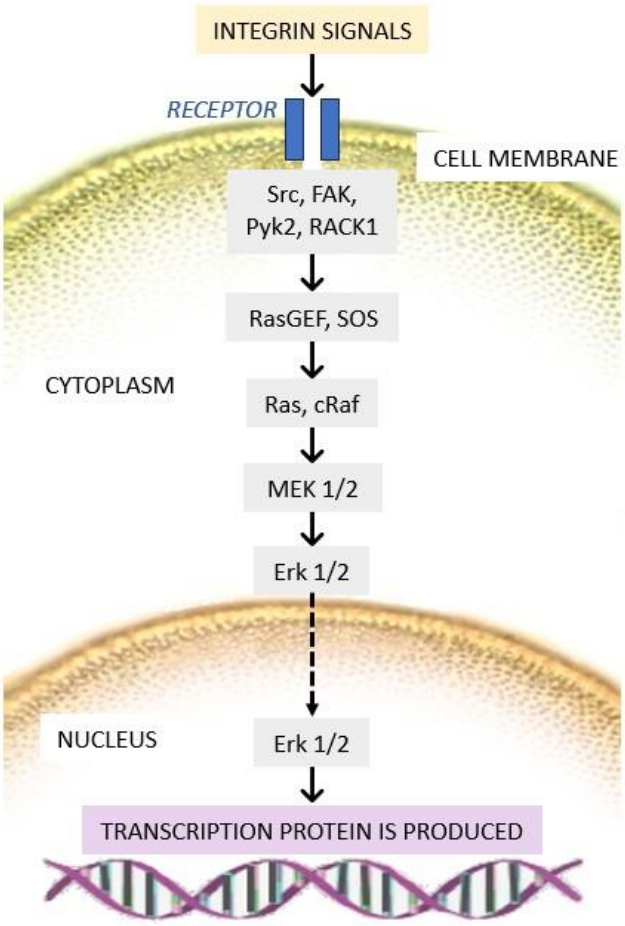

Fig. 1. *Integrin signaling on the cell cytoplasmic receptor leads to the activation of a nuclear transcription protein cascade.*

DISCUSSION

The MAPK pathway is intricately connected with infection, immunity, and inflammation by way of cell signaling and activation of immune responses. MAPK is also involved in the pathophysiology of infections, including sepsis, a severe condition in which the immune system responds improperly to infection, leading to organ dysfunction and possible failure (10). MAPK pathways regulate immune cell functions such as macrophage activation, T-cell differentiation, and the production of pro-inflammatory mediators (11).

In sepsis, the dysregulated host response is characterized by organ dysfunction that can be serious and life-threatening. Sepsis is a condition that occurs when the body's immune response to infection causes widespread inflammation, leading

to tissue damage, organ failure, and potential death (12). Inflammation is a critical component of the immune response to infection but, if left unchecked, can cause severe tissue damage.

Both the MAPK and RIPK pathways contribute to the production of pro-inflammatory cytokines such as TNF, IL-1β, and IL-6 (5). These cytokines help fight infection but can lead to hyperinflammatory states if unregulated. During sepsis, activation of immune signaling pathways such as MAPK and RIPK becomes dysregulated. Hyperinflammation due to excessive cytokine production is often called a "cytokine storm". Along with cell death (both apoptotic and necroptotic), this cytokine storm is a key feature of sepsis (13), and therefore, controlling inflammation and balancing immune responses are critical to managing this disease.

Pathogens use integrins to enter cells (14). Integrins are transmembrane receptors that facilitate cell adhesion to the extracellular matrix, which transmits signals to the intracellular environment, a biological process known as "outside-in signaling" (15) (Fig.1). Integrins are involved in the activation and migration of immune cells that respond to pathogens. These proteins allow cells of the immune system to reach the site of infection by migrating through the walls of blood vessels (16).

By binding integrins or other cell surface receptors, pathogens can interact with host MAPKs and integrins to facilitate their own survival and induce MAPK activation (17,18). Integrins bind to the extracellular matrix or specific pathogens, triggering the activation of MAPKs such as ERK and JNK, which regulate inflammation and/or apoptosis (19). Bacteria can interact with integrins on epithelial cells, triggering MAPK pathways that lead to the production of inflammatory cytokines, which help induce an immune response (20). Some viruses are known to hijack the MAPK pathway to promote viral replication and avoid apoptosis; while bacterial pathogens can use integrins to enter cells and manipulate MAPK signaling to suppress immune responses or induce cell survival signals (21-23).

The onset of sepsis can cause a “cytokine storm” that is generated mainly by IL-1, TNF, and IL-6 (24). These cytokines are produced by various cells, including macrophages, and they can cause harm by damaging tissue and organs. Cytokines mediate inflammatory processes and activate the NF-kB, MAPK, and JNK signaling pathways (25).

Serine-threonine kinase 1 is an apoptosis signaling regulator and stress regulator that is expressed in nucleated cells and activates several kinases (26). The activation of kinase 1 induces transcription factors to generate inflammatory cytokines (27).

The body responds to infections through various signaling pathways, including the MAPK and RIPK pathways, which mediate immune and inflammatory responses (28). RIPKs are specifically involved in the decision of cells to choose their fate: whether to survive, to die, or to release inflammatory signals (29). Pathogens such as bacteria and viruses can trigger RIPK inflammation pathways, leading to activation of immune cells, the release of pro-inflammatory cytokines, and sometimes, exaggerated inflammation.

RIPK signaling plays a dual role in immune defense and inflammation (30). RIPKs are critical for regulating cell death and inflammatory signaling (31). RIPK1 and RIPK3, in particular, are involved in necrosis that occurs in response to infection and inflammatory stimuli (32). In infections, RIPK activation can help control the spread of pathogens by inducing cell death or exacerbating tissue damage which contributes to sepsis.

RIPK1 is promising therapeutic target for the cure of many neurodegenerative diseases. Phosphorylation of this kinase mediates apoptosis. RIPK1 regulates cell survival, apoptosis, and inflammation, while RIPK3 is more specifically involved in promoting necrosis. RIPK1 is the first member of the Ser/Thr RIPK family, and it is constitutively localized in the cytoplasm; however, nuclear translocation of RIPK1 has also been reported, although its function in the nucleus has not yet been determined (33,34). Indeed, RIPK1 has been implicated in TNF-induced cell death and has been proposed as a target for cancer therapy (35). RIPK1 regulates various enzymes, activates inflammatory responses, inhibits kinase activity, and reduces cell death by increasing resistance to TNF-induced necrosis (36).

CONCLUSIONS

Infections stimulate the immune system through MAPK and RIPK signaling, regulating inflammation and apoptosis. Pathogens often use integrins to enter host cells. Once inside, or after binding to the cell surface, pathogens activate MAPK pathways (ERK and JNK) to initiate immune responses and induce inflammation.

MAPK pathways are activated to defend the body, but pathogens often manipulate this pathway to support their replication, spread, and evasion of the immune system. These interconnected reactions make MAPK and integrins important players in the balance between immune defense and pathogen survival. Immune responses help fight infections, but their dysregulation (as occurs during sepsis), can lead to excessive inflammation and cell death, causing damage to tissues and cells. The study of these biochemical pathways is fundamental for the development of therapeutic strategies for sepsis and inflammatory diseases.

Conflict of interest
The authors declare that they have no conflict of interest.

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