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Review Article

The Human Angiogenin–Proliferating Cell Nuclear Antigen Interaction

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Abstract

The ANG gene in humans encodes angiogenin (ANG), also known as ribonuclease 5, a small protein of 123 amino acids. Angiogenin is a powerful inducer of angiogenesis, which results in the formation of new blood vessels. Ang interacts with DNA to affect protein synthesis levels and hydrolyzes cellular RNA, which increases the production of rRNA in a promoter-like manner. Through angiogenesis and by activating genes that prevent apoptosis, Ang is linked to neurological disorders and cancer (Lee 2013).

Keywords: Angiogenesis, Angiogenin, Neurogeneration, Ribosome biogenesis

INTRODUCTION

Angiogenin (ANG), a secreted protein belonging to the pancreatic RNase superfamily, functions as a weak ribonuclease. It is a powerful in vivo inducer of angiogenesis and contributes to the development of several human tumours, diabetic retinopathy, and rheumatoid arthritis. In the synthesis of ribosomes and the development of stress granules, ANG is crucial. Additionally, it has been demonstrated to be a neuroprotective and neurotrophic factor. Parkinson's illness and Amyotrophic Lateral Sclerosis (ALS) are both attributed to ANG. ANG-ALS mutations that influence neuronal survival, change catalytic activity, and lack the capacity to generate stress granules (Steuer et al., 2019).

The sole angiogenic factor with ribonucleolytic activity is angiogenin (ANG), a member of the RNase A superfamily. Recent research revealed that ANG expression was increased in a number of cancer types. A growing body of research suggests that ANG, through promoting both tumour angiogenesis and cancer cell proliferation, is crucial to the development of cancer. Leucine rich repeats (LRRs), which are found in a broad family of proteins that are differentiated by their presentation of enormous surface areas to promote protein-protein interactions, make up virtually all of the human ribonuclease inhibitor (RI), a cytoplasmic protein. RI may have biological effects other than suppressing RNase A activity (Pascal 2006). The investigation proved that RI might inhibit the action of angiogenin (ANG) by interacting closely with it in vitro. Cell growth, survival, proliferation, apoptosis, and angiogenesis are all influenced by the PI3K/AKT/mTOR signalling pathway. We recently discovered that increasing RI suppressed angiogenin and the PI3K/AKT signalling pathway, which in turn caused apoptosis and decreased the development of murine melanoma cells. However, ANG receptors have not yet been discovered, their associated signal transduction pathways are not well understood, and the fundamental mechanisms by which ANG and RI interact are still completely unknown. Therefore, we propose that RI could work in concert with intracellular ANG to suppress its biological activity by blocking its nuclear translocation and controlling the PI3K/AKT/mTOR signalling pathway. Here, utilising co-immunoprecipitation (Co-IP) and GST pull-down, we revealed for the first time that ANG may interact with RI endogenously and exogenously. Additionally, we used an optical confocal laser microscope to detect the colocalization of ANG and RI in cells. The fact that these two proteins interact physically in live cells was further validated by the fluorescence resonance energy transfer (FRET) experiment. Then, we showed that upregulating ANG, including the ANG His37Ala mutant, clearly reduced the expression of RI and triggered the phosphorylation of important downstream targets of the PI3K/AKT/mTOR signalling cascade. Last but

not least, increasing ANG promoted tumour angiogenesis, carcinogenesis, and metastasis in vivo. Our results together revealed a unique method by which ANG controls the PI3K/AKT/mTOR signalling pathway via RI, suggesting a potential therapeutic target for the treatment of cancer (Crown et al., 1988). It has been established that angiogenin (ANG), a 14-kDa pro-angiogenic secreted protein, is involved in tumour invasion and cell migration, both of which need the proteolytic cleavage of plasminogen to produce plasmin. However, it remained unknown how ANG controls plasmin production and cell movement. In these experiments, we found that highly invasive metastatic breast cancer cells had higher amounts of ANG that was both released and bound to the cell surface. Infiltrating ductal carcinomas showed very high levels of ANG in the tumour cells. By using immunofluorescence and immunoprecipitation analysis, ANG was found to colocalize and interact with other members of the plasminogen activation system (PAS), including annexin A2 (A2), calpactin (S100-A10), and urokinase plasminogen activator receptor (uPAR), at the leading edges of the cell surfaces. The prevalence of ANG, A2, and S100-A10 in the lipid raft (LR) and non-lipid raft (NLR) sections of the cell membranes was shown by analysis of the two. Contrarily, uPAR was mostly found in the NLR fractions, indicating that ANG and uPAR interact at the boundary between the LR and NLR areas. The expression of A2, S100-A10, and uPAR in T47D and MDA-MB-231 breast cancer cell lines was unaffected by ANG knockdown, although cell migration and plasmin formation were reduced. When ANG was neutralised by monoclonal antibodies, MDA-MB-231 cells moved less freely. uPAR and uPA were seen to interact in the presence of ANG, which is required for the production of plasmin. In contrast, uPAR did not interact with uPA in the absence of ANG, and FAK and Src kinases were seen to be dephosphorylated. Recombinant ANG was added exogenously to MDA-MB-231 cells that had been ANG knocked down to restore FAK phosphorylation, uPAR interactions with uPA, plasmin production, and cell migration. According to our findings, ANG plays a unique function in the uPAR interactome by facilitating the interaction of uPAR with uPA, which leads in the generation of plasmin and cell movement required for tumour invasion and metastasis of breast cancer cells (Pesce et al., 2012).

A crucial protein called angiogenin is associated with both normal and tumour development angiogenesis. Angiogenin interacts with smooth muscle and endothelial cells, causing the cells to move inside, invade, multiply, and create tubular formations. When Ang binds to actin in smooth muscle and endothelial cells, complexes are formed that activate proteolytic cascades and upregulate the production of proteases and plasmin, which break down the basement membrane's laminin and fibronectin layers. Endothelial cells can enter and move through the extracellular matrix and basement membrane to reach the perivascular tissue. ERK1/2 and protein kinase B/Akt are produced by signal transduction pathways that are triggered by Ang contacts at the cellular membrane of endothelial cells. The invasion of the basement membrane and cell proliferation brought on by additional angiogenesis are caused by the activation of these proteins (Johnson et al., 1999). The translocation of Ang to the cell nucleus is the most significant stage in the angiogenesis process. The CT-rich (CTCTCTCTCTCTCTCCCTC) angiogenin binding element (ABE) in the upstream intergenic region of rDNA is where Ang promotes rRNA transcription after it has been translocated to the nucleus. This activation of other angiogenic components that cause angiogenesis follows. The fact that angiogenin is also an enzyme with an amino acid sequence that is 33% similar to that of bovine pancreatic ribonuclease (RNase A) sets it apart from the other many proteins involved in angiogenesis. Ang primarily cleaves on the 3' side of pyrimidines and follows a transphosphorylation/hydrolysis process, sharing general catalytic characteristics with RNase A (Jencks 1987). Angiogenin cleaves common RNA substrates 105–106 times less effectively than RNase A despite sharing many of the same catalytic residues. The glutamine in residue 117, which inhibits the catalytic site, is the cause of this inefficiency. When this residue is altered, the activity of the ribonuclease is increased between 11 and 30 fold. Despite this apparent weakness, the enzymatic activity of Ang appears to be crucial for biological activity: substitutions of critical catalytic site residues (histidine-13 and histidine-114) invariably result in a 10,000-fold reduction in ribonuclease activity towards tRNA and a nearly complete cessation of angiogenesis activities (Brown 1902).

CONCLUSION

RI may control the activity of ANG in one of the two methods listed below, or both: RI could control the interaction between angiogenin and PI3K/AKT/mTOR. It could also bind to intracellular ANG directly to block the ribonuclease's active centre and prevent nuclear translocation, which would inhibit ANG's ability to promote rRNA transcription and other functions (Olson et al., 2007). Our laboratory is conducting more study on its mechanism and the link of interaction between them. Together, these findings may help to clarify the molecular mechanism underlying ANG's function in cell proliferation and tumour development. Our results show the potential for ANG to act as a biological marker and a useful target for the treatment of bladder cancer (Johnson 2013).

Our discovery of ANG at the leading edges of breast cancer cells may be crucial in resolving a critical issue in the therapeutic therapy of breast cancer, to sum up. It is widely known that a longer period of disease-free time necessitates the total surgical excision of breast tumours. However, partial mastectomy is the most typical surgical result in the event of invasive ductal carcinomas (IDC). The lack of agreement over what defines an ideal negative margin is the primary justification for partial surgery. The absence of definition at the breast tumours' leading edge is one of the main causes of this. This has also resulted in a significant number of reexcisions, even in patients with negative margins, in order

to acquire a margin that is more broadly clean. In order to define guidelines for precise immunohistochemical and imaging detection of margins post-surgery, comprehensive molecular characterisation of the proteins at the leading/ invasive edge of invading tumours is a very important step. Cell surface ANG is a prime candidate alone or in combination with uPA, uRAR, and PAI, which are also highly expressed in breast tumour and tumour stroma, to define margins during breast cancer surgery given our observations of ANG on the leading edges of breast cancer cells and the well-documented observation by others that ANG is highly expressed in primary breast carcinomas. Further research is necessary to identify the function of ANG in breast cancer cell invasion when it occurs in vivo.

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