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**Rapid Communication**

# Cancer and Ras/Raf/ERK Pathway: The Role of New Regulators in Response to Physical Activity, Exercise, and Training

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## ABSTRACT

**Background.** Cancer is the second and most common cause of death in developed countries, and epidemiological evidence suggests a similar trend in developing countries. Cancer is currently the cause of twelve percent of all deaths worldwide. The ERK pathway contains important modulators suitable for growth and proliferation, especially tumors. This pathway is activated by oxidative stress, growth factors, intracellular increases in calcium levels, and stimulation of glutamate receptors. The Sprouty/Spred family acts as definitive negative regulators of the Ras/Raf/ERK signal. **View Points.** The Sprouty/Spred family specifically inhibits ERK activity in response to a wide range of factors such as fibroblast growth factor (FGF), platelet growth factor (PDGF), vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell-derived growth factor (GDNF). This family can inhibit MAPK activity and exert its effect on the downstream level. Typically, these proteins inhibit growth by modulating RTK signaling and suppressing the MAPK_ERK signaling pathway, suppressing cell proliferation, migration, and differentiation. On the other hand, through tyrosine kinase receptors, VEGF causes growth, proliferation, survival, and migration of endothelial cells and increases vascular permeability. **Objectives.** Research on the effect of exercise at various levels on the Sperouty/Spred family in both inactive healthy individuals and patients, especially in cancer situations, has not been performed. So, future research can be directed in this way.

**KEYWORDS:** ***MAPK Signaling Pathway, Sprouty, Spred, Tumor, Growth, Proliferation.***

## INTRODUCTION

Phosphorylation is a simple change via the addition of one or more phosphate groups to a protein molecule, such as the glycolysis pathway, which is essential in the metabolism of living organisms. This action is usually based on the amino acid serine or threonine, but in rare cases, it is performed on the amino acid tyrosine and sometimes on lysine. The phosphate entry into a protein enters a negative charge, which causes conformation. This binding is done by enzymes called kinases (1). To date, more than a hundred types of protein kinases are known, but one of the most famous is the large family of Mitogen-Activated Protein Kinases (MAPKs) that control numerous cellular functions. Mitogens are signals from the outside of the cell that send messages about mitosis and cell division induction.

The MAPK signaling pathway has been extensively studied in recent years. This pathway plays a critical role in signal transduction from protein kinases and phosphatases. One of the subunits of MAPK is Extracellular signal–Regulated Kinases (ERKs), which is the most well-known kinase in this pathway (2, 3).

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ERK protein kinase is phosphorylated and activated by threonine and tyrosine residues (4). This protein activates many proteins and transcriptional factors for different purposes. ERK activation causes the expression of more than 600 genes (5), and its effect on gene expression transcription is achieved either by activating messaging pathways in the cytoplasm or by demyelinating and moving to the nucleus and phosphorylating transcription factors (6). In the cytosol, the ERK exerts its effects in this way, activating proteins such as p90 ribosomal S6 kinase ($P90^{RSK}$) that transfers to the nucleus, activates the Serum Response Factor (SRF) transcription factors (7). In the nucleus, it can also activate agents such as ETS domain-containing protein (Elk1), Activating Transcription Factor 2 (ATF2), Activating Protein-1 (AP1), cAMP Responsive Element Binding (CREB), and Myocyte-specific enhancer factor 2C (MEF2C) (8-10).

The activity of this transcription factor is expressed by genes involved in various processes such as mitochondrial biogenesis (11), angiogenesis (12), or mitotic cell proliferation (13) and meiosis, and post-mitotic function such as differentiation (14), apoptosis (15) and cyclin D expression; helps regenerate muscle cells and repair muscle damage (16). The MAPK pathway, and especially the ERK, can be activated by many factors. Physical activity can also activate this pathway through various mechanisms such as growth factors secretion and muscle tension, oxidants, and pH reduction (16).

On the other hand, the ERK pathway contains important modulators suitable for growth and proliferation. This pathway is activated by intracellular increases in calcium levels, oxidative stress, growth factors, and stimulation of glutamate receptors (17). The MAPK cascading process initiates cell proliferation responses leading to Ras (Recovery Activation Signal) activation via agonists that stimulate protein kinase C, and growth factors that act on tyrosine kinase receptors. In the cascading process, both protein kinase C and Ras activate Raf (Rapidly Accelerated Fibrosarcoma) kinase, activating MAPK/ERK Kinase (MEK). Phosphorylated MEK activates and phosphorylates the ERK, which in turn phosphorylates transcription factors, protein substrates, and other protein kinases that are important in promoting cell proliferation and other cellular responses. Altered activity levels of MAPK factors lead to altered transcription of essential genes in the cell cycle (18).

**New Regulators of Ras/Raf/Erk Pathway.** The Sprouty/Spred family acts as definitive negative regulators of the Ras/Raf/ERK signal (19-22). Drosophila Sprouty was discovered as an FGF signal antagonist in 1998 (20, 21). In mammals, there are four Sprouty homologs (Sprouty 1-4). Sproutys was later shown to suppress ERK activation induced by various growth factors such as FGF, platelet-derived growth factor, VEGF-A, neurotrophic factor, and GDNF in a particular cell type and a specific growth factor (23).

Many factors in many cancers disrupt Ras/Raf/ERK pathway regulation. Several negative regulators accurately quantify the Ras/Raf/ERK pathway, including Ras GTPase-activating proteins, MAPK phosphatases, and the Sprouty/Spred family (21). Since the Sprouty/Spred family is one of the most important suppressors of the Ras/Raf/ERK pathway, many researchers have further investigated the role of Sprouty and Spred as tumor suppressors during tumorigenesis and metastasis (23).

It is believed that Sproutys have several mechanisms to suppress the Ras/Raf/ERK pathway. Sprouty generally act upstream of Ras because they cannot suppress active Ras mutations (20). However, Sprouty4 inhibits VEGF-A-induced ERK activity by direct binding to c-Raf (Mason et al., 2006). Interestingly, in mammals, Sproutys do not suppress the EGF signaling; Instead, they activate signaling by binding to c-Cbl, an E3 ubiquitin-protein ligase for EGFR (21). Sprouty2 can also suppress Rac1 activation and cell migration through the tyrosine phosphatase 1B (21). In addition, Sprouty1 and Sprouty2 have been reported to be negative regulators of the TGF-β-Smad signaling (24).

Spreds inhibit ERK activation in collaboration with Ras and neurofibromin and suppress phosphorylation and Raf activation (19, 25). Spreds can also regulate the activation of small GTPases, Ras, Rap1, and Rho (19). In Spred1, Ras/Raf/ERK pathway inhibition was known when the two tyrosine residues Y377/Y420 were phosphorylated (26). The other three tyrosine residues Y303/Y343/Y353 in CRD, are essential for regulating Spred2 activity (27).

The Sprouty/Spred family is induced by many signals from the tyrosine kinase receptor and acts as negative feedback regulators of Ras/Raf/ERK signaling (19-22). The mRNA and protein levels of members of this family are highly regulated by a variety of mechanisms, including epigenetic and post-translational changes (28, 29).

The Sprouty/Spred family negatively regulates the VEGF-A and VEGF-C signaling pathways, and besides, angiogenesis and lymphangiogenesis are essential processes for tumor development (22). These findings suggest that the expression of the Sprouty/Spred family in the microscopic environment of the tumor also indirectly affects tumorigenesis and metastasis (30, 31).

**The Role of Physical Activity, Exercise, and Training on the Ras/Raf/Erk Pathway.** However, studies have shown that physical activity increases the expression of ERK genes and proteins (32). In most of these studies, the response of ERK to one or more sessions of activity was evaluated, and immediately after the activity, the level of activity and the amount of phosphorylated ERK was examined. The ERK is activated immediately after the activity in trained and untrained cycling protocols in individuals (33-35), resistance and strength training (36-38), and in situ studies (15, 39, 40). However, few studies have examined the long-term adaptation of this protein and achieved different results. In this regard, it was reported that eccentric contraction of the biceps muscle increases total ERK and phosphorylation after 48 hours; But running downhill after 48 hours did not increase total ERK and phosphorylation (41). Another study reported a significant increase in total ERK protein content of FHL muscle after eight weeks of resistance training (5 sessions per week) in male Sprague Dawley rats, but no significant change was observed in its phosphorylated form; As long-term resistance training is probably not a proper intervention to activate ERK (42).

Besides, there are enough reports about the positive effects of various types of physical activity and growth factors. A session of high-intensity interval training (HIIT) on changes in serum vascular endothelial growth factor (VEGF) leads to the onset of the angiogenesis process (43). Also, ten weeks of HIIT, three sessions per week and 40 minutes per session with an intensity of 70 to 75 maximal heart rate in men with prostate cancer significantly increased VEGF and FGF levels in the experimental group compared to the control group (44).

However, the mechanisms underlying changes in growth factors in exercise and training are not well understood. Since Sprouty/Spred proteins have been shown to act downstream of a wide range of growth factor stimuli, including fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet growth factor (PDGF), Hepatocyte growth factor, and nerve growth factor (NGF) (45), physical activity, exercise, and training seems to be able to affect Sprouty/Spred by affecting growth factors, which has not yet been studied in this situation.

## CONCLUSION

Since most cancers occur in the elderly, it is expected that this disease's incidence and mortality will soon increase. Therefore, paying attention to the cancer control program is necessary globally. Physical activity, exercise, and training as essential health behavior play a vital role in the prevention and treatment of cancer and with different mechanisms to prevent its recurrence and complications of treatment and improve the quality of life of these patients. However, the related mechanism of physical activity on the tumor growth inhibition is not fully understood, and the role of new regulators such as the Sperouty/Spred family needs to be studied in the future.

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