Metformin, aging and cancer

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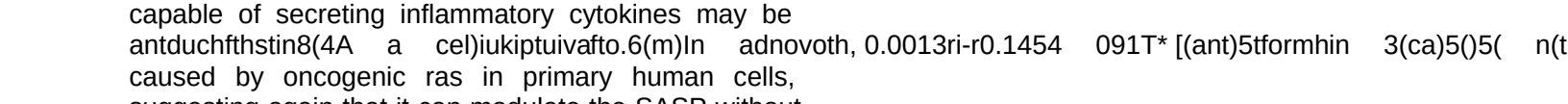
Many cancers are associated with aging [1]. Metformin, a widely used antidiabetic drug, has been linked to a reduced cancer incidence in some retrospective, hypothesis-generating studies [2]. Since cancer and aging may share certain molecular processes, it is plausible that metformin may prevent cancer by acting on the aging process. Consistent with this idea, several studies report a life span extension in animal models after treatment with metformin [3].

What is the mechanism by which aging may increase cancer incidence? Although many molecular changes correlate with aging, the presence of senescent cells capable of secreting inflammatory cytokines may be



caused by oncogenic ras in primary human cells, suggesting again that it can modulate the SASP without allowing proliferation of potentially malignant cells. The primary site of action of metformin is considered to be the complex I of the electron transport chain [2]. However, molecular details of the interaction between metformin and complex I remain to be identified. Complex I is one of the main cellular sources for reactive oxygen species (ROS) and we have shown that metformin can prevent ROS production by senescent cells [8]. It is thus plausible that ROS links senescence to NF-kB activation and that metformin interferes with this mechanism by acting on complex I (Fig 1). Metformin is not immunosuppressive so its ability to inhibit NF-kB is likely confined to certain pro-inflammatory contexts such as senescence. We thus propose that metformin prevents cancer by modulating the SASP in tissues where senescent cells were not naturally cleared.

Many questions remain to be addressed in order to fully characterize metformin actions. Our results were obtained using cultured senescent fibroblasts and macrophages; other cell types should be studied as well. In addition, it remains to be determined if metformin can achieve this anti-SASP activity in vivo or whether it can influence the clearance of senescent cells by modulating the SASP. Anisimov and colleagues reported that metformin extends life span in female mice but not males [3] and it would be interesting to study whether NF-kB and SASP inhibition by metformin is gender dependent. Additional epidemiological data and laboratory experiments may justify well-designed clinical studies to evaluate metformin as a cancer preventive agent in specific contexts where its

recently described actions would be hypothesized to be useful.

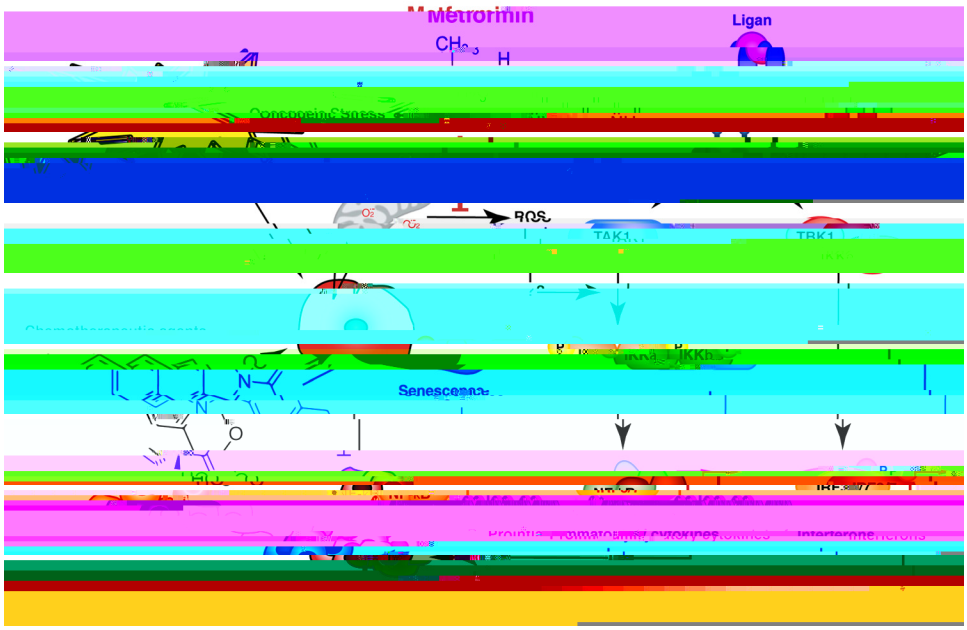


Figure 1. Metformin inhibits the activation of IKK kinases in senescent cells. The model proposes that metformin reduces ROS generation by mitochondria preventing the activation of IKK kinases a step that is ROS sensitive. Metformin does not affect the activation of the interferon response in senescent cells suggesting that it modulates the senescence associated secretory phenotype in a way that reduces chronic inflammation but not tumor suppression.

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