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Mechanistic Studies of the Bioavailability Barrier Network (BBN) and its Negative Impact on the Disposition and Chemopreventative Efficacy of Dietary Phytochemicals

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Polyhydroxlyated phytochemicals such as flavonoids, isoflavonoids and resveratrol have received major attention for their abilities to decrease the risk of coronary heart disease, ischemic stroke and most importantly prevent various forms of cancer including but not limited to colorectal and lung. However, a major conundrum observed in the clinic is that these chemopreventative phytochemicals all have extremely poor bioavailability.

To investigate the mechanisms in which our body can limit the amount of phytochemicals in the systemic circulation, we investigated the disposition of phytochemicals in four aspects of 1) absorption 2) distribution 3) metabolism and 4) excretion/elimination. Utilization of in vitro (e.g., ATPase assays, Cell lines, Vesicular transport assays), in situ (simultaneous 4-intestinal site perfusion models) and in vivo (e.g., knockout animals) methods as well as modeling & simulation (i.e., PBPK), we have discovered a barrier network which explains this observed phenomenon. Overall, this barrier network is not only governed by the following: 1) metabolism of these phytochemicals (typically phase II) 2) elimination of metabolites utilizing active transporting proteins (ABC efflux transporters) but is also dependent on the interaction between these two steps. This mechanism of coupling is extremely important as it governs the dispositional process of phytochemicals.

However, additional complexities are introduced as we attempt to disrupt this coupling process and observe an unexpected compensation via other proteins (both metabolic and transporters) within the same superfamily. Therefore, we propose here a bioavailability barrier network worthy of further characterization in order to better understand the disposition of phytochemicals.

Biography

Dr. Stephen Wang received his training in pharmaceutical sciences at the Texas Medical Center under Professor Ming Hu. Dr. Wang currently serves as a principal scientist in the department of Drug Metabolism and Pharmacokinetics at Millennium Pharmaceuticals in Cambridge MA. Previously, Dr. Wang served as a senior scientist in the department of Drug Metabolism and Pharmacokinetics at Merck. Dr. Wang's research interests focus on the disposition of xenobiotics in an effort to improve bioavailability of chemopreventive agents. Dr. Wang has made significant contributions in the field with a consistent publication track record of over 25 manuscripts in peer-reviewed scientific journals and various book chapters.