Researchers Link Master Regulator of Innate Immunity to the Hypoxic Response

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Survival of all animals depends on their ability to withstand microbial infections and adapt to fluctuations in oxygen concentrations. These abilities depend on two ancient, evolutionary gene expression responses called the innate immune response and the hypoxic response.

In a new study published in the advanced online edition of the journal *Nature* on April 23, researchers at the University of California, San Diego School of Medicine reveal that a single protein is essential to both responses. This understanding may lead to new therapies to boost the body's immune function or to limit inflammatory damage in tissues deprived of oxygen.

The research, led by Michael Karin, Ph.D., professor of pharmacology in UCSD's Laboratory of Gene Regulation and Signal Transduction, shows that transcription factor NF kappa B (NF-κβ) -- previously known for its role as the master regulator of the innate immune response -- is also a critical regulator of the hypoxic response.

More than ten years ago, the Karin lab identified an enzyme called Iκβ kinase beta (IKKB) as the critical activator of NF-Iκβ. In this study, the UCSD researchers interfered with activation of NF-Iκβ by inactivating IKKB in different cells and tissues of a laboratory mouse. When they examined how macrophages deficient in IKKB responded to bacterial infections or oxygen deprivation, the researchers found that, in addition to the expected defect in activation of NF-Iκβ, the macrophages also failed to accumulate HIF-1α, the master regulator of the hypoxic

response. HIF-1α is normally accumulated in cells experiencing low ambient oxygen, or hypoxia; in turn, it activates several genes responsible for generating energy to allow cell survival.

Previous work by UCSD co-contributors Victor Nizet, MD, professor of pediatrics and pharmacy and Randall S. Johnson, Ph.D., professor of biology, showed that bacterial infections -- which deplete infected cells and tissues of critical oxygen -- lead to accumulation of HIF-1α and activation of the hypoxic response.

"The hypoxic response is important in order for macrophages and other immune cells to kill and eliminate bacteria. The surprising result of the new study is the discovery that HIF-1α accumulation is dependent on activation of NF-Iκβ," said Karin.

The NF-Iκβ and HIF-1α pathways have been extensively investigated as targets for new drug therapies. "Our new understanding of the interrelationship of NF-Iκβ and the hypoxic response provides clues toward new treatment strategies to boost the immune function of white blood cells in infected tissues." said Nizet. "Inhibition of the hypoxic response in macrophages might also limit inflammatory damage to brain tissues following stroke or cardiac arrest".

A unique series of mice with specific genetic alterations of HIF-1α or IKKB in various cells and tissues have been developed in the Karin and Johnson laboratories to continue these promising lines of investigation.

Source: University of California - San Diego

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