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General Audience Summary
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As in healthy tissues, tumors require blood vessels to deliver oxygen and nutrients to the mass in order to grow. Angiogenesis is the process by which these new blood vessels grow. Without the process of angiogenesis and the creation of new blood vessels, tumors cannot survive. Therapies that target and inhibit angiogenesis have several advantages over conventional therapies, such as being effective against a wide variety of cancers, targeting only growing vessels as opposed to stable vessels, and targeting the cells that line the inside of the new vessels (endothelial cells) as opposed to tumor cells. A natural inhibitor of angiogenesis is called pigment-epithelial derived factor (PEDF). Using an angiogenesis inhibitor found naturally in the body allows for minimal toxic side effects. Our lab has been able to determine which part of the PEDF protein has these anti-angiogenic effects and synthesized a peptide that contains only that region, called 34mer. The mechanism by which PEDF and 34mer is anti-angiogenic has not been totally elucidated. PEDF is known to regulate proteins that bind to DNA and initiate the creation, or transcription, of other proteins. The proteins that initiate the transcription of other proteins are known as transcription factors. In order to determine the transcription factors that were regulated by PEDF and 34mer, an experiment was performed that measured the extent of activation of many transcription factors at once by PEDF and 34mer. Many of the transcription factors that were activated are known to control the processes by which cells divide and proliferate. In this proposal, we will investigate the pathways that lead to the activation of these transcription factors by PEDF and 34mer. Our overall hypothesis is PEDF and 34mer blocks angiogenesis in endothelial cells by regulating transcription factors that control cell division and proliferation, such as Rb, C/EBPalphą and Ets-1. The results of this study will help uncover new pathways PEDF utilizes to inhibit angiogenesis, specifically by inhibiting cell division and proliferation. By studying the pathways PEDF utilizes, new therapeutic targets can be identified and treatments developed to augment the effects of anti-angiogenic therapies. Developing drugs that target these intermediates will treat a wide variety of cancers with minimal toxic side effects.