Wnt signaling in age-related Transcriptome Changes in Sentinel Lymph Node and Their Association with Recurrence in Node-Positive Melanoma Patients

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Abstract

Background: Age is an important risk factor for melanoma. Older patients have a greater risk of melanoma mortality, yet a lower incidence of sentinel lymph node (SLN) metastasis. This highlights the need for further studies into aged-related SLN biology.

Methods: Three independent sets of RNA samples from patients with melanoma metastatic to the SLN were used in this study. The first dataset included 97 melanoma patients selected from the Sunbelt Melanoma Trial. Total RNA from these SLN samples was used for microarray experiments. A multivariate linear regression model was fitted for each gene of each sample about age (<60 years vs. ≥60), disease status (recurrence vs. no recurrence), and interaction of age and disease status. Differential expressed genes (DEGs) with a p-value of less than 0.05 were identified on age, recurrence status and the interaction of age and recurrence status. The second dataset of RNA samples includes 12 patients chosen form the Brown Cancer Center Bio-Repository at the University of Louisville. NanoString was performed to identify the immune genes related to age and pathways that differentiate the recurrence and non-recurrence in the younger and older groups. nSolver software was used to differentiate the genes with a p<0.05. The third dataset of 36 samples from the Brown Cancer Center Bio-Repository was used for microarray and NanoString data.

Results: We showed that FOS, NR4A2, PTGS2, and LINCO00518 were all upregulated in recurrence vs. the non-recurrence group. However, the older group had a much higher fold change (FC) than that of the younger group (FC>4 vs. FC<2, p<0.05). IL1B was downregulated in the younger group, but was upregulated in the older group when comparing recurrence vs. non-recurrence. The expression of one of the Wnt pathway genes, Wnt10b, was upregulated only 1 fold in the older group in comparing recurrence versus non-recurrence (p<0.05). The expressions of all those genes were confirmed by RT-PCR. All of these significant genes converged at Wnt signaling pathway.

Conclusions: The Wnt pathway, specifically Wnt10b, is a major pathway associated with melanoma recurrence in older patients. These findings may lead to development of new therapeutic targets and strategies.

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